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Breast Cancer
Updates & Future Trends

Current and Expected New Treatments in Breast Cancer

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Medical Trends

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ASCO Oncology Self-Study Series, Breast Cancer: Updates & Future Trends
Current And Expected New Treatments In Breast Cancer

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Learning Objectives

Knowledge and skills acquired upon completion of this volume:

1. Summarize the ASCO guidelines on adjuvant use of biphosphonates or bone-modifying agents in hormone-receptor positive breast cancer.
2. Explain the new treatments in triple negative breast cancer: the arrival of immunotherapy and PARP inhibitors.
3. Assess the new recommendations for management of HR + advance breast cancer: the arrival of cyclin-dependent kinase 4/6 inhibitor.
4. Appraise the consensus guidelines from the Society of American Society for SLN in operable breast cancer.
5. Assess the new recommendations on disease management for patients with HER2-positive breast cancer in adjuvant setting.

Syllabus

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Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update

(J Clin Oncol 2017;35(24):2838–2847.)

Purpose: This focused update addresses the use of MammaPrint (Agendia, Irvine, CA) to guide decisions on the use of adjuvant systemic therapy.

Methods: ASCO uses a signals approach to facilitate guideline updates. For this focused update, the publication of the phase III randomized MINDACT (Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy) study to evaluate the MammaPrint assay in 6,693 women with early-stage breast cancer provided a signal. An expert panel reviewed the results of the MINDACT study along with other published literature on the MammaPrint assay to assess for evidence of clinical utility.

Recommendations: If a patient has hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative, node-negative breast cancer, the MammaPrint assay may be used in those with high clinical risk to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good-prognosis population with potentially limited chemotherapy benefit. Women in the low clinical risk category did not benefit from chemotherapy regardless of genomic MammaPrint risk group. Therefore, the MammaPrint assay does not have clinical utility in such patients. If a patient has hormone receptor–positive, HER2-negative, node-positive breast cancer, the MammaPrint assay may be used in patients with one to three positive nodes and a high clinical risk to inform decisions on withholding adjuvant systemic chemotherapy. However, such patients should be informed that a benefit from chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node. The clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic therapy in patients with hormone receptor–positive, HER2-negative, node-positive breast cancer at low clinical risk, nor any patient with HER2-positive or triple-negative breast cancer, because of the lack of definitive data in these populations.

Introduction

The American Society of Clinical Oncology (ASCO) Clinical Practice Guideline on the use of biomarkers to guide adjuvant therapy for early-stage invasive breast cancer was most recently published in February 2016.[1]

ASCO Guidelines are updated at regular intervals; however, there may be new evidence that potentially changes a recommendation and becomes available between scheduled updates. ASCO uses a signals approach to facilitate guideline updates. This approach is intended to identify new,

The bottom line

Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: ASCO clinical practice guideline focused update

Guideline question

For women with early-stage invasive breast cancer, which other biomarkers have demonstrated clinical utility to guide decisions on the need for adjuvant systemic therapy?

Target population

Women with early-stage invasive breast cancer being considered for adjuvant systemic therapy

Target audience

Medical, surgical, and radiation oncologists; oncology nurses and physician assistants; pathologists; general practitioners; and patients

Methods

An Expert Panel was convened to update the clinical practice guideline recommendations based on a review of recently published literature.

Focused update recommendation(s)

Recommendation 1.1.1 (update of 2016 recommendation 1.7): If a patient has **ER/PgR–positive, HER2-negative, node-negative**, breast cancer, the MammaPrint assay may be used in those with **high clinical risk** per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.1.2 (update of 2016 recommendation 1.7): If a patient has **ER/PgR–positive, HER2-negative, node-negative**, breast cancer, the MammaPrint assay **should not** be used in those with **low clinical risk** per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy, because women in the low clinical risk category had excellent outcomes and did not appear to benefit from chemotherapy even with a genomic high-risk cancer (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.2.1 (update of 2016 recommendation 1.7): If a patient has **ER/PgR–positive, HER2-negative, node-positive**, breast cancer, the MammaPrint assay may be used in patients with one to three positive nodes and at **high clinical risk** per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. However, such patients should be informed that a benefit of chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node (Type: evidence based; Evidence quality: high; Strength of recommendation: moderate).

Recommendation 1.2.2 (update of 2016 recommendation 1.7): If a patient has **ER/PgR–positive, HER2-negative, node-positive**, breast cancer, the MammaPrint assay **should not** be used in patients with one to three positive nodes and at **low clinical risk** per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy. There are insufficient data on the clinical utility of MammaPrint in this specific patient population (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 1.3 (update of 2016 recommendation 1.8): If a patient has **HER2-positive** breast cancer, the clinician **should not** use the MammaPrint assay to guide decisions on adjuvant systemic therapy. Additional studies are required to address the role of MammaPrint in patients with this tumor subtype who are also receiving HER2-targeted therapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 1.4 (update of 2016 recommendation 1.9): If a patient has **ER/PgR negative** and **HER2-negative (triple negative)** breast cancer, the clinician **should not** use the MammaPrint assay to guide decisions on adjuvant systemic chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

Refer to Table 1 for the full list of the original recommendations for question 1.

potentially practice-changing data (ie, signals) that might translate into revised practice recommendations. The approach relies on routine literature searches and the expertise of ASCO Guideline Panel members to identify signals. For this focused update, the publication of the "Microarray in node-negative and one to three positive lymph node disease may avoid chemotherapy" (MINDACT) study, a randomized controlled trial on a 70-gene assay (MammaPrint; Agendia, Irvine, CA) provided the signal.[2]

The decision to update this aspect of the guideline was intended to convey any recommendation changes to the practicing community in a timely fashion. Although evidence on other aspects of the guideline may have become available after release of the guideline, no other strong signal likely to affect the recommendations has been identified to date. This approach acknowledges that frequent updating is not practical or necessary unless indicated by practice-changing evidence. It is important to note that new evidence, published in a peer-reviewed journal, about any ASCO guideline may be submitted at any time. Please access the ASCO Guidelines Wiki for more information on evidence submission at http://www.asco.org/guidelineswiki. All new evidence submissions are reviewed by ASCO Staff for study selection eligibility requirements and by the Expert Panel co-chairs for a content assessment. If the new evidence is determined to constitute a signal, it will prompt an expedited update on the topic.

Focused updates for Clinical Practice Guidelines are approved by the Clinical Practice Guideline Committee, and this update reflects new evidence about recommendations 1.7 to 1.9 on MammaPrint in the previous version of this guideline.[1] This focused update reviews and analyzes new data about these recommendations while applying the same criteria of clinical utility as described in the 2016 guideline.

As stated in the 2016 guideline, a biomarker-based test is judged to have clinical utility if use of the test is associated with a favorable balance of benefits to harm compared with treatment of the patient in the absence of the biomarker test result. Benefits may include improvement in survival end points such as event-free survival (EFS), disease-free survival (DFS), progression-free survival (PFS), or overall survival (OS).[1] The Use of Biomarkers Update Committee clarified that reduction in toxicity of treatment also can be considered a benefit. For example, a biomarker test that provides evidence that a patient can be treated effectively with hormonal therapy alone provides benefit to that patient by avoiding the potential serious toxicity of chemotherapy.

Guideline questions

For women with early-stage invasive breast cancer, which other biomarkers have demonstrated clinical utility to guide decisions on the need for adjuvant systemic therapy: (a) in patients with estrogen receptor (ER) and/or progesterone receptor (PgR)–positive, human epidermal growth factor receptor 2 (HER2)-negative (node-negative or node-positive) breast cancer; (b) in patients with HER2-positive breast cancer; and (c) in patients with triple-negative breast cancer?

As this focused update addresses the role of MammaPrint in early breast cancer, only the first clinical question from the original guideline is addressed here.

Methods

This ASCO Clinical Practice Guideline focused update provides revised recommendations with a comprehensive discussion of the relevant literature for this specific biomarker identified through the methodology described above. The full guideline to which this revision applies and additional information are available at www.asco.org/breast-cancer-guidelines and www.asco.org/guidelineswiki. The complete list of recommendations, including the updated recommendation(s), is in Table 1.

Key points

- *The decision to update this aspect of the guideline was intended to convey any recommendation changes to the practicing community in a timely fashion.*
- *It is important to note that new evidence, published in a peer-reviewed journal, about any ASCO guideline may be submitted at any time.*
- *All new evidence submissions are reviewed by ASCO Staff for study selection eligibility requirements and by the Expert Panel co-chairs for a content assessment.*
- *This focused update reviews and analyzes new data about these recommendations while applying the same criteria of clinical utility as described in the 2016 guideline.*
- *The Use of Biomarkers Update Committee clarified that reduction in toxicity of treatment also can be considered a benefit.*
- *As this focused update addresses the role of MammaPrint in early breast cancer, only the first clinical question from the original guideline is addressed here.*
- *This ASCO Clinical Practice Guideline focused update provides revised recommendations with a comprehensive discussion of the relevant literature for this specific biomarker identified through the methodology described.*

TABLE 1 - Summary of original recommendations for question 1 with focused updated recommendations

Recommendation no.	Recommendation	Evidence rating
1.1	If a patient has ER/PgR–positive, HER2-negative (node-negative) breast cancer, the clinician may use the 21-gene RS (Oncotype DX; Genomic Health, Redwood, CA) to guide decisions for adjuvant systemic chemotherapy.	Type: evidence based Evidence quality: high Strength of recommendation: strong
1.2	If a patient has ER/PgR–positive, HER2-negative (node-positive) breast cancer, the clinician should not use the 21-gene RS (Oncotype DX; Genomic Health) to guide decisions for adjuvant systemic chemotherapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: moderate
1.3	If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use the 21-gene RS (Oncotype DX; Genomic Health) to guide decisions for adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong
1.4	If a patient has ER/PgR–positive, HER2-negative (node-negative) breast cancer, the clinician may use the 12-gene risk score (EndoPredict; Sividon Diagnostics, Köln, Germany) to guide decisions for adjuvant systemic chemotherapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: moderate
1.5	If a patient has ER/PgR–positive, HER2-negative (node-positive) breast cancer, the clinician should not use the 12-gene risk score (EndoPredict; Sividon Diagnostics) to guide decisions for adjuvant systemic chemotherapy.	Type: evidence based Evidence quality: insufficient Strength of recommendation: moderate
1.6	If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use 12-gene risk score (EndoPredict; Sividon Diagnostics) to guide decisions for adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong
1.7 Recommendation 1.1.1 in 2017	**If a patient has ER/PgR–positive, HER2-negative, node-negative, breast cancer, the MammaPrint (Agendia, Irvine, CA) assay may be used in those with high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good-prognosis population with potentially limited chemotherapy benefit.**	**Type: evidence based Evidence quality: high Strength of recommendation: strong**
1.7 Recommendation 1.1.2 in 2017	**If a patient has ER/PgR–positive, HER2-negative, node-negative, breast cancer, the MammaPrint (Agendia) assay should not be used in those with low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy, because women in the low clinical risk category had excellent outcomes and did not appear to benefit from chemotherapy even with a genomic high-risk cancer.**	**Type: evidence based Evidence quality: high Strength of recommendation: strong**
1.7 Recommendation 1.2.1 in 2017	**If a patient has ER/PgR–positive, HER2-negative, node-positive, breast cancer, the MammaPrint (Agendia) assay may be used in patients with one to three positive nodes and at high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good-prognosis population with potentially limited chemotherapy benefit. However, such patients should be informed that a benefit of chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node.**	**Type: evidence based Evidence quality: high Strength of recommendation: moderate**

■ **TABLE 1 - Summary of original recommendations for question 1 with focused updated recommendations (*continued*)**

Recommendation no.	Recommendation	Evidence rating
1.7 Recommendation 1.2.2 in 2017	**If a patient has ER/PgR–positive, HER2-negative, node-positive, breast cancer, the MammaPrint (Agendia) assay should not be used in patients with one to three positive nodes and at low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy. There are insufficient data on the clinical utility of MammaPrint in this specific patient population.**	**Type: informal consensus Evidence quality: low Strength of recommendation: moderate**
1.8 Recommendation 1.3 in 2017	**If a patient has HER2-positive breast cancer, the clinician should not use the MammaPrint (Agendia) assay to guide decisions on adjuvant systemic therapy. Additional studies are required to address the role of MammaPrint in patients with this tumor subtype who are also receiving HER-2–targeted therapy.**	**Type: informal consensus Evidence quality: low Strength of recommendation: moderate**
1.9 Recommendation 1.4 in 2017	**If a patient has ER/PgR–negative and HER2-negative breast cancer (triple-negative), the clinician should not use the MammaPrint (Agendia) assay to guide decisions on adjuvant systemic chemotherapy.**	**Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong**
1.10	If a patient has ER/PgR–positive, HER2-negative (node-negative) breast cancer, the clinician may use the PAM50 ROR score (Prosigna Breast Cancer Prognostic Gene Signature Assay; NanoString Technologies, Seattle, WA) in conjunction with other clinicopathologic variables to guide decisions on adjuvant systemic therapy.	Type: evidence based Evidence quality: high Strength of recommendation: strong
1.11	If a patient has ER/PgR–positive, HER2-negative (node-positive) breast cancer, the clinician should not use the PAM50 ROR score (Prosigna Breast Cancer Prognostic Gene Signature Assay; NanoString Technologies) to guide decisions on adjuvant systemic therapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: moderate
1.12	If a patient has HER2-positive breast cancer, the clinician should not use the PAM50-ROR score (Prosigna Breast Cancer Prognostic Gene Signature Assay; NanoString Technologies) to guide decisions on adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong
1.13	If a patient has triple-negative breast cancer, the clinician should not use the PAM50-ROR score (Prosigna Breast Cancer Prognostic Gene Signature Assay; NanoString Technologies) to guide decisions for adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong
1.14	If a patient has ER/PgR–positive, HER2-negative, node-negative breast cancer, the clinician may use the Breast Cancer Index (bioTheranostics, San Diego, CA) to guide decisions on adjuvant systemic therapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: moderate
1.15	If a patient has ER/PgR–positive, HER2-negative, node-positive breast cancer, the clinician should not use the Breast Cancer Index (bioTheranostics) to guide decisions on adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong
1.16	If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use the Breast Cancer Index ((bioTheranostics) to guide decisions on adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong

TABLE 1 - Summary of original recommendations for question 1 with focused updated recommendations (*continued*)

Recommendation no.	Recommendation	Evidence rating
1.17	If a patient has ER/PgR–positive, HER2-negative (node-positive or node-negative) breast cancer, the clinician should not use the five-protein assay Mammostrat (GE Healthcare, Aliso Viejo, CA) to guide decisions on adjuvant systemic therapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: moderate
1.18	If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use the five-protein assay Mammostrat (GE Healthcare) to guide decisions on adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong
1.19	If a patient has ER/PgR–positive, HER2-negative (node-positive or node-negative) breast cancer, the clinician should not use IHC-4 to guide decisions on adjuvant systemic chemotherapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: moderate
1.20	If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use IHC-4 to guide decisions on adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong
1.21	If a patient has ER/PgR–positive, HER2-negative (node-negative) breast cancer, the clinician may use the uPA and PAI-1 to guide decisions on adjuvant systemic therapy.	Type: Evidence based Evidence quality: high Strength of recommendation: weak
1.22	If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use the uPA and PAI-1 to guide decisions on adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: weak
1.23	The clinician should not use CTCs to guide decisions for adjuvant systemic therapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: strong
1.24	If a patient has ER/PgR–positive, HER2-negative (node-positive or node-negative) breast cancer, the clinician should not use TILs to guide decisions for adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong
1.25	If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use TILs to guide decisions on adjuvant systemic therapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: strong
1.26	Ki67 labeling index by immunohistochemistry should not be used to guide the choice of adjuvant chemotherapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: moderate
1.27	If a patient has ER/PgR–positive, HER2-negative (node-negative) breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, the clinician should not use multiparameter gene expression or protein assays (Oncotype DX, EndoPredict, PAM50, Breast Cancer Index, or IHC-4) to guide decisions on extended endocrine therapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: moderate

Focused update recommendations are in bold. Clinical question 1 is as follows: For women with operable invasive breast cancer and with known ER/PgR and HER2 status, which other biomarkers have demonstrated clinical utility to guide decisions on the need for adjuvant systemic therapy?
CTC, circulating tumor cell; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC-4, immunohistochemistry 4; MINDACT, Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy; PAI-1, plasminogen activator inhibitor type 1; PgR, progesterone receptor; ROR, risk of recurrence; RS, recurrence score; TIL, tumorinfiltrating lymphocyte; uPA, urokinase plasminogen activator.

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

Guideline update process

ASCO uses a signals approach to facilitate guideline updating.[3] This approach is intended to identify new, potentially practice-changing data (ie, signals) that might translate into revised practice recommendations. The approach relies on routine literature searching and the expertise of ASCO guideline panel members to identify signals.

For this focused update, the publication of the randomized controlled trial on MammaPrint provided the signal. The full ASCO Update Committee was then convened to review the evidence.

The Expert Panel met via conference calls to consider the evidence for each of the 2017 recommendations on MammaPrint. The guideline was circulated in draft form to the Expert Panel for review and approval. ASCO's Clinical Practice Guidelines Committee reviewed and approved the final document. Because this was a focused update based on the signal described

Key points

- *The use of words like "must," "must not," "should," and "should not" indicate that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases.*
- *In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient.*
- *ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.*
- *All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact.*
- *In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.*
- *The Expert Panel met via conference calls to consider the evidence for each of the 2017 recommendations on MammaPrint.*

Key points

- *The MINDACT study was a randomized trial that included 6,693 women with histologically proven operable invasive breast cancer, zero to three positive nodes, and no distant metastases.*
- *Each participant's genomic risk was determined by using the MammaPrint assay, and clinical risk was determined by using a modified version of Adjuvant! Online.*
- *First, participants who were allocated to chemotherapy could elect to be randomly assigned to receive an anthracycline-containing regimen or a docetaxel-plus-capecitabine regimen.*
- *Second, participants with hormone receptor–positive breast cancer could be randomly assigned to a sequential regimen of tamoxifen for 2 years followed by letrozole for 5 years, or to 7 years of letrozole only.*
- *The study included 6,693 participants, of whom 5,914 (88.4%) had ER/PgR–positive tumors, 6,043 (90.3%) had HER2-negative tumors, and 640 (9.6%) had triple-negative tumors.*
- *Of the 6,693 participants, 2,745 (41.0%) had tumors with low clinical and low genomic risks, 592 (8.8%) had tumors with low clinical risk and high genomic risk, 1,550 (23.2%) had tumors with high clinical risk and low genomic risk, and 1,806 (27.0%) had tumors with high clinical and high genomic risks.*

above, only MammaPrint was reviewed by the Panel for this update.

Results

Study characteristics

The MINDACT study was a randomized trial that included 6,693 women with histologically proven operable invasive breast cancer, zero to three positive nodes, and no distant metastases.[2] Patients were recruited from 2007 to 2011. Only patients with node-negative disease were enrolled initially, and the study was amended to include women with one to three positive nodes in 2009. Each participant's genomic risk was determined by using the MammaPrint assay, and clinical risk was determined by using a modified version of Adjuvant! Online (version 8.0 with HER2 status).[4,5] Individuals with both low clinical and low genomic risk did not receive chemotherapy, but those at high clinical and high genomic risk received adjuvant chemotherapy. Those with discordant clinical and genomic risk results (high/low or low/high) were randomly assigned to chemotherapy or to no chemotherapy. Women in all groups were recommended to receive 7 years of hormonal therapy, if appropriate, on the basis of ER/PgR status.

The study included additional optional random assignments. First, participants who were allocated to chemotherapy could elect to be randomly assigned to receive an anthracycline-containing regimen or a docetaxel-plus-capecitabine regimen. Second, participants with hormone receptor–positive breast cancer could be randomly assigned to a sequential regimen of tamoxifen for 2 years followed by letrozole for 5 years, or to 7 years of letrozole only. Premenopausal women who entered random assignment had to have adequate ovarian function suppression during letrozole therapy. Results from these random assignments are yet to be reported.

The primary analysis of the study, which was reported in the recent publication,[2] was to assess whether, among patients with high-risk clinical features and a low-risk gene-expression profile who did not receive chemotherapy, the lower boundary of the 95% CI for the rate of 5-year survival without distant metastasis (distant metastasis–free survival, or DMFS) was 92% or greater. A prespecified secondary analysis was to estimate the efficacy of chemotherapy in those patients with discordant clinical and genomic risk results who were randomly assigned to chemotherapy versus no chemotherapy, but the study was not designed to detect a significant difference. An additional secondary analysis was to determine the proportion of patients who were assigned chemotherapy according to the clinical risk compared with the genomic risk.

The study included 6,693 participants, of whom 5,914 (88.4%) had ER/PgR–positive tumors, 6,043 (90.3%) had HER2-negative tumors, and 640 (9.6%) had triple-negative tumors. Of the 6,693 participants, 2,745 (41.0%) had tumors with low clinical and low genomic risks, 592 (8.8%) had tumors with low clinical risk and high genomic risk, 1,550 (23.2%) had tumors with high clinical risk and low genomic risk, and 1,806 (27.0%) had tumors with high clinical and high genomic risks. This first report included a cutoff date of March 1, 2016, which corresponded to a median follow-up time of 5.0 years. Of the 644 women who represented the primary test population (ie, those with high clinical risk and low genomic risk who did not receive chemotherapy), the DMFS at 5 years was 94.7% (95% CI, 92.5% to 96.2%), thus demonstrating a lower boundary of the 95% CI for the rate of DMFS of at least 92%. In the 749 women in the intention-to-treat population with a high clinical risk and low genomic risk who were randomly assigned to receive chemotherapy, the 5-year DMFS was 95.9% (95% CI, 94.0% to 97.2%) compared with a 5-year DMFS of 94.4% (95% CI, 92.3% to 95.9%) in women who were randomly assigned to not receive chemotherapy. The difference between these two groups was

1.5 percentage points, with an adjusted hazard ratio for distant metastasis or death with chemotherapy versus no chemotherapy of 0.78 (95% CI, 0.50 to 1.21; *P* = .27). In terms of other end points in this group with high clinical risk and low genomic risk who received chemotherapy per the intention-to-treat population (and per-protocol population) assessment, the DMFS was 1.5% (and 1.9%) higher, respectively; DFS was 2.8% (and 3%) higher, respectively; and OS was 1.4% (and 1.5%) higher, respectively, compared with no chemotherapy. Given that a subset of the patients received a nonstandard adjuvant chemotherapy regimen of docetaxel plus capecitabine, and that the follow-up was only 5 years in a predominantly ER/PgR–positive cohort who received up to 7 years of endocrine therapy, a small chemotherapy benefit in patients with high clinical risk and low genomic risk cannot be excluded.

Patients at low clinical risk but high genomic risk who received chemotherapy had a 5-year DMFS of 95.8% (95% CI, 92.9% to 97.6%) compared with 95.0% (95% CI, 91.8% to 97.0%) among those who did not receive chemotherapy. The adjusted hazard ratio for distant metastasis or death with chemotherapy versus no chemotherapy in this group was 1.17 (95% CI, 0.59 to 2.28; *P* = .66). Thus, a chemotherapy benefit is unlikely in women with tumors at low clinical risk regardless of genomic subtype.

Guideline recommendations

Clinical question

For women with operable invasive breast cancer which other biomarkers have demonstrated clinical utility to guide decisions on the need for adjuvant systemic therapy?

Recommendation 1.1.1 (update of Recommendation 1.7). If a patient has **ER/PgR–positive, HER2-negative, node-negative**, breast cancer, the MammaPrint assay may be used in those with **high clinical risk** per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.1.2 (update of Recommendation 1.7). If a patient has **ER/PgR–positive, HER2-negative, node-negative**, breast cancer, the MammaPrint assay **should not** be used in those with **low clinical risk** per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy as women in the low clinical risk category had excellent outcomes and did not appear to benefit from chemotherapy even with a genomic high-risk cancer (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Clinical interpretation of literature review. The recently published MINDACT[2] study informs the revision of the 2007 and 2016 ASCO Guidelines.[1,6] In the MINDACT study, the MammaPrint assay was able to identify patients with node-negative, ER/PgR–positive, HER2-negative breast cancer with high clinical risk (as determined by using a modified version of Adjuvant! Online) but low genomic risk who have a favorable outcome when treated with endocrine therapy alone: the 5-year rate of DMFS was 93.9% (95% CI, 90.6% to 96.1%). This was similar to the DMFS of the women randomly assigned to receive chemotherapy: 95.5% (95% CI, 92.5% to 97.3%).[2] Additional retrospective studies of MammaPrint also support its prognostic value in ER/PgR–positive breast cancer.[7–12] Together, these data indicate that MammaPrint can provide guidance about the prognosis of women with ER/PgR–positive, HER2-negative breast cancer and a high clinical risk but low genomic risk, whose outcome is likely to be favorable even in the absence of chemotherapy. When reviewing these data with individual patients with high clinical risk and low genomic risk, the clinician should acknowledge that a small

Key points

- *A subset of the patients received a nonstandard adjuvant chemotherapy regimen of docetaxel plus capecitabine, and that the follow-up was only 5 years in a predominantly ER/PgR–positive cohort who received up to 7 years of endocrine therapy.*
- *A small chemotherapy benefit in patients with high clinical risk and low genomic risk cannot be excluded.*
- *Patients at low clinical risk but high genomic risk who received chemotherapy had a 5-year DMFS of 95.8% (95% CI, 92.9% to 97.6%) compared with 95.0% (95% CI, 91.8% to 97.0%) among those who did not receive chemotherapy.*
- *The adjusted hazard ratio for distant metastasis or death with chemotherapy versus no chemotherapy in this group was 1.17 (95% CI, 0.59 to 2.28; P = .66).*
- *If a patient has ER/PgR–positive, HER2-negative, node-negative, breast cancer, the MammaPrint assay may be used in those with high clinical risk per MINDACT categorization.*
- *If a patient has ER/PgR–positive, HER2-negative, node-negative, breast cancer, the MammaPrint assay should not be used in those with low clinical risk per MINDACT categorization.*
- *The recently published MINDACT study informs the revision of the 2007 and 2016 ASCO Guidelines.*

Key points

- *The MINDACT study was not designed to detect a significant difference in favor of chemotherapy and is underpowered to do so retrospectively.*
- *The clinician should consider that MINDACT included an optional random assignment to anthracycline-containing versus nonanthracycline-containing regimens, and whether the specific chemotherapy assignment affected patient outcome is not yet known.*
- *The MammaPrint assay should not be recommended to patients with low clinical risk who will receive endocrine therapy for hormone receptor–positive breast cancer.*
- *If a patient has ER/PgR–positive, HER2-negative, node-positive, breast cancer, the MammaPrint assay may be used in patients with one to three positive nodes and at high clinical risk per MINDACT categorization.*
- *If a patient has ER/PgR–positive, HER2-negative, node-positive, breast cancer, the MammaPrint assay should not be used in patients with one to three positive nodes and at low clinical risk per MINDACT categorization.*
- *In the MINDACT study, 1,404 patients had node-positive breast cancers. Of these, 737 patients were categorized as high clinical risk but low genomic risk.*

benefit from chemotherapy cannot be excluded, because the MINDACT study was not designed to detect a significant difference in favor of chemotherapy and is underpowered to do so retrospectively. In addition, the clinician should consider that MINDACT included an optional random assignment to anthracycline-containing versus nonanthracycline-containing regimens, and whether the specific chemotherapy assignment affected patient outcome is not yet known. Last, the median duration of follow-up was only 5 years at the time of the 2016 publication. Additional follow-up and assessment of the clinical outcomes for key prognostic subgroups are needed.

Women with node-negative cancers and low clinical risk (as determined by using a modified version of Adjuvant! Online) had excellent outcomes regardless of genomic risk, and even those patients with high genomic risk did not appear to benefit from chemotherapy. Thus, in patients with node-negative cancers and low clinical risk, who will have an excellent outcome with endocrine therapy alone, MammaPrint does not provide significant clinical utility. Therefore, the MammaPrint assay should not be recommended to patients with low clinical risk who will receive endocrine therapy for hormone receptor–positive breast cancer.

Recommendation 1.2.1 (update of Recommendation 1.7). If a patient has **ER/PgR–positive, HER2-negative, node-positive**, breast cancer, the MammaPrint assay may be used in patients with one to three positive nodes and at **high clinical risk** per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. However, such patients should be informed that a benefit of chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node (Type: evidence based; Evidence quality: high; Strength of recommendation: moderate).

Recommendation 1.2.2 (update of Recommendation 1.7). If a patient has **ER/PgR–positive, HER2-negative, node-positive**, breast cancer, the MammaPrint assay **should not** be used in patients with one to three positive nodes and at **low clinical risk** per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy. There are insufficient data on the clinical utility of MammaPrint in this specific patient population (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Clinical interpretation of literature review. In the MINDACT study, 1,404 patients had node-positive breast cancers. Of these, 737 patients were categorized as high clinical risk (determined by using a modified version of Adjuvant! Online) but low genomic risk. These patients had a favorable outcome when treated with endocrine therapy alone (5-year rate of survival without distant metastasis, 95.6% (95% CI, 92.7% to 97.4%) compared with 96.3% (95% CI, 93.1% to 98.1%) among such patients randomly assigned to receive chemotherapy. On the basis of these results, the Panel felt that the MammaPrint assay may be used in patients with positive nodes and high clinical risk to identify those whose outcome is predicted to be sufficiently favorable that chemotherapy is unlikely to provide meaningful benefit. However, the Panel noted that there were several important limitations to the MINDACT data. The first is that the MINDACT study was not designed to detect a significant difference in favor of chemotherapy and is underpowered to do so retrospectively. Second, a separate outcome assessment of the subgroup of patients with ER/PgR–positive, HER2-negative, node-positive cancers was not performed. Third, only a minority (31.1%) of these patients with high clinical risk, low genomic risk, and node-positive disease had more than one node involved.[2] Fourth, no specific information is available for other key prognostic characteristics, such as tumor grade, in the node-positive subgroup. Fifth, because

patients with node-positive disease were only enrolled starting in 2009, their follow-up is likely shorter than the overall 5-year median follow-up of the entire study population. Last, study participants may have received an anthracycline-containing regimen or a nonstandard regimen, and the impact of the specific chemotherapy regimen on chemotherapy benefit is unknown. Given these limitations, and the concern that patients with node-positive disease are generally at greater potential risk for undertreatment, the Panel felt that although the MammaPrint assay maybe used in patients with one to three positive nodes, such patients should be informed that given the available data, a benefit from chemotherapy cannot be excluded. In addition, the assay should be used with some caution in patients with two to three positive nodes because of the relatively limited number of such patients in the MINDACT study.

The utility of the MammaPrint assay in patients with lymph node–positive disease assessed at low clinical risk per MINDACT categorization is not clear, because the number of patients was small and was not analyzed separately. It is possible that patients in this category may not benefit from chemotherapy use regardless of genomic risk. Given the limited data available at this time, the Panel does not recommend the routine use of MammaPrint in women with node-positive tumors and low clinical risk.

Recommendation 1.3 (update of Recommendation 1.8). If a patient has **HER2-positive** breast cancer, the clinician **should not** use the MammaPrint assay to guide decisions on adjuvant systemic therapy. Additional studies are required to address the role of MammaPrint in patients with this tumor subtype who are also receiving HER2-targeted therapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Clinical interpretation of literature review. Currently, the standard of care for the adjuvant treatment of patients with HER2-positive tumors includes both chemotherapy and anti-HER2 agents.[13] In MINDACT, only 8% of patients (n = 124) had HER2-positive tumors with high clinical risk and low genomic risk and were randomly assigned to chemotherapy or not. In addition, results of this subgroup were not reported separately.[2] There are, therefore, insufficient data to support the use of MammaPrint in HER2-positive breast cancer. It is possible that patients with HER2-positive disease might not need chemotherapy if their prognoses are sufficiently favorable. Knauer et al[8] performed a retrospective, grade-C study to address whether the MammaPrint assay might identify such patients. This study involved 168 patients with HER2-positive tumors from a pooled database who were classified by the MammaPrint assay as having a good or a poor prognosis. Of these, 89 (53%) patients did not receive adjuvant chemotherapy or HER2-targeted therapy. With a median follow-up of 7.4 years, MammaPrint classified 22% of patients with a good prognosis as having a 10-year DMFS of 84% compared with 78% of patients with a poor prognosis as having a 10-year DMFS of 55%. The hazard ratios were 4.5 (95% CI, 1.1 to 18.7; $P = .04$) and 3.8 (95% CI, 0.9 to 15.8; $P = .07$) for DMFS and breast cancer-specific survival, respectively.[8]

Thus, the MammaPrint assay appears to have prognostic value in HER2-positive breast cancer in a retrospective study.[8] However, the Panel does not consider the data sufficiently robust or a suggestion of a 10-year distant DFS of 84%[8] sufficiently favorable to omit chemotherapy from an adjuvant regimen. Given the small HER2-positive subgroup in MINDACT and the known substantial benefit women with HER2-positive tumors derive from the addition of anti-HER2 agents to adjuvant chemotherapy, the Panel concluded that the data do not support use of the MammaPrint assay to decide whether a patient with HER2-positive breast cancer may safely forgo adjuvant chemotherapy.

Key points

- *Study participants may have received an anthracycline-containing regimen or a nonstandard regimen, and the impact of the specific chemotherapy regimen on chemotherapy benefit is unknown.*
- *The Panel felt that although the MammaPrint assay maybe used in patients with one to three positive nodes, such patients should be informed that given the available data, a benefit from chemotherapy cannot be excluded.*
- *The utility of the MammaPrint assay in patients with lymph node–positive disease assessed at low clinical risk per MINDACT categorization is not clear, because the number of patients was small and was not analyzed separately.*
- *It is possible that patients in this category may not benefit from chemotherapy use regardless of genomic risk.*
- *If a patient has HER2-positive breast cancer, the clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic therapy.*
- *It is possible that patients with HER2-positive disease might not need chemotherapy if their prognoses are sufficiently favorable.*
- *This study involved 168 patients with HER2-positive tumors from a pooled database who were classified by the MammaPrint assay as having a good or a poor prognosis.*

Key points

- *Although patients with triple-negative breast cancer were included in the prospective MINDACT study, the number of patients with this tumor subtype was small (n = 640 [9.6%]).*
- *The majority of women with this subtype (n = 566 [88%]) were classified as high clinical and high genomic risk and were not randomly assigned.*
- *The Panel felt strongly that until data from larger data sets are available, the MammaPrint assay should not be used to guide clinical decisions in patients with triple-negative breast cancer.*
- *The available data suggest that only a minority of patients with ER/PgR–positive breast cancer derive significant benefit from adjuvant chemotherapy.*
- *In this focused update of the 2016 ASCO Clinical Practice Guideline, we review data from the recently reported MINDACT study, which prospectively evaluated another gene expression signature, the 70-gene MammaPrint assay. In the MINDACT study.*
- *The MammaPrint assay was able to identify patients with high clinical risk but low genomic risk who had a relatively favorable prognosis in the absence of adjuvant chemotherapy.*
- *The assay had similar functionality in both node-negative and node-positive cancers.*

Recommendation 1.4 (update of Recommendation 1.9). If a patient has **ER/PgR–negative and HER2-negative (triple-negative)** breast cancer, the clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

Clinical interpretation of literature review. Although patients with triple-negative breast cancer were included in the prospective MINDACT study, the number of patients with this tumor subtype was small (n = 640 [9.6%]). The majority of women with this subtype (n = 566 [88%]) were classified as high clinical and high genomic risk and were not randomly assigned. Therefore, the absolute number of women with triple-negative breast cancer and a low genomic risk who did not receive chemotherapy was extremely small, and this subgroup was not analyzed separately. Given that no other therapies (eg, endocrine therapy or HER2-targeted therapy) are recommended for these patients, the Panel felt strongly that until data from larger data sets are available, the MammaPrint assay should not be used to guide clinical decisions in patients with triple-negative breast cancer.

Discussion

Reduction of overtreatment in patients with early-stage breast cancer is an important goal. For several reasons, such a reduction would likely have the greatest societal and individual impact in patients with ER/PgR–positive disease. First, this is the most common type of breast cancer. Second, outcomes for this subtype generally are favorable for the majority of patients. Third, the available data suggest that only a minority of patients with ER/PgR–positive breast cancer derive significant benefit from adjuvant chemotherapy. Fortunately, it is clear from a number of biomarker studies that genomic assays that measure the expression of a relatively small number of genes in breast tumor tissue can provide important prognostic and possibly predictive information that can be used to identify patients with early-stage hormone receptor–positive breast cancer for whom chemotherapy is unlikely to be associated with a meaningful clinical benefit. Several of these genomic signatures, including Oncotype DX, EndoPredict, PAM50 risk of recurrence score, and Breast Cancer Index, were noted as having clinical utility for this purpose for patients with node-negative ER/PgR–positive cancers in a 2016 ASCO Clinical Practice Guideline.[1]

In this focused update of the 2016 ASCO Clinical Practice Guideline, we review data from the recently reported MINDACT study, which prospectively evaluated another gene expression signature, the 70-gene MammaPrint assay. In the MINDACT study, the MammaPrint assay was able to identify patients with high clinical risk but low genomic risk who had a relatively favorable prognosis in the absence of adjuvant chemotherapy. The assay had similar functionality in both node-negative and node-positive cancers. On the basis of these results, the Panel recommended that the MammaPrint assay could be used to guide decisions on withholding adjuvant systemic chemotherapy in patients with ER/PgR-positive lymph node–negative breast cancer and in select patients with lymph node–positive cancers. In both patients with node-positive and with node-negative disease, evidence of clinical utility of the MammaPrint assay was only apparent in those determined to be at high clinical risk, defined by a modified version of Adjuvant! Online. The Panel therefore did not recommend the use of the MammaPrint assay in any patient determined to be at low clinical risk. Of note, at the time of publication of this guideline update, the Adjuvant! Online website was not functional. As an alternative, clinicians can determine a patient's clinical risk status by using the printed version of the Adjuvant!

Now that there are several assays with clinical utility, particularly in patients with node-negative cancers, how does one select the assay to use for a particular patient? At this time, head-to-head comparisons of the different assays are limited. Sestak et al[14] did attempt one such comparison, but this study was limited by methodologic constraints.[15] Clearly, additional work is needed to allow clinicians to choose the optimal assay for individual patients. Panel members caution that there are no data to suggest that ordering more than one assay in an individual patient will be helpful to guide treatment decisions and do not recommend the use of more than one test. Clinicians should choose a test that they are most comfortable with to guide treatment decisions.

It should be noted that although the Panel concluded that several genomic assays have clinical utility in guiding decisions on withholding adjuvant systemic chemotherapy, none of these assays are perfect. In the available studies, some patients still developed recurrent disease despite favorable assay results, and many patients with poor-prognosis genomic scores remain disease free even in the absence of chemotherapy. Thus, improvements are needed in the assays to additionally reduce overtreatment but minimize risk of recurrence.

Key points

- *There are no data to suggest that ordering more than one assay in an individual patient will be helpful to guide treatment decisions and do not recommend the use of more than one test.*
- *It should be noted that although the Panel concluded that several genomic assays have clinical utility in guiding decisions on withholding adjuvant systemic chemotherapy, none of these assays are perfect.*

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Treatment Efficacy, Adherence, and Quality of Life Among Women Younger Than 35 Years in the International Breast Cancer Study Group TEXT and SOFT Adjuvant Endocrine Therapy Trials

(J Clin Oncol 2017;35(27):3113–3122.)

Purpose: To describe benefits and toxicities of adjuvant endocrine therapies in women younger than 35 years with breast cancer (n = 582) enrolled in the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT).
Methods: In SOFT, women still premenopausal after surgery with or without chemotherapy were randomly assigned to tamoxifen alone, tamoxifen plus ovarian function suppression (OFS), or exemestane plus OFS. In TEXT, all received OFS with or without concomitant chemotherapy and were randomly assigned to exemestane plus OFS or tamoxifen plus OFS. We summarize treatment efficacy, quality of life, and adherence of the cohort of women younger than 35 years in SOFT and TEXT, alongside data from the cohort of older premenopausal women.
Results: For 240 human epidermal growth factor receptor 2–negative patients younger than 35 years enrolled in SOFT after receiving chemotherapy, the 5-year breast cancer–free interval (BCFI) was 67.1% (95% CI, 54.6% to 76.9%) with tamoxifen alone, 75.9% with tamoxifen plus OFS (95% CI, 64.0% to 84.4%), and 83.2% with exemestane plus OFS (95% CI, 72.7% to 90.0%). For 145 human epidermal growth factor receptor 2–negative patients younger than 35 years in TEXT, 5-year BCFI was 79.2% (95% CI, 66.2% to 87.7%) with tamoxifen plus OFS and 81.6% (95% CI, 69.8% to 89.2%) with exemestane plus OFS. The most prominent quality of life symptom for patients younger than 35 years receiving OFS was vasomotor symptoms, with the greatest worsening from baseline at 6 months (on the order of 30 to 40 points), but loss of sexual interest and difficulties in becoming aroused were also clinically meaningful (≥ 8-point change). The level of symptom burden was similar in older premenopausal women. A total of 19.8% of women younger than 35 years stopped all protocol-assigned endocrine therapy early.
Conclusion: In women younger than 35 years with hormone receptor-positive breast cancer, adjuvant OFS combined with tamoxifen or exemestane produces large improvements in BCFI compared with tamoxifen alone. Menopausal symptoms are significant but are not worse than those seen in older premenopausal women.

Introduction

Women younger than 35 years with breast cancer have historically had poor outcomes, with increased rates of both local and distant recurrence.[1–5] Although women younger than 35 years have higher rates of triple-negative breast cancer, it is paradoxically in the hormone receptor (HR)–positive subgroup that the most significantly worse outcomes have been observed. Some data[6] come from earlier

Key points

- *In the US Intergroup INT0101 trial for node-positive HR-positive disease, women younger than 40 years treated with chemotherapy plus OFS (goserelin) with or without tamoxifen had 9-year disease-free survivals of 64% and 55%.*
- *It has been hypothesized that the difference in outcomes is related to a greater ratio of luminal B to luminal A cancers in women younger than 35 years.*
- *In SOFT and TEXT, HR-positive/human epidermal growth factor receptor 2 (HER2)–negative women younger than age 35 years had a 5-year BCFI of 79%,* vs. *95% for women age 45 to 49 years.*
- *Symptom-specific quality of life (QoL; focusing on symptoms related to endocrine therapy) was worse with the addition of OFS.*
- *We hypothesized that women younger than 35 years would report more endocrine-related symptoms.*
- *TEXT enrolled 2,660 women in the intention-to-treat (ITT) population within 12 weeks after definitive surgery and randomly assigned them to 5 years of exemestane plus OFS or 5 years of tamoxifen plus OFS.*
- *OFS was achieved by gonadotropin-releasing hormone (GnRH) agonist triptorelin, bilateral oophorectomy, or ovarian irradiation.*

trials, in which premenopausal women with HR-positive tumors received chemotherapy but no endocrine therapy, and the authors suggested that differences in outcomes were related to differential likelihood of undergoing chemotherapy-induced ovarian function suppression (OFS). However, age-related differences in outcomes persist in the face of endocrine therapy. In the US Intergroup INT0101 trial for node-positive HR-positive disease, women younger than 40 years treated with chemotherapy plus OFS (goserelin) with or without tamoxifen had 9-year disease-free survivals of 64% and 55%, *vs*. 69% and 62% for premenopausal women age 40 years or older.[7] It has also been hypothesized that the difference in outcomes is related to a greater ratio of luminal B to luminal A cancers in women younger than 35 years.[8] Yet, a recent large analysis of US National Comprehensive Cancer Network data on women presenting with breast cancer between January 2000 and December 2007, when endocrine therapy was standard for all women with HR-positive disease, found significantly worse outcomes among women ≤40 years old specifically for the group with luminal A tumors.[9]

The Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) have recently demonstrated that for premenopausal women with HR-positive breast cancer and high-risk clinicopathologic factors, treatment with OFS plus exemestane can produce an absolute improvement of 10% to 15% in 5-year breast cancer–free interval (BCFI).[10] In SOFT and TEXT, HR-positive/human epidermal growth factor receptor 2 (HER2)–negative women younger than age 35 years had a 5-year BCFI of 79%, *vs*. 95% for women age 45 to 49 years.[10] Symptom-specific quality of life (QoL; focusing on symptoms related to endocrine therapy) was worse with the addition of OFS.[11,12] We hypothesized that women younger than 35 years would report more endocrine-related symptoms. We present a summary of benefits and risks of endocrine therapy that includes OFS specific to women younger than 35 years to help facilitate joint decision making.

Methods

The designs and conduct of the TEXT and SOFT phase III trials have been described.[13–15] Ethics committees at participating centers approved the protocols, and all patients provided written informed consent. In both trials, eligible premenopausal women with surgically resected, invasive early-stage breast cancer with ≥ 10% estrogen receptor (ER)– and/or progesterone receptor (PR)-expressing cells were randomly assigned between November 2003 and March 2011.

TEXT enrolled 2,660 women in the intention-to-treat (ITT) population within 12 weeks after definitive surgery and randomly assigned them to 5 years of exemestane plus OFS or 5 years of tamoxifen plus OFS. OFS was achieved by gonadotropin-releasing hormone (GnRH) agonist triptorelin, bilateral oophorectomy, or ovarian irradiation. Chemotherapy was optional and, when administered, was started concurrently with triptorelin.

SOFT randomly assigned 3,047 women in the ITT population to 5 years of exemestane plus OFS or tamoxifen plus OFS or tamoxifen alone. Patients who did not receive chemotherapy were enrolled within 12 weeks after definitive surgery; those patients who received (neo)adjuvant chemotherapy were enrolled within 8 months after the final dose of chemotherapy, after a premenopausal estradiol level was confirmed.

The trial end points were: disease-free survival (DFS), defined as the time from random assignment to the first appearance of: invasive recurrence of breast cancer (local, regional, or distant), invasive contralateral

breast cancer, second nonbreast invasive cancer, or death; BCFI, from random assignment to the recurrence of invasive breast cancer or invasive contralateral breast cancer; distant recurrence-free interval (DRFI), from random assignment to recurrence at a distant site; overall survival, from random assignment to death from any cause. Overall survival is not yet mature after a median follow-up of 6 years in TEXT and 5.6 years in SOFT.

The trials used the International Breast Cancer Study Group QoL core form and a symptom-specific module focusing on symptoms related to endocrine therapy at baseline, 6, 12, 18, and 24 months, and annually during years 3 to 6. All indicators were in the linear analog self-assessment format and ranged from 0 to 100, with higher numbers indicating a better QoL. A clinically significant change was conservatively defined as ≥ 8-point difference.[11,12]

Statistical considerations

Comparisons of characteristics between age groups used Fisher's exact tests. The association of age younger than 35 years at random assignment with end points used Cox proportional hazard modeling, stratified by trial, chemotherapy receipt, and lymph node status and adjusted for other prognostic and treatment characteristics (number of positive lymph nodes, tumor size, grade, receptor status, HER2 status/therapy, local therapy) and treatment assignment. The distributions of time-to-event end points among patients with HER2-negative tumors were estimated using the Kaplan-Meier method. Adherence to protocol-assigned therapy was estimated from cumulative incidence of cessation, with competing risk of a DFS event, and compared between age groups using Gray's test. Changes in QoL indicators from baseline were summarized as mean and 95% CI, estimated using mixed-effects models (of all time points) adjusting for treatment assignment, with focus on estimates at the 6-, 24-, and 60-month time points among the chemotherapy cohorts.[11,12]

Results

Study population

A total of 5,707 women were enrolled in the SOFT and TEXT ITT populations (Figure 1). Of these, 582 (10.2%) were younger than 35 years at random assignment and form the basis of this analysis. This includes 11.5% and 8.7% of the SOFT and TEXT ITT populations, respectively.

Characteristics of the cohort of women younger than age 35 years

Although ER and/or PR positivity was only required to be ≥ 10% for enrollment, the vast majority of patients had strongly ER-positive/PR-positive tumors.[16] However, in the population younger than 35 years there was a higher percentage of women with ER-positive/PR-negative tumors (17.4% *vs*. 7.7% in premenopausal women ≥ 35 years old by local assessment). Overall, the women younger than 35 years enrolled had higher-risk tumor characteristics than the older premenopausal women (Table 1): 47.1% had a tumor > 2 cm *vs*. 33.9% of women age ≥ 35 years, 55.5% (*vs*. 39.3%) had node-positive disease, 41.8% (*vs*. 21.6%) had grade 3 histology, 43.5% (*vs*. 27.8%) had lymphovascular invasion, and 50.9% (*vs*. 33.3%) had Ki-67 levels ≥ 20% on central pathology review. The majority of women younger than 35 years were treated with chemotherapy: 329 (94%) of 350 in SOFT and 191 (82%) of 232 in TEXT.

Independent prognostic value of age

In the study population, age younger than 35 years at random assignment was associated with higher risk of a breast cancer event (hazard ratio [HR], 1.53; 95% CI, 1.24 to 1.88 *vs*. age ≥ 35 years), distant recurrence (HR, 1.52; 95% CI, 1.21 to 1.91), and DFS event (HR, 1.43; 95% CI, 1.18 to 1.74) even after controlling for

Key points

- *The trials used the International Breast Cancer Study Group QoL core form and a symptom-specific module focusing on symptoms related to endocrine therapy at baseline, 6, 12, 18, and 24 months, and annually during years 3 to 6.*
- *All indicators were in the linear analog self-assessment format and ranged from 0 to 100, with higher numbers indicating a better QoL.*
- *A clinically significant change was conservatively defined as ≥8-point difference.*
- *The distributions of time-to-event end points among patients with HER2-negative tumors were estimated using the Kaplan-Meier method.*
- *Adherence to protocol-assigned therapy was estimated from cumulative incidence of cessation, with competing risk of a DFS event, and compared between age groups using Gray's test.*
- *Changes in QoL indicators from baseline were summarized as mean and 95% CI, estimated using mixed-effects models (of all time points) adjusting for treatment assignment, with focus on estimates at the 6-, 24-, and 60-month time points among the chemotherapy cohorts.*
- *A total of 5,707 women were enrolled in the SOFT and TEXT ITT populations (Figure 1). Of these, 582 (10.2%) were younger than 35 years at random assignment and form the basis of this analysis.*

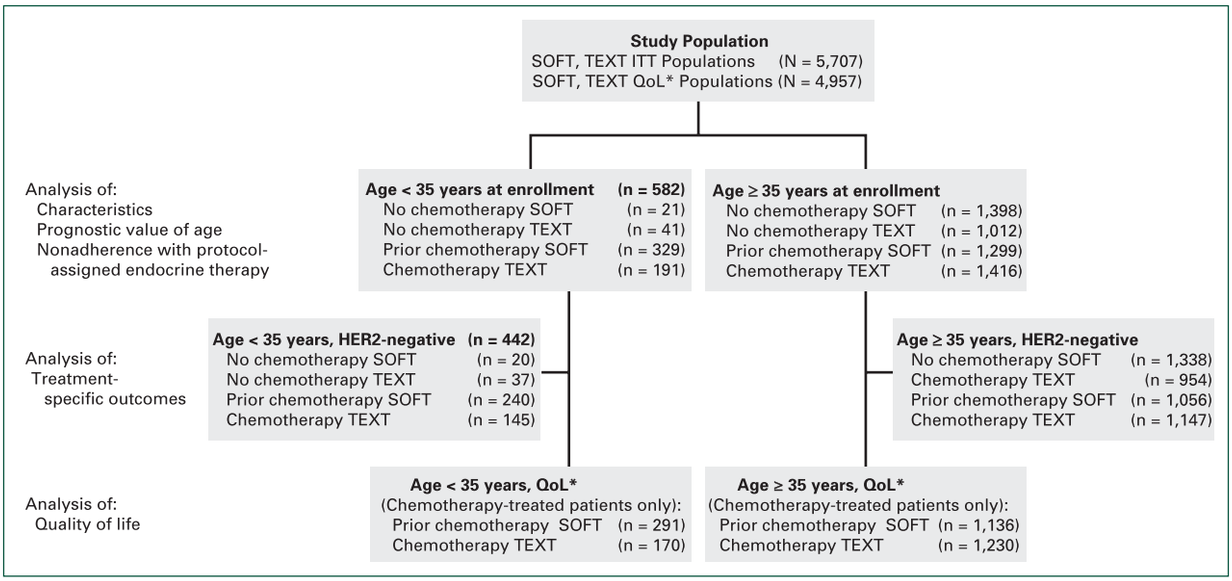

FIGURE 1 ■ Flow diagram of analysis populations. (*) Quality-of-life (QoL) populations were 87% of the intention-to-treat (ITT) populations, after exclusion of patients having eligibility exemption and of patients at centers not compliant with QoL submission.[11,12]

HER2, human epidermal growth factor receptor 2; SOFT, Suppression of Ovarian Function Trial; TEXT, Tamoxifen and Exemestane Trial.

■ TABLE 1 - Patient, tumor, and treatment characteristics according to age at random assignment in the SOFT and TEXT randomized trials

Characteristic	Age at random assignment			
	< 35 years		≥ 35 years	
	No.	%	No.	%
No. patients	582	100.0	5,125	100.0
Trial/chemotherapy cohort				
No chemotherapy TEXT	41	7.0	1,012	19.7
No chemotherapy SOFT	21	3.6	1,398	27.3
Chemotherapy TEXT	191	32.8	1,416	27.6
Prior chemotherapy SOFT	329	56.5	1,299	25.3
Age at random assignment, years				
< 25	13	2.2	–	–
25–29	128	22.0	–	–
30–34	441	75.8	–	–
35–39	–	–	995	19.4
40–44	–	–	1,830	35.7
45–49	–	–	1,803	35.2
≥ 50	–	–	497	9.7
Race/ethnicity				
Other	14	2.4	117	2.3
Asian	29	5.0	144	2.8

■ **TABLE 1 - Patient, tumor, and treatment characteristics according to age at random assignment in the SOFT and TEXT randomized trials (*continued*)**

Characteristic	Age at random assignment			
	< 35 years		≥ 35 years	
	No.	%	No.	%
Black/African American	16	2.7	143	2.8
Hispanic/Latino/South American native	71	12.2	250	4.9
White	452	77.7	4,471	87.2
BMI, kg/m^2				
Unknown	17	2.9	119	2.3
Normal (< 25)	341	58.6	2,699	52.7
Overweight (25 to < 30)	124	21.3	1,293	25.2
Obese (≥ 30)	100	17.2	1,014	19.8
Ever pregnant				
Unknown	5	0.9	33	0.6
No	221	38.0	789	15.4
Yes	356	61.2	4,303	84.0
Pregnant at diagnosis				
Unknown	5	0.9	31	0.6
No	563	96.7	5,073	99.0
Yes	14	2.4	21	0.4
Menstruation status at random assignment				
Unknown	8	1.4	90	1.8
Normal	381	65.5	3,643	71.1
Irregular (cycles continuing)	128	22.0	729	14.2
Persistent amenorrhea*	65	11.2	663	12.9
Hormone receptor status				
ER-positive/PR-positive	455	78.2	4,574	89.2
ER-positive/PR-negative	101	17.4	396	7.7
ER-negative/PR-positive	18	3.1	86	1.7
Other†	8	1.4	69	1.3
HER2 status				
Negative	442	75.9	4,495	87.7
Positive	140	24.1	630	12.3
Ki-67 expression by CPR				
Unknown (no tissue for CPR)	120	20.6	980	19.1
< 20%	166	28.5	2,440	47.6
≥ 20%	296	50.9	1,705	33.3
No. nodes positive				
Unknown	–	–	29	0.6
N0	259	44.5	3,096	60.4

■ **TABLE 1 - Patient, tumor, and treatment characteristics according to age at random assignment in the SOFT and TEXT randomized trials (*continued*)**

Characteristic	Age at random assignment			
	< 35 years		≥ 35 years	
	No.	%	No.	%
N-positive 1–3	203	34.9	1,443	28.2
N-positive 4–9	86	14.8	405	7.9
N-positive ≥ 10	34	5.8	152	3.0
Tumor size, cm				
≤ 2	289	49.7	3,306	64.5
> 2–5	237	40.7	1,561	30.5
> 5	37	6.4	176	3.4
Unknown	19	3.3	82	1.6
Tumor grade				
1	63	10.8	1,181	23.0
2	266	45.7	2,756	53.8
3	243	41.8	1,107	21.6
Unknown	10	1.7	81	1.6
Vessel invasion (lymphatics and/or blood vessels)				
No	300	51.5	3,409	66.5
Yes	253	43.5	1,423	27.8
Not assessed/unknown	29	4.9	293	5.8
Primary invasive histology				
Ductal	537	92.3	4,259	83.1
Lobular	15	2.6	598	11.7
Other	30	5.2	268	5.2
Locoregional treatment				
Mastectomy, no radiotherapy	124	21.3	1,262	24.6
Mastectomy with radiotherapy	174	29.9	793	15.5
Other‡	16	2.7	64	1.2
BCS with radiotherapy	268	46.0	3,006	58.7
Axillary lymph node dissection				
Unknown	1	0.2	3	0.1
No (sentinel lymph node biopsy only)	158	27.1	2,134	41.6
Yes	423	72.7	2,988	58.3

The distributions of all factors were significantly different according to age at random assignment ($P < .001$ by Fisher's exact tests).
*Persistent amenorrhea was primarily among patients in SOFT who had received prior chemotherapy: 59 of 65 (91%) younger than 35 years and 564 of 663 (85%) age ≥ 35 years.
†Other includes ER-unknown and PR-unknown, or ER-negative and PR-negative (who were ineligible).
‡Other includes BCS without radiotherapy, or radiotherapy unknown; radiotherapy was required after BCS and optional after mastectomy.
BCS, breast-conserving surgery; BMI, body mass index; CPR, central pathology review; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; SOFT, Suppression of Ovarian Function Trial; TEXT, Tamoxifen and Exemestane Trial.

treatment and disease characteristics (which included HER2 status).

Treatment-specific outcomes of women younger than 35 years with Her2-negative disease

TEXT and SOFT began enrollment before the widespread use of adjuvant trastuzumab for patients with HER2-positive breast cancer. Because women enrolled in these trials with HER2-positive disease did not all receive anti-HER2 therapy according to current standards, we chose to exclude HER2-positive disease from the efficacy analysis for this report.

Four hundred forty-two women younger than 35 years had HER2-negative disease. After a median follow-up of 6.0 and 5.6 years in TEXT and SOFT, respectively, 102 (23%) had invasive breast cancer events (*vs*. 384 [8.5%] of 4,495 for ≥ 35 years of age). Recurrence at a distant site was reported in 81 patients (18.3%). Death was reported in 50 patients (11.3%); 49 of these deaths occurred in women who had received chemotherapy.

The number of women younger than 35 years with HER2-negative disease who did not receive chemotherapy was small (n = 57; SOFT = 20, TEXT = 37); these women seem to have low-risk tumors (94% node-negative, 84% ≤2 cm, and 23% grade 1). In this cohort, eight patients (14%) had invasive breast cancer events, including three distant recurrences and one death.

In the cohort of women younger than age 35 years who had received chemotherapy before SOFT enrollment, 5-year BCFI was 67.1% (95% CI, 54.6% to 76.9%) for tamoxifen alone, 75.9% (95% CI, 64.0% to 84.4%) for tamoxifen plus OFS, and 83.2% (95% CI, 72.7% to 90.0%) for exemestane plus OFS (Figure 2). Their 5-year DRFI was 74.6% (95% CI, 62.7% to 83.2%) for tamoxifen alone, 77.3% (95% CI, 65.5% to 85.5%) for tamoxifen plus OFS, and 84.4% (95% CI, 74.0% to 90.9%) for exemestane plus OFS.

For women younger than 35 years enrolled in TEXT who received chemotherapy, the 5-year BCFI was 79.2% (95% CI, 66.2% to 87.7%) with tamoxifen plus OFS and 81.6% (95% CI, 69.8% to 89.2%) with exemestane plus OFS. Their 5-year DRFI was 80.9% (95% CI, 68.1% to 89.0%) for tamoxifen plus OFS and 81.0% (95% CI, 68.8% to 88.8%) with exemestane plus OFS.

QoL

Most patients younger than 35 years are likely to receive chemotherapy as part of adjuvant treatment, and 94% and 82% of women younger than 35 years enrolled in SOFT and TEXT did receive chemotherapy and are the focus of QoL analysis. In TEXT, the baseline QoL assessment occurred before adjuvant chemotherapy. In SOFT, the baseline QoL assessment occurred after chemotherapy (median, 3.5 months from last dose of chemotherapy); approximately 40% had also received tamoxifen before enrollment.

Women enrolled in the prior-chemotherapy SOFT cohort generally had worse baseline QoL symptoms but reported better coping than those enrolled in TEXT (Table 2). Other global indicators were similar between these cohorts. This is expected, because patients in SOFT had already received chemotherapy (and possibly tamoxifen). For patients in SOFT with prior chemotherapy, only a few baseline symptom-specific QoL indicators differed by ≥ 8 points between women younger and older than 35 years (hot flushes [mean difference, 10; 95% CI, 6 to 14], sweats [mean difference, 10; 95% CI, 6 to 13], bone or joint pain [mean difference, 9; 95% CI, 5 to 12]), with women younger than 35 years being less affected for all. The greatest difference in baseline global QoL indicators between women younger and older than 35 years in the SOFT prior-chemotherapy cohort was only 5 points (95% CI, 2 to 8 points) for coping effort, and the women younger than 35 years were more affected.

Key points

- *TEXT and SOFT began enrollment before the widespread use of adjuvant trastuzumab for patients with HER2-positive breast cancer.*
- *Recurrence at a distant site was reported in 81 patients (18.3%). Death was reported in 50 patients (11.3%); 49 of these deaths occurred in women who had received chemotherapy.*
- *The number of women younger than 35 years with HER2-negative disease who did not receive chemotherapy was small (n = 57; SOFT = 20, TEXT = 37); these women seem to have low-risk tumors (94% node-negative, 84% ≤2 cm, and 23% grade 1).*
- *In this cohort, eight patients (14%) had invasive breast cancer events, including three distant recurrences and one death.*
- *Most patients younger than 35 years are likely to receive chemotherapy as part of adjuvant treatment, and 94% and 82% of women younger than 35 years enrolled in SOFT and TEXT did receive chemotherapy and are the focus of QoL analysis.*
- *In TEXT, the baseline QoL assessment occurred before adjuvant chemotherapy.*
- *In SOFT, the baseline QoL assessment occurred after chemotherapy (median, 3.5 months from last dose of chemotherapy); approximately 40% had also received tamoxifen before enrollment.*

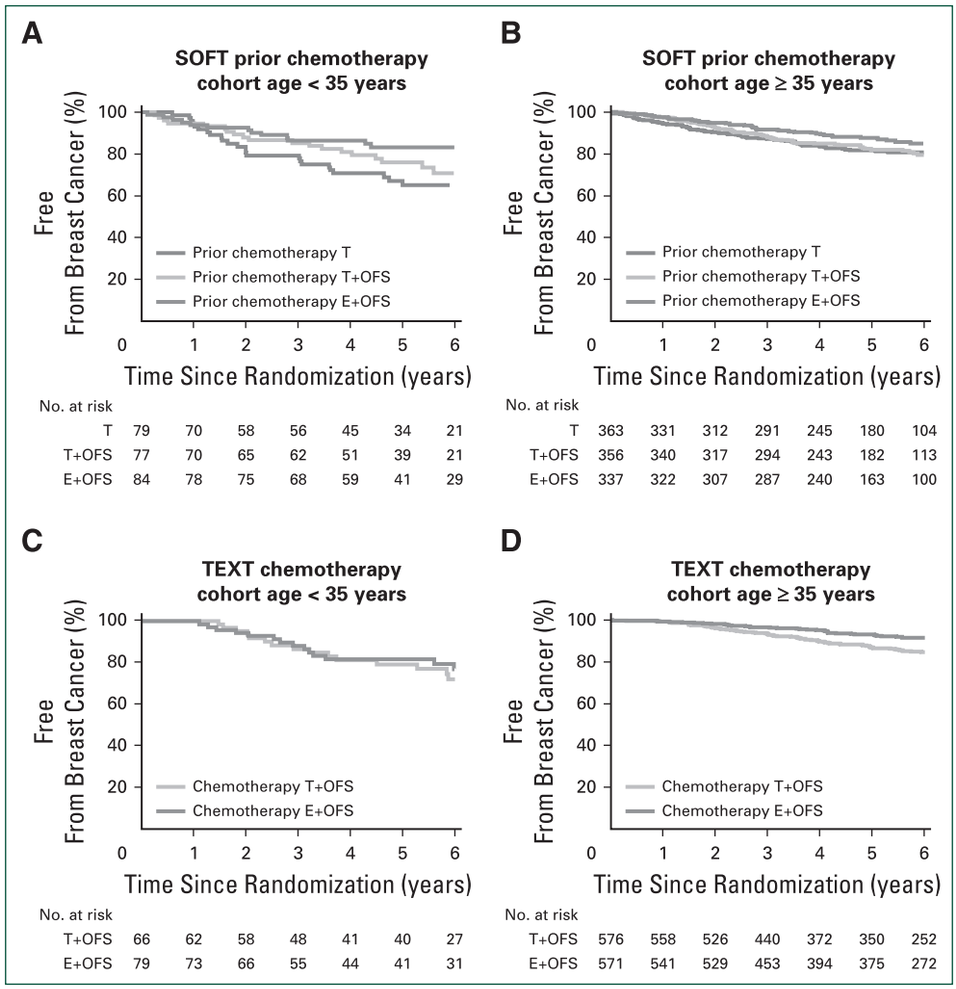

FIGURE 2 ■ Kaplan-Meier estimates of breast cancer–free interval (BCFI) among patients with human epidermal growth factor receptor 2–negative disease in the chemotherapy cohorts of the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT), according to age at random assignment and treatment assignment. Median follow-up was 5.6 years in SOFT and 6.0 years in TEXT. (A, B) SOFT prior chemotherapy, age younger than 35 years and ≥ 35 years. (C, D) TEXT chemotherapy, age younger than 35 years and ≥ 35 years.

E, exemestane; OFS, ovarian function suppression; T, tamoxifen.

Key points

- *The most prominent change in symptom-specific QoL in the women younger than age 35 years in SOFT who had prior chemotherapy was an increase in symptoms seen between baseline and the 6-month time point.*

Because of the baseline QoL differences between patients in SOFT and TEXT, and to isolate the added toxicity of OFS combined with oral endocrine therapy from that of chemotherapy, we have focused on the 291 women younger than age 35 years who had received chemotherapy before enrollment in SOFT (Figure 3). The most prominent change in symptom-specific QoL in the women younger than age 35 years in SOFT who had prior chemotherapy was an increase in symptoms seen between baseline and the 6-month time point; in general, symptoms improved over time thereafter. Vasomotor symptoms (hot flushes, sweats) showed the greatest worsening from baseline to 6 months (on the order of 30- to 40-point change with OFS). Thereafter, vasomotor symptoms improved in women younger than 35 years receiving OFS but without reaching baseline, whereas scores worsened over time in patients younger than 35 years receiving tamoxifen alone. Changes in gynecologic symptoms were smaller than for vasomotor symptoms but were clinically meaningful

TABLE 2 - Quality-of-life symptom and global indicator scores at baseline according to cohort and age at random assignment

Indicator	Cohort and age at random assignment					
	Chemotherapy TEXT			Prior chemotherapy SOFT		
	<35 years	≥ 35 years		<35 years	≥ 35 years	
	Mean score ± SD	Mean score ± SD	Mean difference* (95% CI)	Mean score ± SD	Mean score ± SD	Mean difference* (95% CI)
No. of patients[†]	170	1,230		291	1,316	
Symptom indicators						
Vasomotor						
Hot flushes	91 ± 19	92 ± 17	–0 (–3 to 3)	80 ± 27	69 ± 32	10 (6 to 14)
Sweats (including night sweats)	86 ± 22	88 ± 19	–2 (–6 to 1)	83 ± 23	73 ± 29	10 (6 to 13)
Gynecologic or sexual						
Vaginal discharge	85 ± 21	90 ± 16	–6 (–8 to –3)	76 ± 25	80 ± 23	–4 (–7 to –1)
Vaginal dryness	93 ± 15	94 ± 12	–1 (–3 to 1)	81 ± 25	80 ± 26	1 (–3 to 4)
Vaginal itching/ irritation	91 ± 16	93 ± 14	–3 (–5 to –0)	87 ± 21	86 ± 22	1 (–2 to 4)
Loss of sexual interest[‡]	81 ± 25	78 ± 27	3 (–2 to 7)	73 ± 29	66 ± 31	7 (3 to 11)
Difficulty in becoming aroused	87 ± 19	84 ± 20	3 (–1 to 6)	74 ± 27	72 ± 27	2 (–2 to 6)
Musculoskeletal or neurologic pain						
Bone or joint pain	89 ± 15	88 ± 20	2 (–2 to 5)	83 ± 24	74 ± 28	9 (5 to 12)
Headaches	82 ± 23	85 ± 21	–3 (–6 to 0)	82 ± 23	82 ± 23	–1 (–4 to 2)
Constitutional or psychological						
Sleep disturbance	76 ± 25	71 ± 27	5 (1 to 9)	72 ± 29	66 ± 29	6 (2 to 10)
Tiredness	64 ± 27	65 ± 26	–1 (–5 to 3)	56 ± 28	56 ± 26	0 (–3 to 4)
Troubled by weight gain	90 ± 17	88 ± 20	1 (–2 to 5)	72 ± 32	69 ± 31	3 (–1 to 7)
Being irritable	73 ± 23	74 ± 24	–1 (–5 to 3)	70 ± 25	73 ± 24	–3 (–6 to 0)
Global indicators						
Physical well-being	78 ± 20	77 ± 22	0 (–3 to 4)	78 ± 22	77 ± 21	1 (–2 to 4)
Mood	69 ± 24	70 ± 24	–1 (–5 to 3)	74 ± 22	75 ± 22	–1 (–4 to 2)
Coping effort	58 ± 28	60 ± 28	–2 (–6 to 3)	65 ± 27	70 ± 25	–5 (–8 to –2)
Treatment burden	74 ± 25	76 ± 24	–2 (–6 to 2)	71 ± 25	72 ± 24	–2 (–5 to 2)
Health perception	70 ± 21	70 ± 22	–0 (–4 to 3)	72 ± 21	73 ± 21	–1 (–4 to 2)

Quality-of-life scores for all indicators range from 0 to 100, with higher scores indicating a better state.
*Because of rounding, the mean difference between age groups may be different from the differences between the mean scores.
[†]The quality-of-life population was 87% of the intention-to-treat populations. The number of patients who answered each question differs slightly from the overall number of patients in the respective group.
[‡]Loss of sexual interest was to be answered only by patients who reported that they had been sexually active in the past 6 months (n = 127, 941, 229, 812 in the four groups, respectively).
SD, standard deviation; SOFT, Suppression of Ovarian Function Trial; TEXT, Tamoxifen and Exemestane Trial.

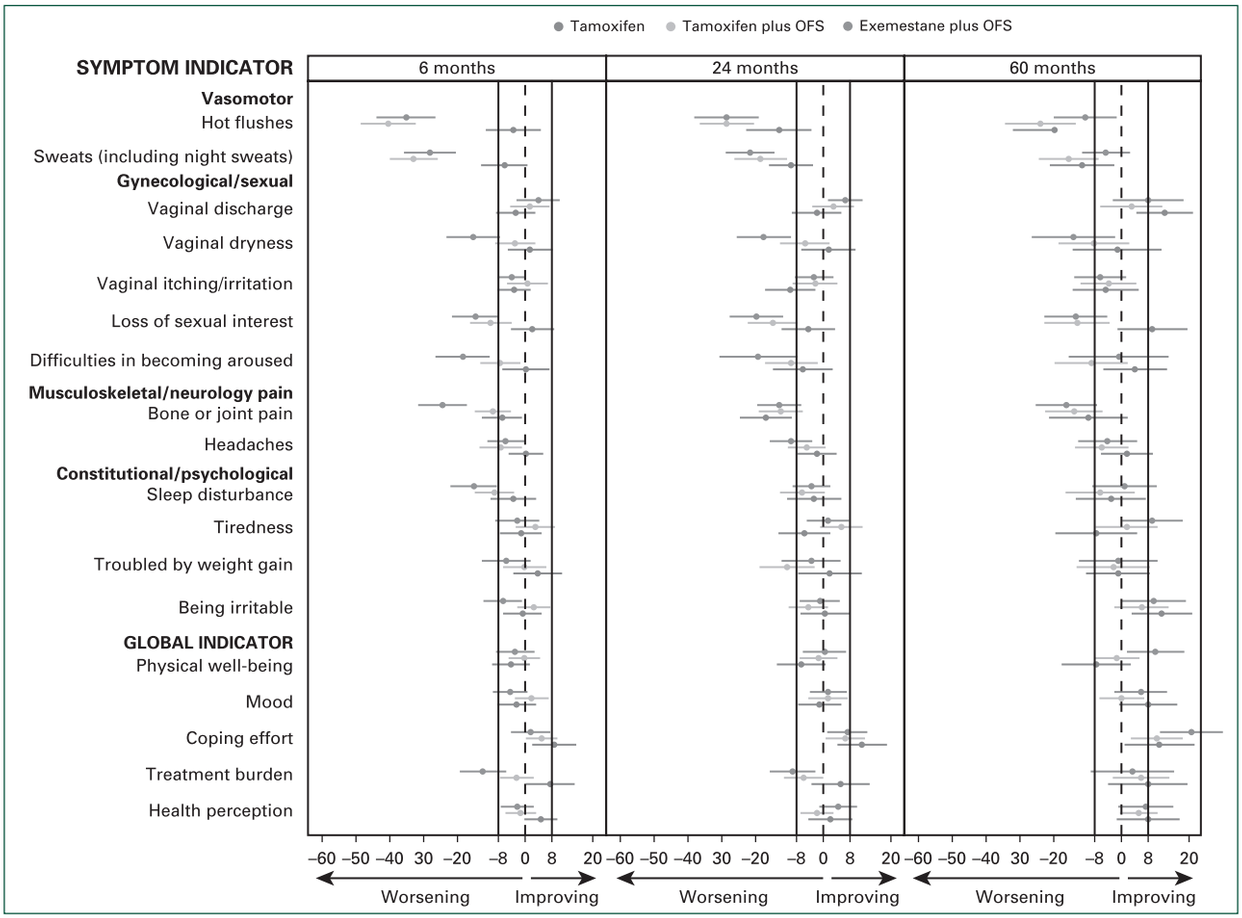

FIGURE 3 ■ Change in quality-of-life symptom and global indicator scores from baseline (mean with 95% CI), for 291 patients in the Suppression of Ovarian Function Trial who were younger than 35 years at random assignment and had received prior chemotherapy. Plus or minus 8 is the minimal clinical meaningful change of quality-of-life scores, indicated by dashed vertical lines.

OFS, ovarian function suppression.

Key points

- *Women treated with exemestane plus OFS noted increase in bone/joint pain at the 6-month time point that stabilized thereafter.*
- *Women younger than 35 years old treated with tamoxifen alone or tamoxifen plus OFS were also found to have an increase in bone/joint pain over time.*

for loss of sexual interest and difficulties in becoming aroused among patients younger than 35 years assigned to OFS and also for vaginal dryness among those receiving exemestane plus OFS; loss of sexual interest and vaginal dryness showed little improvement over time. Women treated with exemestane plus OFS noted increase in bone/joint pain at the 6-month time point that stabilized thereafter. Women younger than 35 years old treated with tamoxifen alone or tamoxifen plus OFS were also found to have an increase in bone/joint pain over time, which was slower in onset but reached a level similar to that of the exemestane plus OFS group by 24 months. Changes in global QoL indicators (physical well-being, mood, coping effort, and health perception) were minimal and similar among treatment groups. Treatment burden was greater than baseline at the 6-month time point in women younger than 35 years treated with exemestane plus OFS but improved over time to baseline levels in all treatment groups.

These data are similar to those previously published for all age groups combined.[11,12] The only clinically meaningful difference (defined as ≥ 8-point difference) between the younger than 35 years and ≥ 35 years age groups when adjusted for assigned endocrine therapy was a greater worsening in sweats for women younger than 35 years (eg, –8; 95% CI, –12 to –3 at 6 months), with similar trend in hot flushes

(data shown only for younger than 35 years old). This should be viewed in the context of the worse hot flushes and sweats present at baseline for participants in SOFT ≥ 35 years of age than those younger than 35 years (Table 2). In both SOFT and TEXT cohorts treated with chemotherapy, the changes in global QoL indicators were similar for the younger than 35 years and the ≥ 35 years age groups.

Nonadherence to protocol-assigned endocrine therapy

All women enrolled in SOFT and TEXT, regardless of chemotherapy use and HER2 status, were included in the adherence analysis. Adherence was defined as continuing assigned endocrine therapy for 5 years or until DFS event; women who were switched to an alternate endocrine therapy were considered nonadherent. Women who initially achieved OFS with a GnRH agonist but subsequently decided on a permanent method of ovarian ablation, such as surgery, were considered adherent; whether a woman received every triptorelin dose on the 28-day (±3 days) schedule per protocol was not taken into account.

Of the women younger than 35 years enrolled in SOFT and TEXT, 19.8% (115 of 582) stopped all protocol-assigned therapy early (19.2% continued receiving protocol-assigned therapy at time of analysis).

Nonadherence with assigned oral endocrine therapy was higher in women younger than 35 years ($P = .01$) than in women ≥ 35 years. The cumulative incidence of nonadherence with oral endocrine therapy in women younger than 35 years at 1 year was 11%, increasing to approximately 17%, 23%, and 25% at 2, 3, and 4 years after random assignment (Figure 4). For those ≥35 years old, it was 9%, 14%, 18%, and 21%, respectively. Of 470 women younger than 35 years assigned to OFS, six never started OFS, 45 (9.6%) chose oophorectomy after receiving some GnRH agonist, and five had oophorectomy as the only means of OFS. Nonadherence with medical OFS, which required monthly injections for 5 years, was significantly higher among patients younger than 35 years ($P = .009$). The cumulative incidence of nonadherence to medical OFS in women younger than 35 years at 1 year was 10%, increasing to approximately 15%, 20%, and 23% at 2, 3, and 4 years after random assignment (Figure 4); for the ≥ 35 years age group it was 8%, 12%, 15%, and 17%, respectively. More women older than 35 years opted for permanent OFS via surgery or radiotherapy.

Discussion

Women younger than 35 years in SOFT and TEXT had worse outcomes overall than

Key points

- *In both SOFT and TEXT cohorts treated with chemotherapy, the changes in global QoL indicators were similar for the younger than 35 years and the ≥ 35 years age groups.*
- *Of 470 women younger than 35 years assigned to OFS, six never started OFS, 45 (9.6%) chose oophorectomy after receiving some GnRH agonist, and five had oophorectomy as the only means of OFS.*
- *Nonadherence with medical OFS, which required monthly injections for 5 years, was significantly higher among patients younger than 35 years (P = .009).*

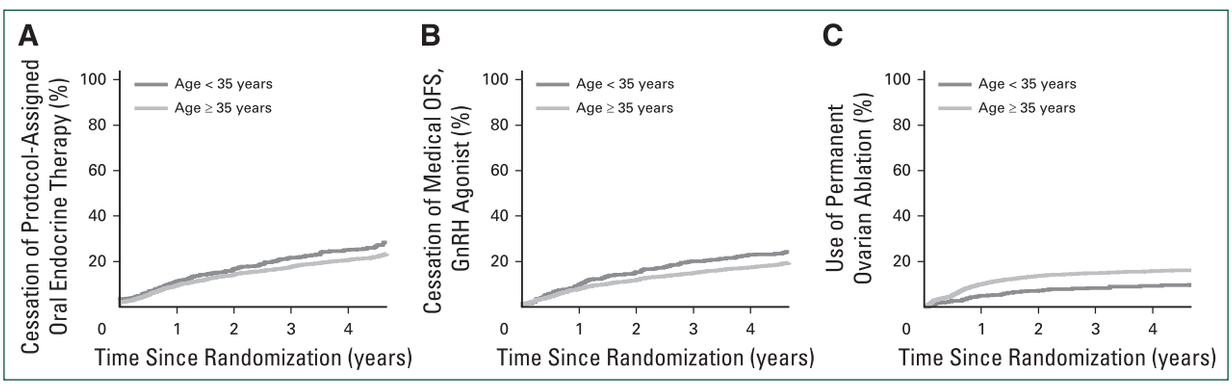

FIGURE 4 ■ Adherence with protocol-assigned endocrine therapy according to age at random assignment. (A) Cumulative incidence of cessation of assigned oral endocrine therapy (exemestane or tamoxifen). (B) Cumulative incidence of cessation of medical ovarian function suppression (OFS) by gonadotropin-releasing hormone (GnRH) agonist; patients switching to permanent OFS are not considered as having ceased medical OFS. (C) Cumulative incidence of permanent ovarian ablation by bilateral oophorectomy or ovarian irradiation.

Key points

- *The number of women younger than 35 years who did not receive adjuvant chemotherapy was small, and the majority of them received OFS.*
- *Only six women younger than 35 years were treated with tamoxifen and no chemotherapy in SOFT.*
- *We had hypothesized that women younger than 35 years might report more severe endocrine symptoms than their older premenopausal counterparts, but that did not seem to be the case.*
- *Symptoms overall improved after the 6-month time point, with the exception of bone and joint pain in the tamoxifen-treated groups and vaginal dryness and loss of sexual interest in the OFS groups.*
- *No data are yet available on patient-reported symptoms at >5 years from enrollment, when protocol-assigned treatment would have stopped, and future analyses will address the reversibility of treatment-induced menopausal symptoms.*
- *Several observational studies have reported that younger age is associated with lower rates of treatment compliance with endocrine therapy, possibly suggesting the level of toxicity (eg, sexual toxicity) is less acceptable to women younger than 35 years.*

older premenopausal women, with 5-year BCFI of only 79% for those younger than 35 years with HER2-negative disease.[18] It may be that recurrence rates will increase by 10 years of follow-up. For women in SOFT with HER2-negative disease who received chemotherapy, outcomes at 5 years were substantially improved by the use of OFS, increasing to a BCFI of 81.6% with the use of exemestane plus OFS from 67.1% for the use of tamoxifen alone. As noted in other studies,[1] there was a higher incidence of HER2 positivity in women younger than 35 years, and the HER2-positive subgroups of SOFT and TEXT will be explored in future analyses.

The number of women younger than 35 years who did not receive adjuvant chemotherapy was small, and the majority of them received OFS. Only six women younger than 35 years were treated with tamoxifen and no chemotherapy in SOFT. Although most guidelines would not suggest the use of OFS in women younger than 35 years with low-risk tumor characteristics, the 5- to 6-year median follow-up is too short for definite conclusions about the value of OFS in this lower-risk group; 50% of recurrences in HR-positive tumors will occur after 5 years.[8,17] A limitation of our study is that genomic testing, which is now widely used to identify women of low risk, was not used in this study.

Benefit from the addition of OFS must be weighed against toxicity. The primary QoL analyses for patients enrolled in TEXT and SOFT have been previously published.[11,12] We had hypothesized that women younger than 35 years might report more severe endocrine symptoms than their older premenopausal counterparts, but that did not seem to be the case. However, all age groups suffered bothersome symptoms. Symptoms overall improved after the 6-month time point, with the exception of bone and joint pain in the tamoxifen-treated groups and vaginal dryness and loss of sexual interest in the OFS groups. Some symptom indicators remained at a level indicating substantial treatment burden necessitating persistent attention to symptom alleviation and supportive care. No data are yet available on patient-reported symptoms at >5 years from enrollment, when protocol-assigned treatment would have stopped, and future analyses will address the reversibility of treatment-induced menopausal symptoms. Future analyses could also consider protocol-assigned and nonprotocol endocrine therapy actually received to assess whether some of the improvement in symptoms over time resulted from cessation of therapy by patients reporting the worst symptoms.

Women younger than 35 years in SOFT and TEXT had a higher rate of nonadherence than those ≥ 35 years of age. Several observational studies have reported that younger age is associated with lower rates of treatment compliance with endocrine therapy, possibly suggesting the level of toxicity (eg, sexual toxicity) is less acceptable to women younger than 35 years.[18–20] In a large medical and pharmacy insurance claims database, Neugut et al[21] found that patients with breast cancer who were younger than 45 years had an odds ratio of 2.0 of nonadherence to oral endocrine therapy compared with women 55 to 64 years of age. The need to come to a physician's office for injectable hormone therapy might further increase the difficulties of endocrine therapy for women younger than 35 years who have competing responsibilities, such as career and childcare.[22] Finally, a desire for pregnancy may also be relevant; only 10% of women younger than 35 years of age opted for oophorectomy. The POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsive breast cancer) trial (ClinicalTrials.gov identifier: NCT02308085) is currently enrolling young women who wish to interrupt endocrine therapy to become pregnant.

In summary, in two international randomized trials of endocrine therapy among

premenopausal women with HR-positive early breast cancer, women younger than 35 years had higher-risk disease characteristics than their older premenopausal counterparts and were also at increased risk for recurrence independent of assessed baseline tumor characteristics and treatment. There was a meaningful clinical benefit in breast cancer outcomes with the addition of OFS to tamoxifen and some additional benefit from use of an aromatase inhibitor with OFS. Longer follow-up is critical to clarify potential survival benefits. There were substantial adverse effects from these combined endocrine treatments, but they were not different in the younger and older than 35 years populations. Despite this, rates of nonadherence were slightly higher in women younger than 35 years. Availability of these age-specific data regarding risks and benefits of combined endocrine therapy will support shared decision making regarding OFS among young women at high risk for recurrence and death from breast cancer and, it is hoped, improve adherence among those who select OFS.

Key points

- *There was a meaningful clinical benefit in breast cancer outcomes with the addition of OFS to tamoxifen and some additional benefit from use of an aromatase inhibitor with OFS.*

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Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline

(J Clin Oncol 2017;35(18):2062–2081.)

Purpose: To make recommendations regarding the use of bisphosphonates and other bone-modifying agents as adjuvant therapy for patients with breast cancer.
Methods: Cancer Care Ontario and ASCO convened a Working Group and Expert Panel to develop evidence-based recommendations informed by a systematic review of the literature.
Results: Adjuvant bisphosphonates were found to reduce bone recurrence and improve survival in postmenopausal patients with nonmetastatic breast cancer. In this guideline, postmenopausal includes patients with natural menopause or that induced by ovarian suppression or ablation. Absolute benefit is greater in patients who are at higher risk of recurrence, and almost all trials were conducted in patients who also received systemic therapy. Most studies evaluated zoledronic acid or clodronate, and data are extremely limited for other bisphosphonates. While denosumab was found to reduce fractures, long-term survival data are still required.
Recommendations: It is recommended that, if available, zoledronic acid (4 mg intravenously every 6 months) or clodronate (1,600 mg/d orally) be considered as adjuvant therapy for postmenopausal patients with breast cancer who are deemed candidates for adjuvant systemic therapy. Further research comparing different bone-modifying agents, doses, dosing intervals, and durations is required. Risk factors for osteonecrosis of the jaw and renal impairment should be assessed, and any pending dental or oral health problems should be dealt with prior to starting treatment. Data for adjuvant denosumab look promising but are currently insufficient to make any recommendation. Use of these agents to reduce fragility fractures in patients with low bone mineral density is beyond the scope of the guideline. Recommendations are not meant to restrict such use of bone-modifying agents in these situations.

Introduction

In women, breast cancer is the most common cancer, accounting for approximately 25% of all cancers.[1,2] Despite improvements in long-term outcomes for early breast cancer, recurrence and death rates are still significant. Bone remains the most common site of breast cancer recurrence. The pivotal effects of the interaction between the tumor and its microenvironment have been recognized for more than 100 years through the so-called seed and soil hypothesis.[3] The results of population studies, preclinical research, and clinical studies in patients with metastatic disease provided a rationale for testing bone-targeted agents in the adjuvant setting.[4]

Despite initial optimism, results from prospectively designed, randomized controlled

Key points

- *In women, breast cancer is the most common cancer, accounting for approximately 25% of all cancers.*

The bottom line

Use of adjuvant bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline

Guideline objective

To make recommendations regarding the use of bisphosphonates and other bone-modifying agents as adjuvant therapy in patients with breast cancer.

Target population

Patients with early or locally advanced (nonmetastatic) breast cancer.

Target audience

Medical oncologists and other clinicians involved in postsurgical (adjuvant) treatment of patients with breast cancer.

Methods

A joint Expert Panel was convened to develop clinical practice guideline recommendations on the basis of a systematic review of the medical literature.

Preamble to recommendations

The focus of this guideline is on the relapse and survival benefit of bone-modifying agents in nonmetastatic breast cancer. This guideline acknowledges that there is clear evidence for the use of bone-modifying agents such as bisphosphonates to reduce the risk of fragility fractures in at-risk populations (such as those with diagnosed low bone mass) and to treat metastatic cancer to the bone. None of the recommendations in this guideline are meant to restrict such use of bone-modifying agents in these situations, although they may influence the specific bisphosphonate selected when given for both bone health and adjuvant therapy. In addition, it is recognized that in many health care settings, bone-modifying agents such as bisphosphonates may currently be available, approved, and/or funded in specific doses and schedules only for the indications of improving bone mass and for treatment of bone metastases. As such, users of this guideline should consider available resources and access—as well as any other barriers within their local health care settings—to using the treatments recommended in this guideline for adjuvant breast cancer.

Qualifying statements are an integral part of the recommendations, and these should always be read and cited together.

Recommendation 1

- It is recommended that administration of bisphosphonates as adjuvant therapy be considered for postmenopausal patients with breast cancer (including patients premenopausal before treatment who have menopause induced by ovarian suppression as detailed in Recommendation 5) deemed candidates for adjuvant systemic therapy.
- The final decision of whether or not to administer bisphosphonates should be made during consultation between the patient and oncologist, taking into account patient and disease characteristics, including risk of recurrence, and weighing the potential benefits and risks (adverse effects).

Qualifying Statements for Recommendation 1

- While the EBCTCG meta-analysis[11] found benefit for bisphosphonates in all subgroups of postmenopausal patients, the absolute benefit was small. For patients with cancers assessed as having low risk of recurrence, the use of bisphosphonates may not result in clinically meaningful effect.
- Considerations in deeming patients at high enough recurrence risk to receive adjuvant systemic therapy may also apply in deciding on bisphosphonate use. The majority of patients (83%) in the meta-analysis had also received adjuvant chemotherapy. Standard clinical and pathologic risk factors and recognized clinical tools may be used, where applicable, to estimate risk of recurrence and mortality.[93,94]
- Risk factors for ONJ and renal impairment should be assessed (Recommendation 6).
- Patients should receive all other recommended breast cancer treatment, including surgery, radiation, and/or systemic therapy (see, for example, the CCO guideline on systemic therapy in early breast cancer).[93]
- There is no information to guide the use of bone-modifying agents for patients receiving systemic adjuvant therapy for completely resected local recurrence.

The bottom line (*continued*)

Recommendation 2

- Zoledronic acid and clodronate are the recommended bisphosphonates for adjuvant therapy in breast cancer.
- There is a need for more information comparing different agents and schedules, and it is recommended that such trials be conducted to establish the utility and optimal administration of other bisphosphonates for adjuvant therapy.

Qualifying Statements for Recommendation 2

- Preliminary data from the SWOG S0307 trial[60,61] suggest that clodronate, ibandronate, and zoledronic acid may provide similar DFS and OS benefit. However, as these data have, to date, only been published in abstract form, no definitive recommendations regarding ibandronate can yet be made. Full publication of the SWOG S0307 trial and results of the TEAM IIb (BOOG 2006-04) trial[77] may support adjuvant ibandronate use. There is a large difference in ibandronate dosage between these trials (50 mg/d) and that used in treating osteoporosis (150 mg/mo orally or 3 mg every 3 months intravenously). This dosage difference should be considered in future comparisons.
- Clodronate has not been studied specifically in patients receiving AIs.
- While the direct evidence from adjuvant trials is considered sufficient only for zoledronic acid and clodronate, others have hypothesized that any agent proven to reduce the risk of fragility fractures in at-risk populations (eg, patients with postmenopausal or drug-induced osteoporosis) may be effective as adjuvant therapy for breast cancer. Given orally for osteoporosis treatment, alendronate has been used daily or weekly, while risedronate and ibandronate have been used daily, weekly, or monthly.[81] Ibandronate has also been used intravenously. Less frequent administration, compared with clodronate, may make these preferable to patients if shown to be of adjuvant benefit. Further trials with adequate power and primary outcomes of DFS and OS are required to determine the optimal agent and dosing schedule.
- Different adverse effect profiles, frequency and route of administration, cost, and regulatory approval may influence selection.

Recommendation 3

- While results for adjuvant denosumab look promising, data are insufficient at this time to make any recommendation regarding its use in the adjuvant setting.
- It is recommended that studies directly comparing denosumab with bisphosphonates and evaluating administration schedules be conducted.

Qualifying Statements for Recommendation 3

- While the ABCSG-18 trial studied denosumab use in postmenopausal women with hormone receptor–positive breast cancer receiving AIs and found clear fracture reduction benefit,[62] DFS results have only been reported as a conference presentation or abstract.[63,64] As survival data have, to date, only been published in abstract form, no definitive recommendations can yet be made. Results are promising but limited compared with the body of evidence for bisphosphonates. Further results of the ABCSG-18 and D-CARE trials[74] may provide stronger evidence for adjuvant denosumab use.

Recommendation 4

- For patients who will receive adjuvant bisphosphonates (Recommendation 1), zoledronic acid at 4 mg intravenously over 15 min (or longer) every 6 months for 3 to 5 years or clodronate orally at 1,600 mg/d for 2 to 3 years are recommended. Different durations may be considered.
- More research is recommended comparing different bone-modifying agents, doses, dosing intervals, and durations.

Qualifying Statements for Recommendation 4

- In jurisdictions where the recommendation cannot be followed due to availability, similar doses and schedules of zoledronic acid or clodronate are considered reasonable.
- The optimal dose and schedule of administration of zoledronic acid and clodronate have not been determined; however, the recommended doses and schedules have been found effective in many of the adjuvant breast cancer trials and result in fewer or less severe adverse effects than regimens used in patients with metastatic disease (ie, 4 mg zoledronic acid every 3 to 4 weeks).
- The optimal duration of adjuvant bone-targeted agents has not been determined; the recommendations reflect durations found effective in the EBCTCG meta-analysis and other trials included in the literature review. It is unclear whether there is benefit to longer-term administration, although studies indicate that the benefit of bisphosphonates continues after administration is

■ The bottom line (*continued*)

stopped due to the persistence of the drug within the bone. There are concerns about adverse effects such as atypical bone fractures based on reports from the osteoporosis literature, and some osteoporosis recommendations allow a treatment holiday from bisphosphonates after 3 to 5 years for patients with a lower risk of fracture.[92,100]

- Administration of clodronate for > 3 years or zoledronic acid for > 5 years has not been evaluated in adjuvant trials, and, therefore, a recommendation of longer duration is not supported at this time. This limitation in the evidence may be especially relevant to patients receiving long-term endocrine therapy, as the recent CCO guideline on systemic treatment[93] includes recommendations for endocrine therapy for up to 10 years based primarily on results from the ATLAS, aTTom, and MA.17 trials.
- The optimal timing to start bisphosphonates after diagnosis of breast cancer is unclear; however, most of the clinical trials started soon after surgery or chemotherapy.

Recommendation 5

- For purposes of adjuvant bisphosphonate use, the definition of menopause should include both natural menopause (at least 12 months of amenorrhea prior to initiation of chemotherapy or endocrine therapy) and menopause induced by ovarian ablation or suppression (but not the cessation of menses due to chemotherapy alone). In women age ≤ 60 years with a previous hysterectomy and ovaries left in place, luteinizing hormone, follicle-stimulating hormone, and serum estradiol should be in the postmenopausal range and measured prior to initiation of any systemic therapy to receive adjuvant bisphosphonates.

Qualifying Statements for Recommendation 5

- As indicated in the recent CCO guideline on systemic therapy in early breast cancer,[93] assessing menopausal status is difficult in patients age ≤ 60 years who experience amenorrhea secondary to chemotherapy or tamoxifen. Cessation of menses does not necessarily denote the absence of ovarian function, and premenopausal estradiol levels can be found in patients with transient chemotherapy-induced amenorrhea.[101] In addition, hormone levels and the absence of menses are unreliable indicators of menopause during treatment with tamoxifen.[102]
- Some publications have suggested that patients experiencing chemotherapy-induced amenorrhea are at high risk for adverse bone effects and may be candidates for bone-modifying agents. Evidence is insufficient to address use of these agents as adjuvant treatment in this population.

Recommendation 6

- A dental assessment is recommended, where feasible, prior to commencement of bisphosphonates, and any pending dental or oral health problems should be dealt with prior to starting treatment, if possible. Patients should be informed of the risk of developing ONJ, especially with tooth extractions and other invasive dental procedures. Patients should inform their dental practitioner of their treatment. Patients with suspected ONJ should be referred to a dental practitioner with expertise in treating this condition. Recent guidelines or position papers by groups such as the International Task Force on Osteonecrosis of the Jaw,[103] the American Association of Oral and Maxillofacial Surgeons,[104] and the American Dental Association[105,106] should be consulted.
- Patients should have serum calcium measured prior to starting treatment. Patients receiving intravenous bisphosphonates (zoledronic acid) should be monitored for renal function prior to starting this treatment, and for serum calcium and increase in serum creatinine throughout the treatment period.
- Calcium and vitamin D supplementation is recommended unless otherwise contraindicated. Oral bisphosphonates and calcium should not be taken concurrently; several monographs suggest an interval of at least 2 hours to allow for maximum absorption.
- Symptoms such as ocular pain or loss of vision may be due to serious inflammatory conditions such as uveitis or scleritis and should be promptly evaluated by an ophthalmologist.

Qualifying Statements for Recommendation 6

- The risk of ONJ increases with frequency, dose, and duration of bisphosphonate administration. Risk can be reduced with appropriate screening prior to treatment and modification of dental care. Risk of ONJ when bisphosphonates are administered, as suggested in Recommendation 4, is lower than for patients receiving higher doses or more frequent administration as is used for cancers with bone metastasis.

The bottom line (*continued*)

- Some organizations advise dental assessment and care prior to any cancer treatment, preferably as soon as possible after diagnosis to allow time for dental procedures and adequate healing prior to treatment.[107–111]
- The CCO formulary monograph for zoledronic acid recommends "comprehensive dental evaluation of both hard and soft tissues before starting bisphosphonate treatment; undergo invasive dental procedures, if needed, before starting bisphosphonate treatment."[112(p6)] US FDA prescribing information for zoledronic acid indicates that "cancer patients should maintain good oral hygiene and should have a dental examination with preventative dentistry prior to treatment with bisphosphonates."[113(p5),114(p2)]
- It is unclear whether bone-modifying therapy should be withheld if invasive dental treatment is required. Some have hypothesized that withholding bone-modifying therapy may allow for better bone healing and suggested stopping treatment 2 months prior to oral surgery and delaying restarting until osseous healing has occurred. The alternative view is that a short break in bisphosphonate administration will have no effect as bone effects of bisphosphonates are maintained for years after treatment stops.
- Hypocalcemia is a known adverse effect of bisphosphonate treatment, especially with the higher doses and more frequent administration given to patients with metastatic cancer. It is relatively rare (< 1%) at lower doses (Recommendation 4) in patients without pre-existing conditions such as renal insufficiency and who have adequate vitamin D status and calcium intake.
- There is conflicting evidence as to whether inflammatory eye conditions are directly caused by bisphosphonates or in conjunction with some underlying inflammatory disease process;[115] however, if not treated promptly, these conditions may lead to blindness. Discontinuation of bisphosphonates may be necessary.[116]

trials (RCTs) that were powered to assess the value of adjuvant bone-targeted therapy in early breast cancer are conflicting.[5] Data have shown that, where benefit exists, it tends to be in women with a low estrogen environment, either through menopause or suppression of ovarian function. This hypothesis was formed largely based on results of the ABCSG-12 trial[6–8] that was conducted in premenopausal patients on ovarian suppression and preplanned subgroup analysis of the AZURE/BIG 1-04 trial.[9,10] Results of the recently published Oxford Overview (Early Breast Cancer Trialists' Collaborative Group [EBCTCG]) analysis of individual patient data have provoked particular interest in this area[11] and are a key portion of the evidence on this topic.

To develop recommendations for the use of bisphosphonates and other bone-modifying agents as adjuvant therapy for patients with breast cancer, the Program in Evidence-Based Care (PEBC) of Cancer Care Ontario (CCO) and ASCO's Clinical Practice Guidelines Committee (CPGC) established a joint guideline panel.

Methods

Guideline development methods

The PEBC practice guidelines development cycle[12,13] and the ASCO guideline development methods include a systematic review, interpretation of evidence, drafting of recommendations, internal review by content and methodology experts (see *Guideline Developers*), and external review by clinicians and other stakeholders.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, addition of newer literature to the original evidence base—this is described in the PEBC Document Assessment and Review Protocol. PEBC guideline recommendations are based on clinical evidence and not on feasibility of implementation; however, a list of implementation considerations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the PEBC Handbook and the PEBC Methods Handbook.

Key points

- *Results of the recently published Oxford Overview (Early Breast Cancer Trialists' Collaborative Group [EBCTCG]) analysis of individual patient data have provoked particular interest in this area and are a key portion of the evidence on this topic.*
- *PEBC guideline recommendations are based on clinical evidence and not on feasibility of implementation; however, a list of implementation considerations is provided along with the recommendations for information purposes.*
- *PEBC guideline development methods are described in more detail in the PEBC Handbook and the PEBC Methods Handbook.*

Key points

- *The PEBC mandate is to improve the lives of Ontarians who are affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.*
- *This guideline was developed by the Adjuvant Bisphosphonates in Breast Cancer Guideline Development Group (GDG), which was convened at the request of the CCO Breast Cancer Disease Site Group.*
- *The Working Group had expertise in medical oncology and health research methodology. Other members of the GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group.*
- *ASCO nominated four members to the Expert Panel and suggested some of the external reviewers.*
- *Per ASCO policy, a patient advocate and a representative from the ASCO Practice Guideline Implementation Network were included on the Expert Panel.*
- *Approval was sought from both the PEBC Report Approval Panel and the ASCO CPGC.*
- *The Working Group and Expert Panel were assembled and managed in accordance with the conflict of interest (COI) policies of PEBC and ASCO.*

ASCO Expert Panel and guidelines staff will work to keep abreast of any substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO will determine the need to update. This is the most recent information as of the publication date. Visit the ASCO Guidelines Wiki at www.asco.org/guidelineswiki/ to submit new evidence.

Guideline developers

PEBC is an initiative of the Ontario provincial cancer system, CCO. The PEBC mandate is to improve the lives of Ontarians who are affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control. PEBC is supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by PEBC is editorially independent from OMHLTC.

This guideline was developed by the Adjuvant Bisphosphonates in Breast Cancer Guideline Development Group (GDG), which was convened at the request of the CCO Breast Cancer Disease Site Group. The project was led by a smaller Working Group that was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in medical oncology and health research methodology. Other members of the GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group.

Traditionally, guideline topics have been determined with CCO and then a search for existing guidelines is conducted to determine whether there are other guidelines that could be endorsed or adapted instead of creating a completely new guideline. The adaptation process can be quite long and costly. In discussion with ASCO, it was determined there would be benefit in codeveloping several guidelines, with either PEBC or ASCO taking the lead and the other organization being involved at various stages. In this manner, input of both groups would be given at an earlier stage in development such that later adaptation would not be required. For this guideline, PEBC took the lead, including planning the project and its scope as well as constituting the Working Group. ASCO nominated four members to the Expert Panel and suggested some of the external reviewers. Per ASCO policy, a patient advocate and a representative from the ASCO Practice Guideline Implementation Network were included on the Expert Panel. Approval was sought from both the PEBC Report Approval Panel and the ASCO CPGC. Internal review consisted of review by the Expert Panel as well as these two approval groups.

Conflicts of interest

The Working Group and Expert Panel were assembled and managed in accordance with the conflict of interest (COI) policies of PEBC[14] and ASCO.[15] All members of the Expert Panel completed the PEBC COI disclosure form. Declared conflicts were evaluated against both PEBC and ASCO COI policies, and the authors met the requirements for both. Potential Report Approval Panel and ASCO CPGC members with any COIs (on the basis of the CCO and ASCO COI policies, respectively) were not eligible to review or approve the guideline; those involved in the process had no conflicts. Targeted external reviewers were required to complete a COI form; conflicts were not a barrier to participation. Potential conflicts for all participants are given in the full document on the CCO website. For purposes of publication, authors completed an additional *Journal of Clinical Oncology*/ASCO COI form, and declarations are available at ascopubs.org/journal/jco.

Search for existing guidelines

A search for existing guidelines was conducted using known guideline-developer Web sites and practice-guideline databases. No guidelines suitable for adaptation or

endorsement were found. A search of the primary literature was required. A European consensus guideline[16] was published subsequent to our literature search. It was evaluated as not meeting our criteria for endorsement; therefore, the guideline process was continued.

Guideline disclaimers

Care has been taken in the preparation of the information contained herein. Nevertheless, any person seeking to consult the report or apply its recommendations is expected to use independent medical judgment in the context of individual clinical circumstances or to seek out the supervision of a qualified clinician. CCO makes no representations or guarantees of any kind whatsoever regarding the report content or its use or application and disclaims any responsibility for its use or application in any way.

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Literature review

The Working Group of the Adjuvant Bisphosphonates in Breast Cancer GDG developed this evidentiary base to inform recommendations as part of a clinical practice guideline. The complete systematic review is included as Section 4 of the multipart evidence-based series on the CCO Web site at https://www.cancercareontario.ca/guidelines-advice/types-of-cancer/breast, and only a brief summary is given in the following sections. On the basis of the objectives of this guideline, the Working Group derived the research questions outlined below.

Research questions

1. Does administration of bisphosphonates or other bone-modifying agents as adjuvant treatment in patients with breast cancer reduce metastasis and/or recurrence and improve survival?
2. Does effectiveness depend on patient or disease characteristics, especially age or menopausal status (either natural or induced menopause)?
3. Do effectiveness and adverse effects differ according to which bisphosphonate or bone-modifying agent is used?

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- *Does administration of bisphosphonates or other bone-modifying agents as adjuvant treatment in patients with breast cancer reduce metastasis and/or recurrence and improve survival?*
- *Does effectiveness depend on patient or disease characteristics, especially age or menopausal status (either natural or induced menopause)?*

Key points

- *During project planning, it was anticipated that the primary evidence base would be the EBCTCG individual patient data meta-analysis.*
- *Initial review of the EBCTCG publication revealed that meta-analysis included data from 26 trials.*
- *There were 24 additional trials that met their inclusion criteria but without data.*
- *Meta-analysis did not report data on adverse effects, nor did it provide references to publications for the included trials.*
- *MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched for the period 2005 to June 6, 2016.*
- *The search included terms for breast cancer, bisphosphonates or bone-modifying agents, and publication type.*
- *Abstracts from major conferences were searched separately for years that were not included in the above databases.*
- *Studies that were primarily designed to evaluate bone-modifying effects such as bone mineral density (BMD) were excluded unless recurrence or survival outcomes were also part of the design (primary or secondary outcomes) and were reported in detail.*

4. What doses, duration of administration, and route (intravenous or oral) are optimal?

Literature search methods

During project planning, it was anticipated that the primary evidence base would be the EBCTCG individual patient data meta-analysis.[11] Initial review of the EBCTCG publication revealed that meta-analysis included data from 26 trials. There were 24 additional trials that met their inclusion criteria but without data. Meta-analysis did not report data on adverse effects, nor did it provide references to publications for the included trials. It focused on bisphosphonates and, therefore, did not include other bone-modifying agents such as denosumab. EBCTCG only included trials that started before 2008. It was therefore considered necessary to conduct a full literature search to identify the included studies, determine the reason for missing data and whether they had been subsequently published, look for more recent data of included trials, identify ongoing or recently completed trials that started around 2008 or later—and were therefore excluded by EBCTCG—and to include trials of nonbisphosphonate bone-modifying agents.

Search for systematic reviews and primary literature

MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched for the period 2005 to June 6, 2016. The search included terms for breast cancer, bisphosphonates or bone-modifying agents, and publication type. Abstracts from major conferences were searched separately for years that were not included in the above databases.

Study selection criteria and process

In the current literature review, studies included were RCTs that evaluated adjuvant or neoadjuvant use of bisphosphonates or other bone-modifying agents (primarily denosumab) compared with some control (none, placebo, other bisphosphonates, or different administration of the same bisphosphonate). Studies that were designed to measure cancer recurrence, survival, or distant metastasis (bone or visceral metastases) provided the strongest evidence. Studies that were primarily designed to evaluate bone-modifying effects such as bone mineral density (BMD) were excluded unless recurrence or survival outcomes were also part of the design (primary or secondary outcomes) and were reported in detail. To be included, studies had to evaluate at least 30 randomly assigned patients. RCTs were excluded that were designed to evaluate agents that primarily modify hormonal levels, such aromatase inhibitors (AIs), tamoxifen, or raloxifene, but which may have secondary bone effects. A review of the titles and abstracts that resulted from the search was conducted by one reviewer (G.G.F.). The same reviewer looked at items that warranted full text review.

Inclusion criteria of the EBCTCG meta-analysis[11] were broader and included any trial in which women were randomly assigned to bisphosphonate versus a control group without bisphosphonate. EBCTCG therefore included several additional trials that were designed primarily with BMD or similar outcomes and for which there was no published data on survival or recurrence outcomes. While some of these trials included large numbers of patients, there were few events of interest (recurrence or survival outcomes) and these additional trials contributed little to the overall meta-analysis.

Results

Literature search results

Of the systematic reviews and meta-analyses found, the EBCTCG individual patient data meta-analysis[11] was the most comprehensive and the main evidence source for the accompanying guideline, supplemented by additional RCTs and updated data that were found in the primary literature search. The EBCTCG

meta-analysis included data from 26 trials,[6–10,17–59] of which 14 met our inclusion criteria on the basis of data in the corresponding publications and 12 did not, primarily because they were BMD studies that did not report recurrence or survival outcomes. The meta-analysis also listed an additional 24 trials for which data were not available.

The literature search combined with the EBCTCG meta-analysis found 27 trials (plus the 12 that did not meet our inclusion criteria). In addition to trials with data included in the EBCTCG meta-analysis, the literature search also found results for the SWOG S0307 (abstract only[60,61]) and ABCSG-18 trials,[62–64] as well as a few small studies.[65–73] While these publications mention at least some outcomes, complete publication or longer follow-up is still required for several of them. SWOG S0307[60,61] compared clodronate versus ibandronate versus zoledronic acid and, as such, gives data not in the EBCTCG meta-analysis. ABCSG-18,[62,63] along with the ongoing D-CARE trial,[74] provides data on denosumab, which is also not in the meta-analysis.

Study design and quality

The EBCTCG[75] is an international collaboration that was formed in 1985 to evaluate studies on early (operable) breast cancer. They obtain individual patient data from all relevant RCTs throughout the world. Individual patient meta-analysis provides the most reliable and least biased means of addressing questions that are not answered in individual RCTs.[76] The individual patient data and several of the reported outcomes are not available except in the meta-analysis. There were also limitations in the meta-analysis, and certain key trials that addressed questions that were not covered in the meta-analysis were looked at in more detail.

Data on a per-trial basis were presented in forest plots, with separate plots for each outcome; these were presented for all patients and separately for the subgroup of postmenopausal patients. In these plots, trials were grouped and results were calculated for categories of clodronate < 2 years or for ≥ 2 years; and for aminobisphosphonate < 1 year, approximately 1 year, 2 years, and > 2 years (of which all trials were for 3 to 5 years). As data were listed by trial, it was possible to determine which bisphosphonate contributed to the results for each of these categories.

A few individual studies in the EBCTCG meta-analysis addressed specific issues, and, therefore, the original publications were looked at in more detail. For these trials, as well as key trials that were not included in the EBCTCG overview, additional details of trial design were looked at to aid in assessing quality. Overall assessment is that study results are of high quality, with the limitation that some outcomes have not yet been completely reported.

Outcomes

EBCTCG meta-analysis. The EBCTCG meta-analysis[11] included data from 18,766 women in 26 trials. Of women with known nodal status, 66% were node positive, and 83% of all study participants had received systemic chemotherapy. Most women (97%) were in trials that investigated the use of bisphosphonate for 2 to 5 years duration. Use of bisphosphonates gave the greatest improvement in bone recurrence (rate ratio [RR], 0.83; $P = .004$) and bone fractures (RR, 0.85; $P = .02$). Other outcomes that included bone recurrence were also improved, although to a lesser extent (distant recurrence: RR, 0.92; $P = .03$; breast cancer mortality: RR, 0.91; $P = .04$; any death: RR, 0.92; $P = .06$; recurrence: RR, 0.94; $P = .08$). There seemed to be no effect on distant recurrence outside bone (RR, 0.98; $P = .69$). Menopausal status was categorized as premenopausal, perimenopausal, or postmenopausal, with postmenopausal being natural or induced (luteinizing hormone-releasing hormone analogs or oophorectomy). For the subgroup of premenopausal patients, bisphosphonate had no significant effect

Key points

- *ABCSG-18, along with the ongoing D-CARE trial, provides data on denosumab, which is also not in the meta-analysis.*
- *The EBCTCG is an international collaboration that was formed in 1985 to evaluate studies on early (operable) breast cancer.*
- *They obtain individual patient data from all relevant RCTs throughout the world. Individual patient meta-analysis provides the most reliable and least biased means of addressing questions that are not answered in individual RCTs.*
- *The individual patient data and several of the reported outcomes are not available except in the meta-analysis.*
- *There were also limitations in the meta-analysis, and certain key trials that addressed questions that were not covered in the meta-analysis were looked at in more detail.*
- *Use of bisphosphonates gave the greatest improvement in bone recurrence (rate ratio [RR], 0.83;* P = *.004) and bone fractures (RR, 0.85;* P = *.02).*
- *Other outcomes that included bone recurrence were also improved, although to a lesser extent (distant recurrence: RR, 0.92;* P = *.03; breast cancer mortality: RR, 0.91;* P = *.04; any death: RR, 0.92;* P = *.06; recurrence: RR, 0.94;* P = *.08).*

Key points

- *There were no treatment differences on the basis of age or menopausal status.*
- *There were small differences in grade 3 to 4 events (10.5% ibandronate, 8.3% clodronate, 8.8% zoledronic acid) and osteonecrosis of the jaw (ONJ; 0.6% ibandronate, 0.3% clodronate, 1.2% zoledronic acid).*
- *The ABCSG-18 trial compared denosumab with placebo in postmenopausal patients with early hormone receptor–positive breast cancer who were administered AIs.*
- *A significant reduction in fractures was reported overall (11.1% vs. 26.2% at 84 months; hazard ratio [HR], 0.5; P < .001) and for various subgroups.*
- *Several trials found in the literature search do not have fully published final results, and follow-up is likely ongoing. In addition, three large ongoing trials without outcome data were found.*
- *TEAM IIb is studying ibandronate and completed enrollment in 2010.*
- *Success A is comparing 2 years with 5 years of zoledronic acid; enrollment was completed in 2007 but survival and metastasis results have not been published.*
- *Clodronate was administered orally at 1,600 mg/d in most studies, although it is sometimes administered intravenously, as in the British Columbia trial.*

on these outcomes. In contrast, in postmenopausal patients, bisphosphonates had greater benefit in all outcomes—that is, lower risk ratios and more highly significant differences—than for the full patient population. Only bisphosphonate effect on distant recurrence outside the bone was not statistically significant ($P = .10$). Again, effect was greatest for bone recurrence (RR, 0.72; $P = .0002$).

Major trials not in the EBCTCG meta-analysis: SWOG S0307. The SWOG S0307 trial[60,61] compared 3 years of clodronate versus ibandronate versus zoledronic acid. It did not include a nonbisphosphonate control or placebo arm. Patients received adjuvant chemotherapy, and 58% were postmenopausal or age ≥ 50 years. It is the only major RCT to directly compare various bisphosphonates. Of note, zoledronic acid, clodronate, and ibandronate were dosed as used in metastatic cancer and are thus much higher than when used in osteoporosis treatment. At the fourth formal interim analysis, the data monitoring committee recommended early reporting as there was no realistic chance of a statistically significant difference. Results have been published only as an abstract, but indicate no differences in 5-year disease-free survival (DFS; 87% to 88%), overall survival (OS; 93%), or fractures. There were no treatment differences on the basis of age or menopausal status. There were small differences in grade 3 to 4 events (10.5% ibandronate, 8.3% clodronate, 8.8% zoledronic acid) and osteonecrosis of the jaw (ONJ; 0.6% ibandronate, 0.3% clodronate, 1.2% zoledronic acid).

Major trials not in the EBCTCG meta-analysis: ABCSG-18. The ABCSG-18 trial[62–64] compared denosumab with placebo in postmenopausal patients with early hormone receptor–positive breast cancer who were administered AIs. A significant reduction in fractures was reported overall (11.1% *vs*. 26.2% at 84 months; hazard ratio [HR], 0.5; $P < .001$) and for various subgroups.

The recent presentation at the San Antonio Breast Cancer Symposium 2015 conference[64] reported the secondary outcome of DFS: 3-year DFS was 93.8% versus 92.6%, 5-year DFS was 88.9% *vs*. 86.8%, and 7-year DFS was 83.5% versus 80.4% (HR, 0.816; 95% CI, 0.66 to 1.00; $P = .051$). While follow-up is ongoing, due to the large decrease in fractures, a patient's choice unblinding option will be implemented in 2016, which will allow those on placebo to switch to denosumab.

Ongoing trials. Several trials found in the literature search do not have fully published final results, and follow-up is likely ongoing. In addition, three large ongoing trials without outcome data were found. TEAM IIb is studying ibandronate and completed enrollment in 2010.[77] Success A is comparing 2 years with 5 years of zoledronic acid; enrollment was completed in 2007 but survival and metastasis results have not been published.[78,79] The D-CARE study is comparing denosumab with placebo in patients with high risk of recurrence. Results should therefore complement those of the ABCSG-18 trial. Enrollment was completed in 2012.[74] As enrollment for these trials was completed a few years ago, they may soon provide additional information on the use of bisphosphonates and denosumab.

Differences in administration. Clodronate was administered orally at 1,600 mg/d in most studies, although it is sometimes administered intravenously, as in the British Columbia trial.[45] Zoledronic acid was administered at 4 mg intravenously either monthly (as used for bone metastasis), every 6 months (as used in osteoporosis trials), or with some intermediate frequency, for example, every 3 months or monthly for the initial period and then every 6 months. Ibandronate was administered orally at 50 mg/d as is used in bone metastasis treatment, except in the ARIBON trial, where it was administered at 150 mg every 28 days as is used in postmenopausal osteoporosis. The EBCTCG meta-analysis authors suggested that effects on bone recurrence

were similar (more intensive: 6.2% bisphosphonate *vs*. 7.5% control; low intensity: 2.2% bisphosphonate *vs*. 3.0% control). Different doses or modes were not directly compared within the same trial.

ONJ. One of the more serious adverse effects of bisphosphonate treatment is ONJ. To lower the risk, many of the more recent trials excluded patients with recent or planned dental or jaw surgery (extraction or implants). ONJ incidence in patients receiving monthly doses of zoledronic acid for 6 months and then every 3 or 6 months thereafter was 1.5% to 2.1% in the AZURE/BIG 01/04 trial[32] and 1.2% in the SWOG S0307 trial.[61] Several smaller trials that administered zoledronic acid at 3 to 4 mg every 3 to 4 weeks for 1 to 2 years also reported ONJ (Washington University, 1.7%;[38] University of Saarland, 2.3%,[36] ProBONE II, 3%[57]). With ibandronate (50 mg/d), ONJ occurred in 0.1% of patients in the GAIN trial[30] and in 0.6% of patients in the SWOG S0307 trial.[61] A systematic review by Varun et al[80] calculated that ONJ occurred in 2.8% of patients with breast cancer who had bone metastasis treated with zoledronic acid (typically 4 mg/mo) or pamidronate.

As development of ONJ is believed to be dependent on both dose and duration of treatment, trials of adjuvant zoledronic acid administered every 6 months, as is more often used in osteoporosis treatment, are also important. ONJ rates were 0.8% in the immediate administration arm of the E-ZO-FAST trial[44] (1.2% reported in ClinicalTrials.gov), 0.45% to 0.95% in the ZO-FAST trial,[43] and 2% (upfront arm) or 1% (delayed arm) in the NO3CC trial.[55] The Z-FAST trial included two suspected cases (0.67%); however, one case was ruled inconsistent with ONJ and the other had insufficient evidence for final evaluation.[41] No cases were found in the ABCSG-12 trial.[8] With clodronate, ONJ occurred in 0.06% of patients in the NSABP B-34 trial[27] and 0.3% in the SWOG S0307 trial. Published reviews of lower dose ibandronate for the treatment of postmenopausal osteoporosis (150 mg/mo orally, or 2 mg every 2 months or 3 mg every 3 months intravenously) reported benefit and with greater effect than a daily oral dose of 2.5 mg.[81,82] ONJ was not detected in the major RCTs, although there have been occasional case reports. Adjuvant studies of ibandronate at these lower doses in early breast cancer were not found.

The ABCSG-18 trial, which administered denosumab at 60 mg every 6 months, found 31 cases of suspected ONJ, but none met the diagnosis after further investigation.

Other adverse effects. The EGCTCG meta-analysis indicates that impaired renal function is a known adverse effect, but gives no incidence data. Dose modifications on the basis of renal function were part of the protocol in several trials. For example, in the AZURE trial,[31] dose reductions and interruptions for renal impairment (calculated creatinine clearance < 60 mL/min) were as specified by the current prescribing information. According to a review on safety and compliance,[83] renal effects are mainly found with bisphosphonates that are administered intravenously at high doses and depend on concentration and infusion rates. Clinically significant serum creatinine increases are rare with zoledronic acid that is administered at 4 mg over 15 min. Other transient acute-phase reactions for intravenous administration occur in approximately one third of patients and include low-grade fever, fatigue, arthralgia or myalgia, nausea, and increased bone pain. These effects were reported in the ABCSG-12 trial.[6] The E-ZO-FAST trial[44] also reported mild transient adverse events with zoledronic acid, including bone pain, pyrexia, and acute-phase reaction.

Serious ocular or ophthalmic adverse effects such as uveitis, scleritis, and episcleritis are extremely rare but may lead to blindness if untreated. The Tel Aviv trial[59] reported scleritis in one patient treated

Key points

- *ONJ incidence in patients receiving monthly doses of zoledronic acid for 6 months and then every 3 or 6 months thereafter was 1.5% to 2.1% in the AZURE/BIG 01/04 trial and 1.2% in the SWOG S0307 trial.*
- *Several smaller trials that administered zoledronic acid at 3 to 4 mg every 3 to 4 weeks for 1 to 2 years also reported ONJ (Washington University, 1.7%).*
- *As development of ONJ is believed to be dependent on both dose and duration of treatment, trials of adjuvant zoledronic acid administered every 6 months, as is more often used in osteoporosis treatment, are also important.*
- *ONJ rates were 0.8% in the immediate administration arm of the E-ZO-FAST trial (1.2% reported in ClinicalTrials.gov), 0.45% to 0.95% in the ZO-FAST trial, and 2% (upfront arm) or 1% (delayed arm) in the NO3CC trial.*
- *The EGCTCG meta-analysis indicates that impaired renal function is a known adverse effect, but gives no incidence data.*
- *According to a review on safety and compliance, renal effects are mainly found with bisphosphonates that are administered intravenously at high doses and depend on concentration and infusion rates.*

Key points

- *Clodronate is administered in large capsules taken daily, which may be difficult to swallow.*
- *Clodronate and ibandronate are to be taken on an empty stomach and require the patient to remain upright for at least 30 minutes.*
- *It is recognized that in many health care settings, bone-modifying agents such as bisphosphonates may currently be available, approved, and/or funded in specific doses and schedules only for the indications of improving bone mass and for treatment of bone metastases.*
- *Criteria for assessing patients for fracture risk were not evaluated in the preparation of this guideline, and other guidelines.*
- *None of the recommendations in this guideline are meant to restrict such use of bone-modifying agents in these situations, although they may influence the specific bisphosphonate selected when given for both bone health and adjuvant therapy.*
- *Of note, no attempt has been made to list all the potential adverse effects of drugs that are mentioned in this guideline, nor contraindications to their use. Drug monograms, formulary, or other prescribing information should be consulted.*

with zoledronic acid; serious ocular adverse events were not reported in the other trials in the current literature review. Symptoms such as ocular pain or loss of vision should be evaluated by an ophthalmologist;[84–86] immediate treatment with steroid eye drops may be required to prevent permanent blindness.[85,87,88]

Oral administration has low absorption (< 5%), and, therefore, high doses, which can cause esophagitis and other gastrointestinal events (mucositis, nausea, vomiting, and diarrhea) are required. Clodronate is administered in large capsules taken daily, which may be difficult to swallow. Clodronate and ibandronate are to be taken on an empty stomach and require the patient to remain upright for at least 30 minutes.

Recommendations, key evidence, and interpretation of evidence

Preamble and implementation considerations

The focus of this guideline is on the relapse and survival benefit of bone-modifying agents in nonmetastatic breast cancer. This guideline acknowledges that there is clear evidence for the use of bone-modifying agents such as bisphosphonates to reduce the risk of fragility fractures in at-risk populations (such as those with diagnosed low bone mass) and to treat metastatic cancer to the bone. In addition, it is recognized that in many health care settings, bone-modifying agents such as bisphosphonates may currently be available, approved, and/or funded in specific doses and schedules only for the indications of improving bone mass and for treatment of bone metastases. As such, users of this guideline should consider available resources and access—as well as any other barriers within their local health care settings—to using the treatments recommended in this guideline for adjuvant breast cancer.

Some of the trials in the literature review excluded patients with low BMD, previous or current bisphosphonate administration, or history of fractures and, thus, do not specifically address patients who are at high risk of fracture, other than as a result of other systemic treatment. Criteria for assessing patients for fracture risk were not evaluated in the preparation of this guideline, and other guidelines, such as those by Osteoporosis Canada,[89] the National Osteoporosis Guideline Group (United Kingdom),[90] and the National Osteoporosis Foundation (United States),[91] as well as the recent review of these by Black and Rosen,[92] should be consulted. None of the recommendations in this guideline are meant to restrict such use of bone-modifying agents in these situations, although they may influence the specific bisphosphonate selected when given for both bone health and adjuvant therapy. In patients who are prescribed these agents as adjuvant therapy, there may be an additional benefit on BMD.

Of note, no attempt has been made to list all the potential adverse effects of drugs that are mentioned in this guideline, nor contraindications to their use. Drug monograms, formulary, or other prescribing information should be consulted. ONJ is discussed in detail in the following recommendations and systematic review. Postmarketing surveillance has reported rare adverse effects, such as inflammatory eye reactions, renal toxicity, and atypical femoral fractures. The risk of renal toxicity and atypical femoral fractures may be increased at higher dosing and prolonged use. Acute inflammatory eye reactions, including conjunctivitis, uveitis, scleritis, episcleritis, and keratitis, are rare but warrant prompt evaluation by an ophthalmologist.[84–86] Treatment is commonly with ophthalmic corticosteroids.[85,87,88] Ongoing postmarketing surveillance of rare adverse effects associated with bisphosphonates is recommended.

Recommendation 1

It is recommended that administration of bisphosphonates as adjuvant therapy be

considered for postmenopausal patients with breast cancer (including patients premenopausal prior to treatment who have menopause induced by ovarian suppression as detailed in Recommendation 5) deemed candidates for adjuvant systemic therapy.

The final decision of whether or not to administer bisphosphonates should be made during consultation between the patient and oncologist, taking into account patient and disease characteristics, including risk of recurrence, and weighing the potential benefits and risks (adverse effects).

Qualifying statements for Recommendation 1

- While the EBCTCG meta-analysis[11] found benefit for bisphosphonates in all subgroups of postmenopausal patients, the absolute benefit was small. For patients with cancers assessed as having low risk of recurrence, the use of bisphosphonates may not result in clinically meaningful effect.
- Considerations in deeming patients at high enough recurrence risk to receive adjuvant systemic therapy may also apply in deciding on bisphosphonate use. The majority of patients (83%) in the meta-analysis had also received adjuvant chemotherapy. Standard clinical and pathologic risk factors and recognized clinical tools may be used, where applicable, to estimate risk of recurrence and mortality.[93,94]
- Risk factors for ONJ and renal impairment should be assessed (Recommendation 6).
- Patients should receive all other recommended breast cancer treatments, including surgery, radiation, and/or systemic therapy (see, for example, the CCO guideline on systemic therapy in early breast cancer).[93]
- There is no information to guide the use of bone-modifying agents for patients receiving systemic adjuvant therapy for completely resected local recurrence.

Key evidence for Recommendation 1

- The EBCTCG meta-analysis[11] found statistically significant benefit for bisphosphonates in all postmenopausal patients with breast cancer for bone recurrence (6.6% *vs*. 8.8%), fracture rates (9.1% *vs*. 10.3%), breast cancer mortality (14.7% *vs*. 18.0%), OS (any death, 21.1% *vs*. 23.5%), and outcomes that included bone recurrence (ie, distant recurrence, any recurrence). These differences did not vary as a function of treatment features (bisphosphonate class, treatment schedule, dose), tumor characteristics (hormone receptor status, nodal status, tumor grade), or concurrent chemotherapy. There was no statistically significant improvement in distant recurrence outside bone.
- Patients in all trials received chemotherapy and/or endocrine therapy. The exception is trials of clodronate, where this was not a condition of the trials or part of the protocol for three of the four main trials (see literature review Table 1); ≥ 95% received systemic treatment in the two largest trials[17,27] and 81% in the smaller German Adjuvant Breast Cancer Group trial.[21] There is therefore no evidence from adjuvant trials in patients not receiving systemic treatment.
- Data for patients with induced menopause (Recommendation 5) were included in the EBCTCG meta-analysis and come mainly from the ABCSG-12 trial.[8] Premenopausal patients received endocrine therapy (tamoxifen *vs*. anastrozole) along with goserelin for ovarian suppression. Zoledronic acid decreased risk of disease progression (HR, 0.77; $P = .042$) and improved DFS (88.4% *vs*. 85.0%; HR, 0.77; 95% CI, 0.60 to 0.99; $P = .042$). OS benefit was statistically significant up to 76 months of follow-up, but not at 94 months (OS, 96.1% *vs*. 94.4%; HR, 0.66; 95% CI, 0.43 to 1.02; $P = .064$). It should be noted that this follow-up is much longer than the 3-year duration of zoledronic acid administration.

Key points

- *While the EBCTCG meta-analysis found benefit for bisphosphonates in all subgroups of postmenopausal patients, the absolute benefit was small.*
- *For patients with cancers assessed as having low risk of recurrence, the use of bisphosphonates may not result in clinically meaningful effect.*
- *Considerations in deeming patients at high enough recurrence risk to receive adjuvant systemic therapy may also apply in deciding on bisphosphonate use.*
- *The majority of patients (83%) in the meta-analysis had also received adjuvant chemotherapy.*
- *Standard clinical and pathologic risk factors and recognized clinical tools may be used, where applicable, to estimate risk of recurrence and mortality.*
- *Risk factors for ONJ and renal impairment should be assessed (Recommendation 6).*
- *Patients should receive all other recommended breast cancer treatments, including surgery, radiation, and/or systemic therapy (see, for example, the CCO guideline on systemic therapy in early breast cancer).*
- *There is no information to guide the use of bone-modifying agents for patients receiving systemic adjuvant therapy for completely resected local recurrence.*

TABLE 1 - Ongoing or not fully reported trials

Trial name (NCT or other trial ID)	No. of patients and characteristics	Arms or comparison	Outcomes reported, notes
SWOG S0307[61,117] NCT00127205	N = 6,097 Age > 18 y	Clodronate (1,600 mg/d PO for 3 years) *vs.* ibandronate (50 mg/d PO for 3 years) *vs.* ZOL (4 mg IV every month × 6 then every 3 months × 2.5 years)	DFS (primary) in abstract only ONJ, fracture, adverse events (secondary) in abstract only Early reporting at 4th interim analysis; no realistic chance of statistically significant difference
TEAM IIb[77] BOOG 2006-04	N = 1,116 Postmenopausal, HR-positive, endocrine therapy	Ibandronate (50 mg/d for 3 years)	Ongoing, results not reported DFS (primary); metastasis, recurrence, OS, 5-year DFS, safety (secondary)
HOBOE, version 2 NCT00412022	N = 1,050 Original version (first 500 patients): age ≥ 18 years (triptorelin if premenopausal); letrozole in both arms Version 2 (after March 2010): premenopausal only; triptorelin + letrozole in both arms	ZOL, 4 mg every 6 months for 5 years	Enrollment complete, results not reported for version 2 or combined DFS (primary, version 2) BMD, OS, toxicity; DFS (original version; secondary)
Success A[78] NCT02181101 EUDRA-CT No. 2005-000490-21	N = 3,754 High-risk; adjuvant chemotherapy	ZOL, 2 years *vs.* 5 years ZOL at 4 mg IV every 3 months for 24 months v every 3 months for 24 months followed by every 6 months for 36 months	Ongoing, results not reported DFS (primary) OS, distant metastasis (secondary)
JONIE-1[66] UMIN000003261	N = 188 Age 20–70 years	ZOL (4 mg IV over 15 min, every 3–4 weeks for 6 months)	pCR (primary) DFS (secondary) in abstract only; follow-up to 2017 planned
Z-FAST Study-Japan[71,72] UMIN000001104	N = 204 Postmenopausal, HR-positive, adjuvant letrozole	ZOL Upfront or delayed start; 4 mg IV every 6 months for 5 years	BMD (primary) reported at 12 months Fracture, adverse events, BMD (secondary) at 36 months in abstract only
CHO-BC-039 NCT02595138	N = 430 (planned) Triple-negative	ZOL	Started 2015, ongoing DFS (primary) OS, adverse effects (secondary)
ABCSG-18[62,63] NCT00556374	N = 3,420 Postmenopausal, HR-positive, receiving nonsteroidal aromatase inhibitors	Denosumab (60 mg SC every 6 months) *vs.* placebo	Time to clinical fracture (primary) DFS (secondary) in abstract only Patients on placebo may switch to denosumab in 2016, follow-up will be ongoing

TABLE 1 - Ongoing or not fully reported trials (*continued*)

Trial name (NCT or other trial ID)	No. of patients and characteristics	Arms or comparison	Outcomes reported, notes
D-CARE[74] NCT01077154	N = 4,500 High risk	Denosumab (120 mg SC monthly for 6 months, then every 3 months for total of 5 years) v placebo	Enrollment completed 2012, ongoing administration of denosumab (5 years) and planned 7.5 years follow-up, no results reported Primary: bone metastasis free survival Secondary: DFS, OS, safety
GeparX[125] NCT02682693	N = 778 (planned) cT1c-cT4a-d BC; HR–; assessed HER2, Ki-67, TIL and RANK status	Neoadjuvant chemotherapy with or without denosumab (120 mg SC every 4 weeks × 6)	Primary: pCR (ypT0 ypN0) Secondary: breast conservation rates, toxicity, compliance, survival

BMD, bone mineral density; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor positive; HR–, hormone receptor negative; IV, intravenously; NCT, National Clinical Trial number; ONJ, osteonecrosis of the jaw; OS, overall survival; pCR, pathologically complete response; PO, orally; SC, subcutaneously; ZOL, zoledronic acid.

Interpretation of evidence for Recommendation 1

- While the EBCTCG meta-analysis indicated a statistically significant survival benefit for all postmenopausal patients, absolute benefit was small and will depend on risk of cancer recurrence. Some of the trials that were included in the meta-analysis were designed with noncancer primary end points such as BMD and were not powered for OS or DFS. Some panelists expressed concern about the methodology of these studies and the meta-analysis. The authors considered the use of bisphosphonates at the recommended levels (Recommendation 4) to have a relatively low risk of ONJ or other serious adverse effects, and, therefore, benefits in reducing bone recurrence and improving survival generally outweigh the risks for most postmenopausal patients (see Recommendations 2 and 4 for further discussion of adverse effects). However, for patients with pre-existing conditions (Recommendation 6) or with very low risk of recurrence, the risk of toxicity may indeed outweigh the benefits. Some of the coauthors expressed uncertainty about recommending adjuvant bisphosphonates for patients with a low risk of breast cancer recurrence. Evidence is insufficient to determine precise subgroups of patients who would or would not benefit, and therefore, the recommendation *to consider* use for all patients who are deemed at high enough risk of relapse to warrant standard adjuvant systemic therapy was deemed most appropriate.
- Some of the guideline authors suggested caution in assuming very young patients (≤ 40 years of age) on ovarian suppression have estrogen levels at a postmenopausal level, and therefore, it is unclear whether they should be considered truly postmenopausal (Recommendation 5).

Recommendation 2

Zoledronic acid and clodronate are the recommended bisphosphonates for adjuvant therapy in breast cancer.

There is a need for more information comparing different agents and schedules, and it is recommended that such trials be conducted to establish the utility and optimal

Key points

- *Some of the trials that were included in the meta-analysis were designed with noncancer primary end points such as BMD and were not powered for OS or DFS.*
- *Some panelists expressed concern about the methodology of these studies and the meta-analysis.*
- *The authors considered the use of bisphosphonates at the recommended levels (Recommendation 4) to have a relatively low risk of ONJ or other serious adverse effects.*
- *The recommendation* to consider *use for all patients who are deemed at high enough risk of relapse to warrant standard adjuvant systemic therapy was deemed most appropriate.*

Key points

- *Preliminary data from the SWOG S0307 trial suggest that clodronate, ibandronate, and zoledronic acid may provide similar DFS and OS benefit.*
- *Full publication of the SWOG S0307 trial and results of the TEAM IIb (BOOG 2006-04) trial may support adjuvant ibandronate use.*
- *There is a large difference in ibandronate dosage between these trials (50 mg/d) and that used in treating osteoporosis (150 mg/mo orally or 3 mg every 3 months intravenously).*
- *Further trials with adequate power and primary outcomes of DFS and OS are required to determine the optimal agent and dosing schedule.*
- *The EBCTCG meta-analysis found that, in postmenopausal patients, clodronate (1,600 mg/d for 2 to 3 years) significantly reduced bone recurrence (4.6% vs. 7.0%; RR, 0.57; 95% CI, 0.41 to 0.79; P = .0007), breast cancer mortality (10.6% vs. 14.2%; RR, 0.66; 95% CI, 0.52 to 0.83; P = .0004).*
- *The GAIN trial found no survival benefit for ibandronate compared with placebo. Preliminary results of the SWOG S0307 trial, which was conducted in women age > 18 years, show no significant survival differences between clodronate, ibandronate, and zoledronic acid.*

administration of other bisphosphonates for adjuvant therapy.

Qualifying statements for Recommendation 2

- Preliminary data from the SWOG S0307 trial[60,61] suggest that clodronate, ibandronate, and zoledronic acid may provide similar DFS and OS benefit. However, as these data have, to date, only been published in abstract form, no definitive recommendations regarding ibandronate can yet be made. Full publication of the SWOG S0307 trial and results of the TEAM IIb (BOOG 2006-04) trial[77] may support adjuvant ibandronate use. There is a large difference in ibandronate dosage between these trials (50 mg/d) and that used in treating osteoporosis (150 mg/mo orally or 3 mg every 3 months intravenously). This dosage difference should be considered in future comparisons.
- Clodronate has not been studied specifically in patients receiving AIs.
- While the direct evidence from adjuvant trials is considered sufficient only for zoledronic acid and clodronate, others have hypothesized that any agent proven to reduce the risk of fragility fractures in at-risk populations (eg, patients with postmenopausal or drug-induced osteoporosis) may be effective as adjuvant therapy for breast cancer. Given orally for osteoporosis treatment, alendronate has been used daily or weekly, while risedronate and ibandronate have been used daily, weekly, or monthly.[81] Ibandronate has also been used intravenously. Less frequent administration compared with clodronate may make these agents preferable to patients if shown to be of adjuvant benefit. Further trials with adequate power and primary outcomes of DFS and OS are required to determine the optimal agent and dosing schedule.
- Different adverse effect profiles, frequency and route of administration, cost, and regulatory approval may influence selection.

Key evidence for Recommendation 2

- The EBCTCG meta-analysis[11] found that, in postmenopausal patients, clodronate (1,600 mg/d for 2 to 3 years) significantly reduced bone recurrence (4.6% *vs*. 7.0%; RR, 0.57; 95% CI, 0.41 to 0.79; *P* = .0007), breast cancer mortality (10.6% *vs*. 14.2%; RR, 0.66; 95% CI, 0.52 to 0.83; *P* = .0004), any death (17.4% *vs*. 21.3%; RR, 0.77; 95% CI, 0.64 to 0.93; *P* = .005), and fractures (8.4% *vs*. 10.7%; RR, 0.77; 95% CI, 0.59 to 0.99; *P* = .05). As indicated in the evidence review, clodronate trials were completed several years ago, and results are based on at least 5 to 10 years follow-up.
- The EBCTCG meta-analysis found that, in postmenopausal patients, zoledronic acid reduced bone recurrence (3.4% *vs*. 4.5%; RR, 0.73; 99% CI, 0.53 to 1.00); the difference in breast cancer mortality was not statistically significant (7.1% *vs*. 7.9%; RR, 0.88; 99% CI, 0.69 to 1.11). For trials with longer (3 to 5 years) zoledronic acid treatment, bone recurrence was 3.4% with zoledronic acid versus 4.6% without (RR, 0.72; 95% CI, 0.57 to 0.92; *P* = .008) and mortality was 8.8% versus 9.8% (RR, 0.87; 95% CI, 0.74 to 1.03; *P* = .10).
- The GAIN trial[30] found no survival benefit for ibandronate compared with placebo. Preliminary results of the SWOG S0307 trial,[60,61] which was conducted in women age > 18 years, show no significant survival differences between clodronate, ibandronate, and zoledronic acid. Further details from a full publication of this trial are required.
- The EBCTCG concluded that no benefit was seen with pamidronate (based on the DBCG 89D trial[28,29]), and numbers were insufficient to assess the efficacy of oral risedronate or alendronate, which are standard treatments for osteoporosis.

Interpretation of evidence for Recommendation 2

- The authors believe the evidence is insufficient to distinguish between clodronate and zoledronic acid. Other

bisphosphonates such as ibandronate may be effective but evidence is more limited. A dissenting opinion among the coauthors was that ibandronate has sufficient evidence for use as adjuvant therapy.

- The authors consider it desirable to have multiple agents with different modes of administration, even if efficacy is similar. Patient preference, regulatory approval, cost, and availability may be factors. Some issues to consider are as follows:
  - Oral bisphosphonates, including daily clodronate, are more likely to cause GI adverse effects than intravenous drugs and can be difficult to swallow for some patients; these issues maybe be especially important for elderly patients and those with gastroesophageal problems.[88,95] Some patients prefer oral medication because a hospital visit is not required.
  - Zoledronic acid is given intravenously and therefore may have a higher compliance rate than that of daily oral medications such as clodronate. Administration once every 6 months is considered more convenient to some patients. Acute-phase response resulting in mild-to-moderate flu-like symptoms may occur after intravenous administration.
  - Some publications indicate a lower risk of renal problems and ONJ with clodronate compared with zoledronic acid; however, comparisons included patients administered zoledronic acid more frequently (monthly) as is used for metastatic disease. As more frequent or higher doses are known to increase the risk of ONJ, these trials may not be directly comparable. Considering trials of zoledronic acid at 4 mg every 6 months, the ABCSG-12 trial[8] found no cases of ONJ, while 0.8% of patients in the E-ZO-FAST trial[44] and 0.45% to 0.95% of patients in the ZO-FAST trial[43] developed ONJ.

Recommendation 3

While results for adjuvant denosumab look promising, data are insufficient at this time to make any recommendation regarding its use in the adjuvant setting.

It is recommended that studies directly comparing denosumab with bisphosphonates and evaluating administration schedules be conducted.

Qualifying statements for Recommendation 3

- While the ABCSG-18 trial studied denosumab use in postmenopausal women with hormone receptor–positive breast cancer receiving AIs and found clear fracture reduction benefit,[62] DFS results have only been reported as a conference presentation or abstract.[63,64] As survival data have, to date, only been published in abstract form, no definitive recommendations can yet be made. Results are promising but limited compared with the body of evidence for bisphosphonates. Further results of the ABCSG-18 and D-CARE trials[74] may provide stronger evidence for adjuvant denosumab use.

Key evidence for Recommendation 3

- In the ABCSG-18 trial,[63] DFS at a median of 4 years follow-up was 90.2% versus 88.1% (HR, 0.816; $P = .051$). In subgroup analysis, DFS benefit appeared greater for patients with tumor size > 2 cm (28% of patients; HR, 0.66; $P = .016$) and those who were estrogen and progesterone receptor positive (83% of patients; HR, 0.75; $P = .013$).[62,63] The magnitude of DFS benefit in the ABCSG-18 trial is comparable to that found in the EBCTCG meta-analysis for bisphosphonates.[63] These data have only been published as an abstract; further DFS follow-up and OS results are pending.
- The patient incidence of adverse events in the ABCSG-18 trial[62] did not differ between the denosumab group (1,366 events [80%]) and the placebo group (1,334 events [79%]), nor did the numbers of serious adverse events (521 *vs*. 511 [30% in each group]). There was no increased risk of hypocalcemia (0.1% with denosumab *vs*. 0.2% placebo),

Key points

- *The authors consider it desirable to have multiple agents with different modes of administration, even if efficacy is similar. Patient preference, regulatory approval, cost, and availability may be factors.*
- *Oral bisphosphonates, including daily clodronate, are more likely to cause GI adverse effects than intravenous drugs and can be difficult to swallow for some patients.*
- *Zoledronic acid is given intravenously and therefore may have a higher compliance rate than that of daily oral medications such as clodronate.*
- *Some publications indicate a lower risk of renal problems and ONJ with clodronate compared with zoledronic acid; however, comparisons included patients administered zoledronic acid more frequently (monthly) as is used for metastatic disease.*
- *It is recommended that studies directly comparing denosumab with bisphosphonates and evaluating administration schedules be conducted.*
- *As survival data have, to date, only been published in abstract form, no definitive recommendations can yet be made. Results are promising but limited compared with the body of evidence for bisphosphonates.*

Key points

- *In the ABCSG-18 trial, time to occurrence of clinical fractures was significantly delayed by denosumab (HR, 0.5; 95% CI, 0.39 to 0.65; P < .001). Clinical fracture rates were 5.0% versus 9.6% at 36 months and 11.1% versus 26.2% at 84 months.*
- *The ABCSG-18 trial provides limited data on DFS benefit (abstract only), along with stronger evidence of benefit in reducing fracture risk.*
- *As the various bisphosphonates and denosumab have different routes and frequency of administration, mechanism of action, and adverse effect profiles, the authors considered that denosumab may be more appropriate for some patients.*
- *Some of the coauthors strongly opposed any recommendation regarding denosumab due to the limited data, and all eventually agreed that while data from the ABCSG-18 trial suggest that use of adjuvant denosumab may be of benefit.*
- *The D-CARE trial completed enrollment in late 2012; with 5 years of denosumab administration and 7.5 years of follow-up, the trial is not expected to be completed until 2022.*
- *The optimal dose and schedule of administration of zoledronic acid and clodronate have not been determined; however, the recommended doses and schedules have been found effective in many of the adjuvant breast cancer trials.*

renal or urinary disorders (2.5% *vs*. 3.1% overall; 0.8% *vs*. 0.6% serious), and no confirmed cases of ONJ. Increased rates of ONJ and hypocalcemia have been found in metastatic trials[96–98] that used higher dosages of denosumab (120 mg monthly metastatic *vs*. 60 mg every 6 months adjuvant).

- In the ABCSG-18 trial, time to occurrence of clinical fractures was significantly delayed by denosumab (HR, 0.5; 95% CI, 0.39 to 0.65; *P* < .001). Clinical fracture rates were 5.0% versus 9.6% at 36 months and 11.1% versus 26.2% at 84 months.[62]

Interpretation of evidence for Recommendation 3

- The ABCSG-18 trial provides limited data on DFS benefit (abstract only), along with stronger evidence of benefit in reducing fracture risk.
- As the overall evidence is stronger for adjuvant bisphosphonates (Recommendation 1) than denosumab and no adjuvant trials directly comparing denosumab with bisphosphonates have been completed, the authors considered it premature to recommend denosumab for general use in adjuvant therapy. There was considerable discussion as to whether to recommend use in selected patients.
- Some of the authors suggested denosumab (60 mg subcutaneously every 6 months for 3 to 5 years) be considered as an alternative to bisphosphonates in patients for whom bisphosphonates would otherwise be recommended but are not suitable due to compliance, intolerance, administration difficulty, or availability.
- As the various bisphosphonates and denosumab have different routes and frequency of administration, mechanism of action, and adverse effect profiles, the authors considered that denosumab may be more appropriate for some patients. The ability to swallow oral medication, distance from hospital facilities for intravenous administration, differential costs to patients or hospitals, intolerance, compliance, and regulatory approval were considered by the authors as factors that may influence drug selection.
- Some of the coauthors strongly opposed any recommendation regarding denosumab due to the limited data, and all eventually agreed that while data from the ABCSG-18 trial suggest that use of adjuvant denosumab may be of benefit, evidence is insufficient at this time to make a recommendation. Further data from the ABCSG-18 trial and D-CARE trial is awaited. The D-CARE trial completed enrollment in late 2012;[74] with 5 years of denosumab administration and 7.5 years of follow-up, the trial is not expected to be completed until 2022.[99]

Recommendation 4

For patients who will receive adjuvant bisphosphonates (Recommendation 1), zoledronic acid at 4 mg intravenously over 15 min (or longer) every 6 months for 3 to 5 years or clodronate orally at 1,600 mg/d for 2 to 3 years are recommended. Different durations may be considered.

More research is recommended comparing different bone-modifying agents, doses, dosing intervals, and durations.

Qualifying statements for Recommendation 4

- In jurisdictions where the recommendation cannot be followed due to availability, similar doses and schedules of zoledronic acid or clodronate are considered reasonable.
- The optimal dose and schedule of administration of zoledronic acid and clodronate have not been determined; however, the recommended doses and schedules have been found effective in many of the adjuvant breast cancer trials (see evidence review) and result in fewer or less severe adverse effects than regimens used in patients with metastatic disease (ie, 4 mg zoledronic acid every 3 to 4 weeks).

- The optimal duration of adjuvant bone-targeted agents has not been determined; the recommendations reflect durations found effective in the EBCTCG meta-analysis and other trials included in the literature review. It is unclear whether there is benefit to longer-term administration, although studies indicate that the benefit of bisphosphonates continues after administration is stopped due to the persistence of the drug within the bone. There are concerns about adverse effects, such as atypical bone fracture based on reports from the osteoporosis literature, and some osteoporosis recommendations allow a treatment holiday from bisphosphonates after 3 to 5 years for patients with a lower risk of fracture.[92,100]
- Administration of clodronate for > 3 years or zoledronic acid for > 5 years has not been evaluated in adjuvant trials, and, therefore, a recommendation of longer duration is not supported at this time. This limitation in the evidence may be especially relevant to patients receiving long-term endocrine therapy, as the recent CCO guideline on systemic treatment[93] includes recommendations for endocrine therapy for up to 10 years based primarily on results from the ATLAS, aTTom, and MA.17 trials.
- The optimal timing to start bisphosphonates after diagnosis of breast cancer is unclear; however, most of the clinical trials started soon after surgery or chemotherapy.

Key evidence for Recommendation 4

- In the EBCTCG meta-analysis,[11] clodronate 1,600 mg/d for 2 to 3 years or zoledronic acid for 3 to 5 years decreased bone recurrence and improved survival (Recommendation 2).
- The meta-analysis did not find a significant difference between low (osteoporosis) and high (cancer metastasis) dose or frequency, but did not subdivide results according to bisphosphonate used. For zoledronic acid, almost all data come from trials of 3 to 5 years administration. Zoledronic acid was used at 4 mg every 6 months in the ABCSG-12 trial[8] and Z-FAST/ZO-FAST/E-ZO-FAST trials[39,41,42] (these trials were conducted in patients receiving endocrine therapy, with primary outcomes of the latter studies being preservation of BMD) and at 4 mg every 3 to 4 weeks (with decreased frequency after six cycles) in the AZURE/BIG 1-04 trial.[9,10,31,32] Adverse events, including ONJ (Recommendation 6) are greater with more frequent administration.
- In most trials, bisphosphonate was started soon after surgery or chemotherapy (within 0 to 12 weeks; see evidence review). In the ZO-FAST trial[42,43] of immediate versus delayed administration of zoledronic acid (until decline in bone density or fracture), DFS and BMD were better with immediate administration, although there was still a DFS benefit (HR, 0.46; $P = .0334$) of starting later compared with none at all.[43]

Interpretation of evidence for Recommendation 4

- As indicated in the Qualifying Statements, optimal dose and timing are unclear, and therefore, we consider those used in the adjuvant and osteoporosis trials to be appropriate. The lower frequency of zoledronic acid (4 mg every 6 months) results in fewer adverse effects than more intensive treatment (eg, 4 mg monthly). While zoledronic acid at 4 mg/month was effective in the AZURE trial (stage II to III cancers), there has been no direct comparison with lower frequency; in the absence of comparative efficacy data but established adverse effects, we are unable to recommend more intensive treatment in the adjuvant setting. We consider it plausible that the risk-benefit balance of more frequent administration may depend on disease stage.
- The authors debated whether to make a recommendation regarding timing of bisphosphonate initiation. It was initially proposed bisphosphonates be started within 6 months of completion

Key points

- *The optimal duration of adjuvant bone-targeted agents has not been determined; the recommendations reflect durations found effective in the EBCTCG meta-analysis and other trials included in the literature review.*
- *It is unclear whether there is benefit to longer-term administration, although studies indicate that the benefit of bisphosphonates continues after administration is stopped due to the persistence of the drug within the bone.*
- *Administration of clodronate for > 3 years or zoledronic acid for > 5 years has not been evaluated in adjuvant trials, and, therefore, a recommendation of longer duration is not supported at this time.*
- *The optimal timing to start bisphosphonates after diagnosis of breast cancer is unclear; however, most of the clinical trials started soon after surgery or chemotherapy.*
- *The meta-analysis did not find a significant difference between low (osteoporosis) and high (cancer metastasis) dose or frequency, but did not subdivide results according to bisphosphonate used.*
- *In most trials, bisphosphonate was started soon after surgery or chemotherapy (within 0 to 12 weeks; see evidence review).*

Key points

- *For purposes of adjuvant bisphosphonate use, the definition of menopause should include both natural menopause and menopause induced by ovarian ablation or suppression.*
- *In women age ≤ 60 years with a previous hysterectomy and ovaries left in place, luteinizing hormone, follicle-stimulating hormone, and serum estradiol should be in the postmenopausal range and measured prior to initiation of any systemic therapy to receive adjuvant bisphosphonates.*
- *As indicated in the recent CCO guideline on systemic therapy in early breast cancer, assessing menopausal status is difficult in patients age ≤ 60 years experiencing amenorrhea secondary to chemotherapy or tamoxifen.*
- *Cessation of menses does not necessarily denote the absence of ovarian function, and premenopausal estradiol levels can be found in patients with transient chemotherapy-induced amenorrhea.*
- *The meta-analysis did not attempt to look at these separately. Most postmenopausal patients were naturally postmenopausal, with the exception being the ABCSG-12 trial conducted in patients with induced menopause.*

of chemotherapy, as this would cover the various timings used in the RCTs as well as concerns some of the authors had about overlapping toxicities of chemotherapy and bisphosphonates, GI effects in particular. While the ZO-FAST trial results suggest immediate initiation is preferable but delayed initiation of zoledronic acid is better than none, this trial was designed primarily as a BMD trial and was not considered sufficient to make a recommendation. As the other included RCTs did not compare timing of initiation, the authors decided not to make any recommendation in this regard.

Recommendation 5

For purposes of adjuvant bisphosphonate use, the definition of menopause should include both natural menopause (at least 12 months of amenorrhea prior to initiation of chemotherapy or endocrine therapy) and menopause induced by ovarian ablation or suppression (but not the cessation of menses due to chemotherapy alone). In women age ≤ 60 years with a previous hysterectomy and ovaries left in place, luteinizing hormone, follicle-stimulating hormone, and serum estradiol should be in the postmenopausal range and measured prior to initiation of any systemic therapy to receive adjuvant bisphosphonates.

Qualifying statements for Recommendation 5

- As indicated in the recent CCO guideline on systemic therapy in early breast cancer,[93] assessing menopausal status is difficult in patients age ≤ 60 years experiencing amenorrhea secondary to chemotherapy or tamoxifen. Cessation of menses does not necessarily denote the absence of ovarian function, and premenopausal estradiol levels can be found in patients with transient chemotherapy-induced amenorrhea.[101] In addition, hormone levels and the absence of menses are unreliable indicators of menopause during treatment with tamoxifen.[102]
- Some publications have suggested that patients experiencing chemotherapy-induced amenorrhea are at high risk for adverse bone effects and may be candidates for bone-modifying agents. Evidence is insufficient to address the use of these agents as adjuvant treatment in this population.

Key evidence for Recommendation 5

- In the EBCTCG meta-analysis,[11] subgroup investigations considered patients postmenopausal if they had undergone either natural or induced menopause, with the latter being either potentially reversible using luteinizing hormone–releasing hormone analogs or permanent by oophorectomy. The meta-analysis did not attempt to look at these separately. Most postmenopausal patients were naturally postmenopausal, with the exception being the ABCSG-12 trial[8] conducted in patients with induced menopause. A small proportion of patients in the ZO-FAST[42,43] and E-ZO-FAST trials[44] (17% and 16% of patients, respectively), and approximately one half of patients in the HOBOE trial,[52] also had induced menopause; these trials provided a relatively small contribution compared with the ABCSG-12 trial.
- The ABCSG-12 trial[8] studied the use of zoledronic acid in premenopausal patients undergoing treatment with goserelin for ovarian suppression and randomly assigned to either tamoxifen or anastrozole. Zoledronic acid improved risk of disease progression (HR, 0.77; $P = .042$) and DFS (88.4% *vs*. 85.0%; HR, 0.77; 95% CI, 0.60 to 0.99; $P = .042$) up to the last follow-up (median 94 months), and OS up to 76 months; the trend for OS continued but was no longer statistically significant at 94 months (HR, 0.66; $P = .064$; Recommendation 1).

Interpretation of evidence for Recommendation 5

- As the EBCTCG meta-analysis authors included both natural and induced menopausal patients to derive their conclusions, we have also used this definition. Of note, evidence in induced

menopausal patients is weaker as it is derived from only one trial.
- Some of the guideline authors suggested caution in assuming very young patients (age ≤ 40 years) on ovarian suppression have estrogen levels at a postmenopausal level, and therefore, it is unclear whether they should be considered truly postmenopausal.

Recommendation 6

A dental assessment is recommended, where feasible, prior to commencement of bisphosphonates, and any pending dental or oral health problems should be dealt with prior to starting treatment, if possible. Patients should be informed of the risk of developing ONJ, especially with tooth extractions and other invasive dental procedures. Patients should inform their dental practitioner of their treatment. Patients with suspected ONJ should be referred to a dental practitioner with expertise in treating this condition. Recent guidelines or position papers by groups such as the International Task Force on Osteonecrosis of the Jaw,[103] the American Association of Oral and Maxillofacial Surgeons,[104] and the American Dental Association[105,106] should be consulted.

Patients should have serum calcium measured prior to starting treatment. Patients receiving intravenous bisphosphonates (zoledronic acid) should be monitored for renal function prior to starting this treatment and for serum calcium and increase in serum creatinine throughout the treatment period.

Calcium and vitamin D supplementation is recommended unless otherwise contraindicated. Oral bisphosphonates and calcium should not be taken concurrently; several monographs suggest an interval of at least 2 hours to allow for maximum absorption.

Symptoms such as ocular pain or loss of vision may be due to serious inflammatory conditions such as uveitis or scleritis and should be promptly evaluated by an ophthalmologist.

Qualifying statements for Recommendation 6

- The risk of ONJ increases with frequency, dose, and duration of bisphosphonate administration. Risk can be reduced with appropriate screening prior to treatment and modification of dental care. Risk of ONJ when bisphosphonates are administered, as suggested in Recommendation 4, is lower than for patients receiving higher doses or more frequent administration as is used for cancers with bone metastasis.
- Some organizations advise dental assessment and care prior to any cancer treatment, preferably as soon as possible after diagnosis to allow time for dental procedures and adequate healing prior to treatment.[107–111]
- The CCO formulary monograph for zoledronic acid recommends "comprehensive dental evaluation of both hard and soft tissues before starting bisphosphonate treatment; undergo invasive dental procedures, if needed, before starting bisphosphonate treatment."[112(p5)] US Food and Drug Administration (US FDA) prescribing information for zoledronic acid indicates that "cancer patients should maintain good oral hygiene and should have a dental examination with preventative dentistry prior to treatment with bisphos phonates."[113(p5),114(p2)]
- It is unclear whether bone-modifying therapy should be withheld if invasive dental treatment is required. Some have hypothesized that withholding bone-modifying therapy may allow better bone healing and suggested stopping treatment 2 months prior to oral surgery and delaying restarting until osseous healing has occurred. The alternative view is that a short break in bisphosphonate administration will have no effect, as bone effects of bisphosphonates are maintained for years after treatment stops.
- Hypocalcemia is a known adverse effect of bisphosphonate treatment, especially with the higher doses and more frequent

Key points

- *Some of the guideline authors suggested caution in assuming very young patients (age ≤ 40 years) on ovarian suppression have estrogen levels at a postmenopausal level, and therefore, it is unclear whether they should be considered truly postmenopausal.*
- *A dental assessment is recommended, where feasible, prior to commencement of bisphosphonates, and any pending dental or oral health problems should be dealt with prior to starting treatment, if possible.*
- *Patients with suspected ONJ should be referred to a dental practitioner with expertise in treating this condition.*
- *Patients receiving intravenous bisphosphonates (zoledronic acid) should be monitored for renal function prior to starting this treatment and for serum calcium and increase in serum creatinine throughout the treatment period.*
- *Calcium and vitamin D supplementation is recommended unless otherwise contraindicated. Oral bisphosphonates and calcium should not be taken concurrently.*
- *The risk of ONJ increases with frequency, dose, and duration of bisphosphonate administration. Risk can be reduced with appropriate screening prior to treatment and modification of dental care. Risk of ONJ when bisphosphonates are administered, as suggested in Recommendation 4.*

Key points

- *There is conflicting evidence as to whether inflammatory eye conditions are directly caused by bisphosphonates or in conjunction with some underlying inflammatory disease process.*
- *As development of ONJ is believed to be dependent on dose and duration of treatment, trials of adjuvant zoledronic acid administered every 6 months, as is more often used in osteoporosis treatment, may be more relevant.*
- *ONJ rates were 0.8% in the immediate administration arm of the E-ZO-FAST trial, 0.45% to 0.95% in the ZO-FAST trial, and 2% (upfront arm) or 1% (delayed arm) in the NO3CC trial.No cases were found in the ABCSG-12 trial.*
- *ONJ was not detected in the major RCTs, although there have been occasional case reports. Adjuvant studies of ibandronate at these lower doses in early breast cancer were not found.*
- *Ocular effects were not noted in the RCTs in the literature review, other than one case of scleritis; trials were too small and not designed to detect rare events.*
- *A recent RCT of intravenous zoledronate for osteopenia found acute anterior uveitis in 8 of 1,001 patients (six had mild-to-moderate uveitis and two had severe uveitis).*

administration given to patients with metastatic cancer. It is relatively rare (< 1%) at lower doses (Recommendation 4) in patients without pre-existing conditions such as renal insufficiency and who have adequate vitamin D status and calcium intake.
- There is conflicting evidence as to whether inflammatory eye conditions are directly caused by bisphosphonates or in conjunction with some underlying inflammatory disease process;[115] however, if not treated promptly, these conditions may lead to blindness. Discontinuation of bisphosphonates may be necessary.[116]

Key evidence for Recommendation 6

- Many recent trials[10,44,51,53,55,74,77,79] excluded patients with current active dental problems involving the jawbone or with recent or planned dental or jaw surgery, including tooth extraction or implants (see Evidence Review). SWOG S0307 required a dental exam within 6 months prior to initiation of treatment.[117] ONJ incidence in patients receiving 6 monthly doses of zoledronic acid and then every 3 or 6 months thereafter was 1.5% to 2.1% in the AZURE/BIG 01/04 trial[32] and 1.2% in the SWOG S0307 trial.[61] With ibandronate (50 mg/d), ONJ occurred in 0.1% of patients in the GAIN trial[30] and in 0.6% of patients in the SWOG S0307 trial.[61]
- As development of ONJ is believed to be dependent on dose and duration of treatment, trials of adjuvant zoledronic acid administered every 6 months, as is more often used in osteoporosis treatment, may be more relevant. ONJ rates were 0.8% in the immediate administration arm of the E-ZO-FAST trial,[44] 0.45% to 0.95% in the ZO-FAST trial,[43] and 2% (upfront arm) or 1% (delayed arm) in the NO3CC trial.[55] No cases were found in the ABCSG-12 trial.[8]
- With clodronate, ONJ occurred in 0.06% of patients in the NSABP B-34 trial[27] and 0.3% in the SWOG S0307 trial.[61] Published reviews of lower-dose ibandronate in the treatment of postmenopausal osteoporosis (150 mg/mo orally, or 2 mg every 2 months or 3 mg every 3 months intravenously) reported a benefit and with greater effect than a daily oral dose of 2.5 mg.[81,82] ONJ was not detected in the major RCTs, although there have been occasional case reports. Adjuvant studies of ibandronate at these lower doses in early breast cancer were not found.
- Most trials gave (or recommended) supplemental vitamin D (400 to 800 IU) and calcium (500 to 1,000 mg). While these were primarily to maintain BMD, it has been suggested they may also minimize mild anemia and serum electrolyte imbalances associated with intravenous bisphosphonates[83] and decrease the risk of osteoclast inhibition–induced hypocalcemia.[118] Trials in metastatic cancer found increased risk of hypocalcemia with denosumab and, thus, a need to monitor for this adverse effect.[88,119] Lower doses of denosumab were used in the ABCSG-18[62] and Freedom trials[120] and resulted in no increase in hypocalcemia.
- Ocular effects were not noted in the RCTs in the literature review, other than one case of scleritis;[59] trials were too small and not designed to detect rare events. A recent RCT of intravenous zoledronate for osteopenia found acute anterior uveitis in 8 of 1,001 patients (six had mild-to-moderate uveitis and two had severe uveitis[85]). Other evidence is mainly from case studies,[121,122] retrospective cohort studies,[86] and adverse effect reporting.[116]

Interpretation of evidence for Recommendation 6

- The evidence suggests risks of adverse effects are low when bone-modifying agents are given at doses in Recommendation 4 and the precautions suggested above are followed.
- The authors agreed that optimizing dental health is always ideal, but there was dissention on whether dental assessment prior to treatment should be required in

all patients. As noted in the key evidence, several trials excluded patients with current dental problems and therefore do not provide evidence for or against dental assessment and treatment. Some coauthors believed it a wise precaution without attendant risk. Others stated there was no evidence it would make a difference in outcomes, that some patients may not have or be able to afford dental care, or that there could be other resource implications. The recommendation therefore contains a proviso, "where feasible."

Other implementation considerations

- It is desirable to have multiple agents with different modes of administration (Recommendation 2).
- As with any novel therapy or new indication for existing medications, cost, access, funding, and drug approval need to be considered in the implementation of treatment recommendations. As mentioned in the preamble of this article, several health care settings currently may only have access to bone-modifying agents to improve bone density or for treatment of metastatic cancer. As such, drug formularies and governing bodies may need to revise approved dose and scheduling parameters for these relevant medications before clinicians may be able to use them. As examples in North America:
  - Zoledronic acid has recently been added to the CCO Drug Formulary (April 2016)[112] for adjuvant treatment of breast cancer in postmenopausal women. Clodronate thus far only has Health Canada Approval for the management of hypercalcemia of malignancy and for treatment of bone metastases, and is included in the CCO Formulary[84] and British Columbia Cancer Agency Cancer Drug Manual[123] for these purposes.
  - Zoledronic acid is approved in the United States for treatment of low bone mass and metastatic disease, and clodronate is not available.
  - Ibandronate is not currently approved for use in Canada. It is approved by the US FDA for the prevention or treatment of postmenopausal osteoporosis.
  - Direct patient cost and health system resource impact should be considered in implementing such recommendations.

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers as well as to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

Limitations of the research and future research

There is an urgent need for trials that directly compare different bone-modifying agents and different doses, schedules, and durations of therapy. Some of the ongoing trials listed in Table 1 may eventually contribute important information. The authors also suggest the following trials be conducted:

- Comparison of single zoledronic acid infusion[124] versus zoledronic acid every 6 months for seven infusions.
- Denosumab versus zoledronic acid every 6 months for seven infusions.
- Denosumab versus clodronate.
- Zoledronic acid versus denosumab: once versus every 6 months versus yearly for 2 or 5 years.
- Risedronate or alendronate (standard osteoporosis treatment) versus denosumab versus zoledronic acid.

Key points

- *It is desirable to have multiple agents with different modes of administration (Recommendation 2).*
- *As with any novel therapy or new indication for existing medications, cost, access, funding, and drug approval need to be considered in the implementation of treatment recommendations.*
- *As mentioned in the preamble of this article, several health care settings currently may only have access to bone-modifying agents to improve bone density or for treatment of metastatic cancer.*
- *Zoledronic acid has recently been added to the CCO Drug Formulary (April 2016) for adjuvant treatment of breast cancer in postmenopausal women.*
- *Zoledronic acid is approved in the United States for treatment of low bone mass and metastatic disease, and clodronate is not available.*
- *Ibandronate is not currently approved for use in Canada. It is approved by the US FDA for the prevention or treatment of postmenopausal osteoporosis.*
- *Direct patient cost and health system resource impact should be considered in implementing such recommendations.*

Primary end points should include DFS, bone-specific DFS, quality of life, and compliance. Other end points of importance are survival, breast cancer–specific survival, adverse events (acute-phase reactions, renal, ONJ), patient-reported outcomes (consider using PRO-CTCAE), and health care costs (patient and system). Trials should appropriately test the postmenopausal hypothesis by stratifying patients by menopausal status at enrollment.

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Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

(J Clin Oncol 2017;35(5):561–564.)

Purpose: To provide current recommendations on the use of sentinel node biopsy (SNB) for patients with early-stage breast cancer.
Methods: PubMed and the Cochrane Library were searched for randomized controlled trials, systematic reviews, meta-analyses, and clinical practice guidelines from 2012 through July 2016. An Update Panel reviewed the identified abstracts.
Results: Of the eight publications identified and reviewed, none prompted a change in the 2014 recommendations, which are reaffirmed by the updated literature review.
Conclusion: Women without sentinel lymph node (SLN) metastases should not receive axillary lymph node dissection (ALND). Women with one to two metastatic SLNs who are planning to undergo breast-conserving surgery with whole-breast radiotherapy should not undergo ALND (in most cases). Women with SLN metastases who will undergo mastectomy should be offered ALND. These three recommendations are based on randomized controlled trials. Women with operable breast cancer and multicentric tumors, with ductal carcinoma in situ, who will undergo mastectomy, who previously underwent breast and/or axillary surgery, or who received preoperative/neoadjuvant systemic therapy may be offered SNB. Women who have large or locally advanced invasive breast cancer (tumor size T3/T4), inflammatory breast cancer, or ductal carcinoma in situ (when breast-conserving surgery is planned) or are pregnant should not undergo SNB.

Introduction

The goal of this 2016 guideline update is to provide oncologists and other clinicians with current recommendations regarding the use of sentinel node biopsy (SNB) for patients with early-stage breast cancer. ASCO first published an evidence-based clinical practice guideline in 2005, with an updated guideline published in 2014.[1] The current update assesses whether the 2014 recommendations remain valid. For a complete list of previous recommendations, visit www.asco.org/breast-sentinel-node-biopsy-guideline.

Methods

Guideline update process

PubMed and the Cochrane Library were searched for randomized controlled trials, systematic reviews, meta-analyses, and clinical practice guidelines for the period from 2012 through July 2016. The disease and intervention search terms were those used for the 2014 guideline update. An Expert Panel, formed in accordance with ASCO's Conflict of Interest Management Procedures for Clinical Practice Guidelines, reviewed the identified abstracts for predefined signals that would suggest the need to change a previous recommendation.

Key points

- *The goal of this 2016 guideline update is to provide oncologists and other clinicians with current recommendations regarding the use of sentinel node biopsy (SNB) for patients with early-stage breast cancer.*
- *ASCO first published an evidence-based clinical practice guideline in 2005, with an updated guideline published in 2014.*

The bottom line

Sentinel lymph node biopsy for patients with early-stage breast cancer: american society of clinical oncology clinical practice guideline update

Guideline questions

How should the results of sentinel node biopsy (SNB) be used in clinical practice? What is the role of SNB in special circumstances in clinical practice? What are the potential benefits and harms associated with SNB?

Target population

Medical oncologists, radiation oncologists, pathologists, surgeons, oncology nurses, patients/caregivers, and guideline implementers.

Target audience

Medical oncologists, surgical oncologists, hospitalists, oncology nurses, patients, and other relevant oncologic professionals.

Methods

An Expert Panel was convened to determine whether previous recommendations remain valid, based on an updated review of evidence from the medical literature.

Recommendations

- *Recommendation 1.* Clinicians should not recommend axillary lymph node dissection (ALND) for women with early-stage breast cancer who do not have nodal metastases (Type: evidence based; benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong).
- *Recommendation 2.1.* Clinicians should not recommend ALND for women with early-stage breast cancer who have one or two sentinel lymph node metastases and will receive breast-conserving surgery with conventionally fractionated whole-breast radiotherapy (Type: evidence based; benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong).
- *Recommendation 2.2.* Clinicians may offer ALND for women with early-stage breast cancer with nodal metastases found in SNB specimens who will receive mastectomy (Type: evidence based; benefits outweigh harms. Evidence quality: low. Strength of recommendation: weak).
- *Recommendation 3.* Clinicians may offer SNB for women who have operable breast cancer who have the following circumstances:
  - 3.1. Multicentric tumors (Type: evidence based; benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate).
  - 3.2. Ductal carcinoma in situ when mastectomy is performed. (Type: informal consensus; benefits outweigh harms. Evidence quality: insufficient. Strength of recommendation: weak).
  - 3.3. Prior breast and/or axillary surgery (Type: evidence based; benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: strong).
  - 3.4. Preoperative/neoadjuvant systemic therapy (Type: evidence based; benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate).
- *Recommendation 4.* There are insufficient data to change the 2005 recommendation that clinicians should not perform SNB for women who have early-stage breast cancer and are in the following circumstances:
  - 4.1. Large or locally advanced invasive breast cancers (tumor size T3/T4) (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak).
  - 4.2. Inflammatory breast cancer (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak).
  - 4.3. Ductal carcinoma in situ when breast-conserving surgery is planned (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong).
  - 4.4. Pregnancy (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak).

Guideline disclaimer

The clinical practice guidelines and other guidance published herein are provided by the American Society of Clinical Oncology (ASCO) to assist providers in clinical decision-making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is atitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an as is basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

This is the most recent information as of the publication date. For the most recent information, and to submit new evidence, please visit www.asco.org/breast-sentinel-biopsy-guideline and the ASCO Guidelines Wiki (www.asco.org/guidelineswiki).

Guideline and conflicts of interest

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

Results

The search yielded 184 publications. After careful review of the identified publications, eight full-text articles were selected for review by the Expert Panel. The Expert Panel concluded that there were no results that change the 2014 guideline recommendations.

Recommendations

The 2016 recommendations are listed in the Bottom Line Box. These recommendations are consistent with the previous (2014) recommendations. Similar to the 2014 recommendations, the Update Committee advises that axillary lymph node

Key points

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- *The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases.*
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- *The search yielded 184 publications. After careful review of the identified publications, eight full-text articles were selected for review by the Expert Panel.*
- *The Expert Panel concluded that there were no results that change the 2014 guideline recommendations.*

dissection can be avoided in patients with one or two positive sentinel nodes only when conventionally fractionated whole-breast radiation therapy is planned. Clinicians should also consider this recommendation with caution in patients with large primary tumors (> 5 cm), those with large or bulky metastatic axillary sentinel lymph nodes, and/or those with gross extranodal extension of the tumor.

Reference

1. Lyman GH, Temin S, Edge SB, et al: Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 32:1365–1383, 2014.

Influential Papers

1. Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, Delaloge S, Li W, Tung N, Armstrong A, Wu W, Goessl C, Runswick S, Conte P. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med 2017;377(6):523–533.

■ BACKGROUND: Olaparib is an oral poly(adenosine diphosphate-ribose) polymerase inhibitor that has promising antitumor activity in patients with metastatic breast cancer and a germline BRCA mutation. METHODS: We conducted a randomized, open-label, phase 3 trial in which olaparib monotherapy was compared with standard therapy in patients with a germline BRCA mutation and human epidermal growth factor receptor type 2 (HER2)-negative metastatic breast cancer who had received no more than two previous chemotherapy regimens for metastatic disease. Patients were randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg twice daily) or standard therapy with single-agent chemotherapy of the physician's choice (capecitabine, eribulin, or vinorelbine in 21-day cycles). The primary end point was progression-free survival, which was assessed by blinded independent central review and was analyzed on an intention-to-treat basis. RESULTS: Of the 302 patients who underwent randomization, 205 were assigned to receive olaparib and 97 were assigned to receive standard therapy. Median progression-free survival was significantly longer in the olaparib group than in the standard-therapy group (7.0 months *vs*. 4.2 months; hazard ratio for disease progression or death, 0.58; 95% confidence interval, 0.43 to 0.80; $P < 0.001$). The response rate was 59.9% in the olaparib group and 28.8% in the standard-therapy group. The rate of grade 3 or higher adverse events was 36.6% in the olaparib group and 50.5% in the standard-therapy group, and the rate of treatment discontinuation due to toxic effects was 4.9% and 7.7%, respectively. CONCLUSIONS: Among patients with HER2-negative metastatic breast cancer and a germline BRCA mutation, olaparib monotherapy provided a significant benefit over standard therapy; median progression-free survival was 2.8 months longer and the risk of disease progression or death was 42% lower with olaparib monotherapy than with standard therapy.

2. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, Suter T, Arahmani A, Rouchet N, Clark E, Knott A, Lang I, Levy C, Yardley DA, Bines J, Gelber RD, Piccart M, Baselga J; APHINITY Steering Committee and Investigators. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med 2017;377(2):122–131.

■ BACKGROUND: Pertuzumab increases the rate of pathological complete response in the preoperative context and increases overall survival among patients with metastatic disease when it is added to trastuzumab and chemotherapy for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer. In this trial, we investigated whether pertuzumab, when added to adjuvant trastuzumab and chemotherapy, improves outcomes among patients with HER2-positive early breast cancer. METHODS: We randomly assigned patients with node-positive or high-risk node-negative HER2-positive, operable breast cancer to receive either pertuzumab or placebo added to standard adjuvant chemotherapy plus 1 year of treatment with trastuzumab. We assumed a 3-year invasive-disease-free survival rate of 91.8% with pertuzumab and 89.2% with placebo. RESULTS: In the trial population, 63% of the patients who were randomly assigned to receive pertuzumab (2400 patients) or placebo (2405 patients) had node-positive disease and 36% had hormone-receptor-negative disease. Disease recurrence occurred in 171 patients (7.1%) in the pertuzumab group and 210 patients (8.7%) in the placebo group (hazard ratio, 0.81; 95% confidence interval [CI], 0.66 to 1.00; $P = 0.045$). The estimates of the 3-year rates of invasive-disease-free survival were 94.1% in the pertuzumab group and 93.2% in the placebo group. In the cohort of patients with node-positive disease, the 3-year rate of invasive-disease-free survival was 92.0% in the pertuzumab group, as compared with 90.2% in the placebo group (hazard ratio for an invasive-disease event, 0.77; 95% CI, 0.62 to 0.96; $P = 0.02$). In the cohort of patients with node-negative disease, the 3-year rate of invasive-disease-free survival was 97.5% in the pertuzumab group and 98.4% in the placebo group (hazard ratio for an invasive-disease event, 1.13; 95% CI, 0.68 to 1.86; $P = 0.64$). Heart failure, cardiac death, and cardiac dysfunction were infrequent in both treatment groups. Diarrhea of grade 3 or higher occurred almost exclusively during chemotherapy and was more frequent with pertuzumab than with placebo

(9.8% *vs*. 3.7%). CONCLUSIONS: Pertuzumab significantly improved the rates of invasive-disease-free survival among patients with HER2-positive, operable breast cancer when it was added to trastuzumab and chemotherapy. Diarrhea was more common with pertuzumab than with placebo.

3. Andreas Schneeweiss, Volker Moebus, Hans Tesch, Claus Hanusch, Carsten Denkert, Kristina Luebbe, Jens Bodo Huober, Peter Klare, Sherko Kummel, Michael Untch, Karin Kast, Christian Jackisch, Jörg Thomalla, Barbara Ingold Heppner, Jens U. Blohmer, Mahdi Rezai, Matthias Frank, Valentina Nekljudova, Gunter Von Minckwitz, and Sibylle Loibl. A randomised phase III trial comparing two dose-dense, dose-intensified approaches (EPC and PM(Cb)) for neoadjuvant treatment of patients with high-risk early breast cancer (GeparOcto). J Clin Oncol 2017;35:15_suppl, 518–518.

■ BACKGROUND: The sequential use of intense does-dense (idd) epirubicin, paclitaxel, cyclophosphamide (EPC) and weekly paclitaxel/liposomal doxorubicin (+/– carboplatin (Cb) in triple negative breast cancer (TNBC) (PM(Cb)) are considered highly efficient regimens for high-risk early stage breast cancer (BC). METHODS: GeparOcto (NCT02125344) patients (pts) received 18 weeks (wks) either EPC (3× E 150 mg/m² q2w followed by 3× P225 mg/m² q2w followed by 3x C 2000 mg/m² q2) or PM(Cb) (12× P 80 mg/m² plus M 20 mg/m² q1w, plus Cb AUC 1.5 q1w in TNBC). For HER2+ BC trastuzumab 6 (8) mg/kg q3w and pertuzumab 420 (840) mg q3w cycles were given concomitantly with P and C. Pts with histologically confirmed, cT1c—cT4a-d BC and central receptor assessment were included. Pts with HER2+ or TNBC were eligible irrespective of nodal status, luminal B-like tumours only if pN+. Primary objective compared pathologic complete response (pCR) rates (ypT0/is ypN0). Sample size calculations assumed a pCR rate of 50% for EPC and 60% for PM(Cb), requiring 950 pts to show superiority of PM(Cb). Secondary objectives compared pCR rates within the stratified subgroups (BC subtype, HER2+ *vs*. HER2– HR+ *vs*. HER2– HR–), amongst others. RESULTS: 961 pts were recruited between 12/2014 and 05/2016, 945 started treatment. Median age was 48 years, 4% T3, 2% T4d, 46% N+, 82% ductal invasive, 66% G3 tumors; 40% were HER2+, 43% TNBC. 347 pts reported SAEs (176 EPC/171 PM(Cb)) and 2 pts died. 35 pneumonias (2 EPC *vs*. 33 PM(Cb)) and 18 pneumonitis (3 EPC *vs*. 15 PM(Cb)) were reported. 16.4% pts with EPC and 33.8% with PM(Cb) discontinued treatment (P < 0.001), mainly due to AEs (47 EPC *vs*. 113 PM(Cb)). Mean treatment duration was 17 wks with EPC and 16 wks with PM(Cb). pCR rate was 48.3% with EPC and 47.6% with PM(Cb) (OR 0.97 (95% CI 0.75–1.25), P = 0.876). pCR rate in TNBC was 48.5% with EPC and 51.7% with PM(Cb); in HER2+ 62.0% *vs*. 57.4% and in Luminal B 14.1% *vs*. 14.6%. CONCLUSIONS: In high-risk early stage breast cancer pts pCR rates of idd EPC compared to weekly PM(Cb) were not significantly different. PM(Cb) appeared to be less feasible.

4. Sylvia Adams, Peter Schmid, Hope S. Rugo, Eric P. Winer, Delphine Loirat, Ahmad Awada, David W. Cescon, Hiroji Iwata, Mario Campone, Rita Nanda, Rina Hui, Giuseppe Curigliano, Deborah Toppmeyer, Joyce O'Shaughnessy, Sherene Loi, Shani Paluch-Shimon, Deborah Card, Jing Zhao, Vassiliki Karantza, and Javier Cortes. Phase 2 study of pembrolizumab (pembro) monotherapy for previously treated metastatic triple-negative breast cancer (mTNBC): KEYNOTE-086 cohort A. J Clin Oncol 2017;35:15_suppl, 1008–1008.

■ BACKGROUND: In KEYNOTE-012, pembro showed durable activity and manageable safety in patients (pts) with PD-L1+ mTNBC. Cohort A of KEYNOTE-086 (NCT02447003) examined the efficacy/safety of pembro in previously treated mTNBC, regardless of PD-L1 expression. METHODS: Pts with centrally confirmed mTNBC, ≥ 1 prior chemotherapy for metastatic disease, and ECOG PS 0-1 had pembro 200 mg Q3W for up to 24 mo; imaging q 9 wk for the first 12 mo, then q 12 wk. Clinically stable pts with PD could remain on pembro until PD confirmed on next assessment. Primary endpoints: ORR (RECIST v1.1, central review) in all pts and pts with PD-L1+ tumors, and safety. Secondary endpoints: DOR, disease control rate (DCR; CR + PR + SD ≥ 24 wk), PFS, and OS. Planned enrollment was 160 pts; analysis based on data as of Nov 10, 2016. RESULTS: 60% of screened PD-L1-evaluable pts had PD-L1+ tumors (combined positive score ≥ 1%). Of 170 pts enrolled (100% women; median age 54 y), 44% had ≥ 3 prior lines of therapy, 51% had elevated LDH, 74% had visceral mets and 62% had PD-L1+ tumors. After a median follow-up of 10.9 mo, 9 (5%) pts remained on pembro. Treatment-related AEs (TRAEs) of any grade and grade 3–4 occurred in 60%

and 12% of pts, respectively; 4% discontinued due to TRAEs. There were no deaths due to AE. Overall ORR was 5% regardless of PD-L1 expression (Table). Best overall response was 0.6% CR, 4% PR, 21% SD; not evaluable (3%). DCR was 8% (95% CI 4–13). Median DOR was 6.3 mo (range 1.2+ to 10.3+); 5 (63%) responders w/o PD at data cutoff. Median PFS and OS were 2.0 mo (95% CI 1.9–2.0) and 8.9 mo (95% CI 7.2–11.2), with 6-mo rates of 12% and 69%, respectively. ORR was numerically lower in pts with poor prognostic factors (e.g., high LDH, liver/visceral mets; Table). CONCLUSIONS: In KEYNOTE-086 Cohort A, pembro monotherapy showed manageable safety and durable responses in a subset of pts with heavily pretreated mTNBC. Randomized studies of monotherapy and combination therapy are ongoing.

5. Sylvia Adams, Sherene Loi, Deborah Toppmeyer, David W. Cescon, Michele De Laurentiis, Rita Nanda, Eric P. Winer, Hirofumi Mukai, Kenji Tamura, Anne Armstrong, Minetta C. Liu, Hiroji Iwata, Larisa Ryvo, Pauline Wimberger, Deborah Card, Yu Ding, Vassiliki Karantza, and Peter Schmid. Phase 2 study of pembrolizumab as first-line therapy for PD-L1–positive metastatic triple-negative breast cancer (mTNBC): Preliminary data from KEYNOTE-086 cohort B. J Clin Oncol 2017;35:15_suppl, 1088–1088.

■ BACKGROUND: Standard first-line treatment for mTNBC is chemotherapy. However, outcomes are poor, and new treatment options are needed. Cohort B of KEYNOTE-086 (NCT02447003) assessed the safety and antitumor activity of pembrolizumab as first-line therapy for patients (pts) with PD-L1–positive mTNBC. METHODS: Men and women with centrally confirmed mTNBC, no prior systemic anticancer therapy for metastatic disease, ECOG PS 0–1, and a tumor PD-L1 combined positive score (CPS) ≥ 1% received pembrolizumab 200 mg Q3W for 24 mo or until disease progression, intolerable toxicity, or investigator or pt decision. Tumor imaging was performed Q9W for 12 mo and Q12W thereafter. Clinically stable pts with PD could remain on pembrolizumab until PD was confirmed on subsequent assessment. Primary end point was safety. Secondary end points included ORR, DOR, and PFS (RECIST v1.1, central review). Planned enrollment was 80 pts. This analysis included all pts who had ≥ 18 wk of follow-up as of Nov 10, 2016. RESULTS: 79 of the first 137 pts with PD-L1–evaluable tumors (58%) had PD-L1 CPS ≥ 1%. Of the first 52 pts enrolled, 100% were women, median age was 53 y, 40% had elevated LDH, 69% had visceral metastases, and 87% received prior (neo)adjuvant therapy. After a median follow-up of 7.0 mo (range 4.4–12.5), 15 (29%) pts remained on pembrolizumab. Treatment-related AEs occurred in 37 (71%) pts, most commonly fatigue (31%), nausea (15%), and diarrhea (13%). 4 (8%) pts experienced 5 grade 3–4 treatment-related AEs: back pain, fatigue, hyponatremia, hypotension, and migraine (n = 1 each). No pts died or discontinued pembrolizumab due to an AE. ORR was 23% (95% CI 14%–36%). Best overall response was CR in 4%, PR in 19%, SD in 17%, PD in 58%, and not assessed in 2%. Median time to response was 8.7 wk (range 8.1–17.7). Median DOR was 8.4 mo (range, 2.1+ to 8.4), with 8 (67%) responses ongoing at cutoff. Median PFS was 2.1 mo (95% CI, 2.0–3.9); estimated 6-mo PFS rate was 29%. CONCLUSIONS: Data from the first 52 pts enrolled in KEYNOTE-086 cohort B suggest that pembrolizumab monotherapy has a manageable safety profile and promising antitumor activity as first-line therapy for PD-L1–positive mTNBC.

6. Peter Schmid, Yeon Hee Park, Eva Muñoz-Couselo, Sung-Bae Kim, Joohyuk Sohn, Seock-Ah Im, Esther Holgado, Yang Wang, Thao Dang, Gursel Aktan, and Javier Cortés. Pembrolizumab (pembro) + chemotherapy (chemo) as neoadjuvant treatment for triple negative breast cancer (TNBC): Preliminary results from KEYNOTE-173. J Clin Oncol 2017;35:15_suppl, 556–556.

■ BACKGROUND: Pembro has shown efficacy and acceptable safety in pts with previously treated metastatic TNBC. The phase Ib KEYNOTE-173 study (NCT02622074) evaluated pembro + chemo as neoadjuvant therapy for locally advanced TNBC. We present cohorts A and B. METHODS: Women aged ≥ 18 y with locally advanced, nonmetastatic TNBC; ECOG PS 0/1; and no prior chemo, targeted therapy, or immunotherapy within 12 mo were eligible. Dosing in A was single-dose pembro followed by 4 cycles of pembro Q3W + nab-paclitaxel (Np) weekly followed by 4 cycles of pembro + doxorubicin + cyclophosphamide Q3W. Dosing in B was the same as in A but with carboplatin Q3W added to pembro + Np. Concentrations were pembro 200 mg; doxorubicin 60 mg/m^2; cyclophosphamide 600 mg/m^2; Np 125 mg/m^2 in A, 100 mg/m^2 in B; and carboplatin AUC 6 (1 cycle = 21 d). DLTs were assessed at cycles 1–3 and 6–7. Dose levels were

deemed toxic if ≥ 3 of the first 6 pts or ≥4 of 10 pts had DLTs. Surgery was 3–6 wk after treatment completion/discontinuation. Primary end points were safety and recommended phase 2 dose of pembro combined with chemo. Key efficacy end points were pathological CR (pCR) rate, defined as ypT0/Tis, ypN0, and ypT0 ypN0, and ORR (RECIST v1.1, investigator). pCR analyses included all pts. RESULTS: By Jan 6, 2017, 10 pts were in each cohort. Median age was 53 y (range 32–71); most pts had invasive ductal histology (90%), primary tumor stage ≥T2 (90%), and nodal involvement (75%). DLTs (myelosuppression) occurred in 7 pts (3 in A, 4 in B) and were unrelated to pembro. Gr 3–4 treatment-related AEs (TRAEs) occurred in 8 pts in A and 10 pts in B; none were fatal. One pt in A and 2 pts in B discontinued for a TRAE (2 ALT elevations with pembro; 1 DVT with chemo). Overall ORR (CR+PR) before surgery was 80% (90% CI, 49–96) in A and 100% (90% CI, 74–100) in B. ypT0/Tis pCR rate was 70% (90% CI, 39–91) in A and 100% (90% CI, 74–100) in B; ypT0 ypN0 pCR rate was 50% (90% CI, 22–78) in A and 90% (90% CI, 61–100) in B; and yT0/Tis ypN0 pCR rate was 60% (90% CI, 30–85) in A and 90% (90% CI, 61–100) in B. CONCLUSIONS: Preliminary data suggest that pembro + chemo as neoadjuvant therapy for TNBC results in manageable toxicity and promising antitumor activity.

7. Matsui K, Yoshikawa A, Oyama K, Nozaki Z, Tanada Y, Earashi M, Kiyohara K, Nagata T, Fukushima W, Shimizu T, Maeda K. Efficacy of T-DM1 in patients with HER2-positive metastatic breast cancer previously treated with pertuzumab. Ann Oncol 2017;28:10_suppl, 103P.

■ BACKGROUND: The standard therapy for primary treatment of HER2-positive metastatic breast cancer (MBC) is combination therapy of pertuzumab (PER), trastuzumab (HER) and docetaxel (DTX). Although the effectiveness of trastuzumab emtansine (T-DM1) after HER treatment has been reported, there are few reports on the effectiveness of T-DM1 for patients treated with PER. We retrospectively investigated the effectiveness of T-DM1 on HER2-positive MBC previously treated with PER. METHODS: Between October 2013 and June 2017, 79 patients with HER2-positive MBC were treated with PER. 44 patients were investigated the subsequent treatment. 34 patients received T-DM1, and 10 patients received treatment other than T-DM1 after PER treatment. RESULTS: Median treatment line was 3.0 (1–9) *vs*. 4.0 (1–9) in the T-DM1 treatment and other than T-DM1 treatment, respectively. The response rate was CR 0% *vs*. 0%, PR 36.0% *vs*. 25%, SD 32.0% *vs*. 62.5%, PD 32.0% *vs*. 12.5%, respectively. The objective response rate was 36.0% *vs*. 20.0%. The clinical benefit rate was 48.0% *vs*. 50.0%. Median time to treatment failure was 6.6 months vs 2.9 months, respectively. There was a significant difference in median overall survival; median not reached *vs*. 19.6 months (P = 0.04). Conclusions: OS was significantly better with administration of T-DM1 after PER treatment. Based on the results of this study, it was confirmed that efficacy of T-DM1 in patients with HER2-positive metastatic breast cancer previously treated with PER.

8. Richard S. Finn, John Crown, Istvan Lang, Katalin Boer, Igor Bondarenko, Sergey O. Kulyk, Johannes Ettl, Ravindranath Patel, Tamas Pinter, Marcus Schmidt, Yaroslav V. Shparyk, Anu Thummala, Nataliya L. Voytko, Camilla Fowst, Xin Huang, Sindy Kim, and Dennis J. Slamon. Overall survival results from the randomized phase II study of palbociclib (P) in combination with letrozole (L) *vs*. letrozole alone for frontline treatment of ER+/HER2– advanced breast cancer (PALOMA-1; TRIO-18). J Clin Oncol 2017;35:15_suppl, 1001–1001.

■ BACKGROUND: Preclinical data identified a synergistic role for P and hormone blockade in blocking growth of ER+ breast cancer (BC) cell lines. PALOMA-1 was an open-label phase II trial comparing progression-free survival (PFS) in patients (pts) with advanced ER+/HER2– BC treated with P+L or L alone. Median PFS increased with addition of P to L to 20.2 mos (*vs*. 10.2 mos with L alone; HR = 0.488), with an acceptable safety profile, leading to accelerated approval by the US FDA. These results were confirmed in the phase 3 PALOMA-2 trial. At the time of the final PFS analysis, overall survival (OS) data were immature with only 61 events in both arms and a median follow-up of <30 mos with a trend in favor of P+L vs L (37.5 *vs*. 33.3 mos; HR = 0.813; P = 0.211). Here we present final OS results. METHODS: PALOMA-1 was a 2-part study evaluating P+L in ER+/HER2– advanced BC. Part 1 enrolled postmenopausal pts with this subtype using only ER+/HER2– while Part 2 enrolled pts of this subtype additionally screened for CCND1 amplification and/or loss of p16. The primary endpoint was investigator-assessed PFS. Secondary endpoints included objective response

rate, OS, safety, and correlative biomarker studies. A total of 165 pts were randomized; 66 in Part 1 and 99 in Part 2. Baseline characteristics were balanced between treatment arms. In both parts, pts were randomized 1:1 to receive P+L or L alone. OS data were collected as well as post-study therapy. RESULTS: As of Dec 2016, there were 116 OS events. Median OS was 37.5 mos (95% CI: 31.4, 47.8) with P+L *vs*. 34.5 mos (95% CI: 27.4, 42.6) for L (HR = 0.897 [95% CI: 0.623, 1.294]; P = 0.281). Median OS was 37.5 vs 33.3 mos (HR = 0.837; P = 0.280) for Part 1 and 35.1 *vs*. 35.7 mos (HR = 0.935; P = 0.388) for Part 2. 78.6% of pts in the P+L arm received post-study systemic therapy *vs*. 86.4% in the L arm. More pts in the L arm received ≥3 lines of therapy (37% *vs*. 18%). Further subgroup analyses and details on post-study therapies will be presented. CONCLUSIONS: In PALOMA-1, P+L provided a statistically non-significant trend towards an improvement in OS. Survival data from the phase III, PALOMA-2 study is awaited.

9. Gabriel N. Hortobagyi, Salomon M. Stemmer, Howard A. Burris, Yoon Sim Yap, Gabe S. Sonke, Shani Paluch-Shimon, Mario Campone, Katarina Petrakova, Kimberly L. Blackwell, Eric P. Winer, Wolfgang Janni, Sunil Verma, Pier Franco Conte, Carlos L. Arteaga, David A. Cameron, Fengjuan Xuan, Michelle Kristine Miller, Caroline Germa, Samit Hirawat, and Joyce O'Shaughnessy. Updated results from MONALEESA-2, a phase 3 trial of first-line ribociclib + letrozole in hormone receptor-positive (HR+), HER2-negative (HER2–), advanced breast cancer (ABC). J Clin Oncol 2017;35:15_suppl, 1038–1038.

■ BACKGROUND: Endocrine therapy (ET) is the basis of first-line (1L) treatment for HR+ ABC. However, ET resistance are almost universal. At the first interim analysis (IA) of MONALEESA-2 (NCT01958021), ribociclib (RIB; cyclin-dependent kinase 4/6 inhibitor) + letrozole (LET) significantly prolonged progression-free survival (PFS) *vs*. placebo (PBO) + LET in patients (pts) with HR+, HER2– ABC.[1] Here we report updated efficacy and safety data from MONALEESA-2 with a further ~11 months of follow-up. METHODS: Postmenopausal women with no prior therapy for ABC were randomized 1:1 to RIB (600 mg/day, 3-weeks-on/1-week-off) + LET(2.5 mg/day, continuous) *vs*. PBO + LET. The primary endpoint was locally assessed PFS. Secondary endpoints include overall survival (OS; key) and safety. OS significance was defined by a p-value threshold of 3.15×10^{-5}. Tumor assessments were performed every 8 weeks for the first 18 months, and every 12 weeks, thereafter. RESULTS: 668 pts were enrolled (334 in each arm). At the second IA for OS (data cut-off Jan 2, 2017), the median duration of follow-up was 26.4 months; 116 deaths and 345 PFS events had occurred. OS data remain immature, with 15.0% *vs*. 19.8% of pt deaths in the RIB + LET *vs*. PBO + LET arm (HR = 0.746; 95% CI: 0.517–1.078; p = 0.059). Updated PFS analyses confirmed continued treatment benefit in the RIB + LET *vs*. PBO + LET arm. The 24-month PFS rates (RIB + LET *vs*. PBO + LET) were 54.7% *vs*. 35.9%. Treatment benefit was consistent across pt subgroups. The most common Grade 3/4 laboratory abnormalities (≥10% of pts; RIB + LET *vs*. PBO + LET) were decreased neutrophils (62.6% *vs*. 1.5%), decreased leukocytes (36.8% *vs*. 1.5%), decreased lymphocytes (16.2% *vs*. 3.9%), and elevated alanine aminotransferase (11.4% *vs*. 1.2%). CONCLUSION: After 26+ months of follow-up, treatment benefit with 1LRIB + LET persists in postmenopausal women with HR+, HER2– ABC. The study remains immature for OS analysis. The safety profile of RIB + LET remains manageable.

10. Cottu P, D'Hondt V, Dureau S, Lerebours F, Desmoulins I, Heudel P, Duhoux F, Levy C, Mouret-Reynier M, Dalenc F, Frenel J, Jouannaud C, Venat-Bouvet L, Nguyen S, Ferrero J, Canon J, Grenier J, Lemonnier J, Vincent-Salomon A, Delaloge S. Letrozole and palbociclib versus 3rd generation chemotherapy as neoadjuvant treatment of luminal breast cancer. Results of the UNICANCER-NeoPAL study. Ann Oncol 2017;28:5_suppl, v605–v649.

■ BACKGROUND: Benefit of neoadjuvant chemotherapy in patients (pts) with luminal breast cancer (LBC) is limited. Palbociclib combined with endocrine treatment has shown impressive results in advanced LBC. We conducted a randomized parallel phase II study, assessing letrozole + palbociclib (LP) as neoadjuvant treatment in LBC. METHODS: Postmenopausal women were eligible if they had a stage II–III ER-positive HER2-negative BC, not candidate for breast conserving surgery (BCS), with either a PAM50 luminal B, or a PAM50 luminal A profile with proven lymph node involvement (N+).

A parallel 1:1 randomization proposed 6 courses of 3rd generation chemotherapy (FEC100 × 3—docetaxel 100 × 3), or 19 weeks (wks) of L 2.5 mg/day plus P 125 mg/day, 3 wks/4. Surgery was performed at wk 20. Primary endpoint was locally assessed Residual Cancer Burden (RCB) rate. Main secondary endpoints included safety, response rate, positive and negative predictive values of PAM50 ROR (risk of recurrence)-defined status, centrally reviewed RCB, and BCS rates. The protocol planned that the trial should be stopped for futility if ≤5 local RCB 0–I events (16.7%) were observed in the first 30 pts in the LP arm. RESULTS: Out of 184 screened pts, 106 women with Stage II–IIIA, PAM50-ascertained LBC were randomized. Pts had T1–2 (73%) or T3 (27%); N+(26.5%); luminal B (89%) tumors. Median ROR score was 68 (22–93). At interim analysis, RCB 0-I was observed in 1 pt in the LP arm and inclusions were stopped. At final analysis, local RCB 0/I/II/III was observed in 3.8%/3.8%/52%/40.4% of pts in the LP arm, and in 5.9%/9.8%/37.3%/47.1% in the chemo arm, respectively. Central and local RCB results were identical. ROR score was not predictive of RCB 0/1. Clinical objective response rates were 74.5% and 76%, and BCS rates 69.2% and 68.6%, in the LP and chemo arms, respectively. Ki67 final median value was significantly lower in the LP arm (3% (range 1–40) *vs*. 8% (2–15), P =.017). Of 19 serious adverse events, 2 occurred in the LP arm and 17 in the chemo arm (P<0.001). CONCLUSIONS: Neoadjuvant LP led to a slightly lower pCR/RCB 0–I rate than chemo, however clinical response and BCS rates were similar in both arms and LP had a much better safety profile. Extensive analyses are ongoing.

11. Martin M, Holmes FA, Ejlertsen B, Delaloge S, Moy B, Iwata H, von Minckwitz G, Chia SKL, Mansi J, Barrios CH, Gnant M, Tomašević Z, Denduluri N, Šeparović R, Gokmen E, Bashford A, Ruiz Borrego M, Kim SB, Jakobsen EH, Ciceniene A, Inoue K, Overkamp F, Heijns JB, Armstrong AC, Link JS, Joy AA, Bryce R, Wong A, Moran S, Yao B, Xu F, Auerbach A, Buyse M, Chan A; ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18(12):1688–1700.

■ BACKGROUND: ExteNET showed that 1 year of neratinib, an irreversible pan-HER tyrosine kinase inhibitor, significantly improves 2-year invasive disease-free survival after trastuzumab-based adjuvant therapy in women with HER2-positive breast cancer. We report updated efficacy outcomes from a protocol-defined 5-year follow-up sensitivity analysis and long-term toxicity findings. METHODS: In this ongoing randomised, double-blind, placebo-controlled, phase 3 trial, eligible women aged 18 years or older (≥20 years in Japan) with stage 1–3c (modified to stage 2–3c in February, 2010) operable breast cancer, who had completed neoadjuvant and adjuvant chemotherapy plus trastuzumab with no evidence of disease recurrence or metastatic disease at study entry. Patients who were eligible patients were randomly assigned (1:1) via permuted blocks stratified according to hormone receptor status (hormone receptor-positive vs hormone receptor-negative), nodal status (0 *vs*. 1–3 *vs*. or ≥4 positive nodes), and trastuzumab adjuvant regimen (given sequentially *vs*. concurrently with chemotherapy), then implemented centrally via an interactive voice and web-response system, to receive 1 year of oral neratinib 240 mg/day or matching placebo. Treatment was given continuously for 1 year, unless disease recurrence or new breast cancer, intolerable adverse events, or consent withdrawal occurred. Patients, investigators, and trial funder were masked to treatment allocation. The predefined endpoint of the 5-year analysis was invasive disease-free survival, analysed by intention to treat. FINDINGS: Between July 9, 2009, and Oct 24, 2011, 2840 eligible women with early HER2-positive breast cancer were recruited from community-based and academic institutions in 40 countries and randomly assigned to receive neratinib (n = 1420) or placebo (n = 1420). After a median follow-up of 5·2 years (IQR 2·1–5·3), patients in the neratinib group had significantly fewer invasive disease-free survival events than those in the placebo group (116 *vs*. 163 events; stratified hazard ratio 0·73, 95% CI 0·57–0·92, P = 0·0083). The 5-year invasive disease-free survival was 90·2% (95% CI 88·3–91·8) in the neratinib group and 87·7% (85·7–89·4) in the placebo group. Without diarrhoea prophylaxis, the most common grade 3–4 adverse events in the neratinib group, compared with the placebo group, were diarrhoea (561 [40%] grade 3 and one [<1%] grade 4 with neratinib *vs*. 23 [2%] grade 3 with placebo), vomiting (grade 3: 47 [3%] vs five [<1%]), and nausea (grade 3: 26 [2%] *vs*. two [<1%]). Treatment-emergent serious adverse events occurred in 103 (7%) women in the neratinib group and 85 (6%) women in the placebo group.

No evidence of increased risk of long-term toxicity or long-term adverse consequences of neratinib-associated diarrhoea were identified with neratinib compared with placebo. INTERPRETATION: At the 5-year follow-up, 1 year of extended adjuvant therapy with neratinib, administered after chemotherapy and trastuzumab, significantly reduced the proportion of clinically relevant breast cancer relapses-ie, those that might lead to death, such as distant and locoregional relapses outside the preserved breast-without increasing the risk of long-term toxicity. An analysis of overall survival is planned after 248 events.

12. Saura C, de Azambuja E, Hlauschek D, Oliveira M, Zardavas D, Jallitsch-Halper A, de la Pena L, Nuciforo P, Ballestrero A, Fornier M.N, Boer K, Ciruelos E, Valero T.R. Wilson V, Stout T.J, Hsu J.Y, Shi Y, Piccart M, Gnant M, Baselga J. Primary results of LORELEI: A phase II randomized, double-blind study of neoadjuvant letrozole (LET) plus taselisib versus LET plus placebo (PLA) in postmenopausal patients (pts) with ER+/HER2–negative early breast cancer (EBC). Ann Oncol 2017;28:5_suppl, LBA10_PR.

■ BACKGROUND: Taselisib is an oral, potent, and selective PI3-kinase (PI3K) inhibitor with enhanced activity against PIK3CA mutant (MUT) cancer cells. Confirmed partial responses were observed in pts with PIK3CA MUT metastatic breast cancer treated with taselisib as a single agent and combined with endocrine therapy (ET). METHODS: 334 postmenopausal pts with ER+/HER2–, Stage I–III, operable EBC and evaluable tumor tissue for centralized PIK3CA genotyping were randomized (1:1) in 90 sites worldwide to receive LET with either taselisib (4 mg 5 days on/2 days off) or PLA for 16 weeks, followed by surgery. Co-primary endpoints: objective response rate (ORR) by centrally assessed breast MRI and pathologic complete response (pCR, ypT0/is N0) rate at surgery, in all randomized pts and in pts with PIK3CA MUT tumors. The sample size was calculated to detect in the PIK3CA MUT subset an absolute increase of 24% in ORR (from 40% to 64%, minimal detectable difference [MDD] 15%; 2-sided α 16%, 80% power), and 18% in pCR (from 1% to 19%; MDD 13%; 2-sided α 4%, 80% power). RESULTS: The study met its primary endpoint: the addition of taselisib to LET increased the ORR from 38% to 56.2% in the PIK3CA MUT subset (N=152; Odds ratio [OR] 2.03, 95% CI 1.06–3.88, P=0.033) and in all randomized pts (from 39.3% to 50%, OR 1.55, 95%CI 1.00–2.38, P=0.049). No significant difference was observed for pCR rate overall or in the PIK3CA MUT subset. Most common G3-4 adverse events in the taselisib arm: gastrointestinal disorders (7.8%), infections (4.8%), and skin/subcutaneous tissue disorders (4.8%). G3-4 hyperglycemia occurred in 1.2% of pts. One sudden death occurred in the taselisib arm, but was considered unrelated to study treatment. Taselisib discontinuation (10.8%) and dose reductions (11.4%) were infrequent. CONCLUSIONS: LORELEI is the first randomized study to demonstrate a significant increase in ORR measured by MRI upon treatment with a PI3K selective inhibitor + ET in ER+/HER2– EBC pts. Toxicity was manageable. Ongoing comprehensive biomarker analyses will provide further insight into the antitumor responses observed with this combination.

13. Rugo HS, Barve A, Waller CF, Hernandez-Bronchud M, Herson J, Yuan J, Sharma R, Baczkowski M, Kothekar M, Loganathan S, Manikhas A, Bondarenko I, Mukhametshina G, Nemsadze G, Parra JD, Abesamis-Tiambeng ML, Baramidze K, Akewanlop C, Vynnychenko I, Sriuranpong V, Mamillapalli G, Ray S, Yanez Ruiz EP, Pennella E; Heritage study investigators. Effect of a proposed trastuzumab biosimilar compared with trastuzumab on overall response rate in patients with ERBB2 (HER2)-Positive metastatic breast cancer: A randomized clinical trial. JAMA 2017;317(1):37–47.

■ IMPORTANCE: Treatment with the anti-ERBB2 humanized monoclonal antibody trastuzumab and chemotherapy significantly improves outcome in patients with ERBB2 (HER2)-positive metastatic breast cancer; a clinically effective biosimilar may help increase access to this therapy. OBJECTIVE: To compare the overall response rate and assess the safety of a proposed trastuzumab biosimilar plus a taxane or trastuzumab plus a taxane in patients without prior treatment for ERBB2-positive metastatic breast cancer. DESIGN, SETTING, AND PARTICIPANTS: Multicenter, double-blind, randomized, parallel-group, phase 3 equivalence study in patients with metastatic breast cancer. From December 2012 to August 2015, 500 patients were randomized 1:1 to receive a proposed biosimilar or trastuzumab plus a taxane. Chemotherapy was administered for at least

24 weeks followed by antibody alone until unacceptable toxic effects or disease progression occurred. INTERVENTIONS: Proposed biosimilar (n = 230) or trastuzumab (n = 228) with a taxane. MAIN OUTCOMES AND MEASURES: The primary outcome was week 24 overall response rate (ORR) defined as complete or partial response. Equivalence boundaries were 0.81 to 1.24 with a 90% CI for ORR ratio (proposed biosimilar/trastuzumab) and –15% to 15% with a 95% CI for ORR difference. Secondary outcome measures included time to tumor progression, progression-free and overall survival at week 48, and adverse events. RESULTS: Among 500 women randomized, the intention-to-treat population included 458 women (mean [SD] age, 53.6 [11.11] years) and the safety population included 493 women. The ORR was 69.6% (95% CI, 63.62%–75.51%) for the proposed biosimilar *vs*. 64.0% (95% CI, 57.81%–70.26%) for trastuzumab. The ORR ratio (1.09; 90% CI, 0.974–1.211) and ORR difference (5.53; 95% CI, –3.08 to 14.04) were within the equivalence boundaries. At week 48, there was no statistically significant difference with the proposed biosimilar *vs*. trastuzumab for time to tumor progression (41.3% *vs*. 43.0%; –1.7%; 95% CI, –11.1% to 6.9%), progression-free survival (44.3% *vs*. 44.7%; –0.4%; 95% CI, –9.4% to 8.7%), or overall survival (89.1% *vs*. 85.1%; 4.0%; 95% CI, –2.1% to 10.3%). In the proposed biosimilar and trastuzumab groups, 239 (98.6%) and 233 (94.7%) had at least 1 adverse event, the most common including neutropenia (57.5% *vs*. 53.3%), peripheral neuropathy (23.1% *vs*. 24.8%), and diarrhea (20.6% *vs*. 20.7%). CONCLUSIONS AND RELEVANCE: Among women with ERBB2-positive metastatic breast cancer receiving taxanes, the use of a proposed trastuzumab biosimilar compared with trastuzumab resulted in an equivalent overall response rate at 24 weeks. Further study is needed to assess safety and long-term clinical outcome.

14. Stebbing J, Baranau Y, Baryash V, Manikhas A, Moiseyenko V, Dzagnidze G, Zhavrid E, Boliukh D, Stroyakovskii D, Pikiel J, Eniu A, Komov D, Morar-Bolba G, Li RK, Rusyn A, Lee SJ, Lee SY, Esteva FJ. CT-P6 compared with reference trastuzumab for HER2-positive breast cancer: a randomised, double-blind, active-controlled, phase 3 equivalence trial. Lancet Oncol. 2017;18(7):917–928.

■ BACKGROUND: CT-P6 is a proposed biosimilar to reference trastuzumab. In this study, we aimed to establish equivalence of CT-P6 to reference trastuzumab in neoadjuvant treatment of HER2-positive early-stage breast cancer. METHODS: In this randomised, double-blind, active-controlled, phase 3 equivalence trial, we recruited women aged 18 years or older with stage I–IIIa operable HER2-positive breast cancer from 112 centres in 23 countries. Inclusion criteria were an Eastern Cooperative Oncology Group performance status score of 0 or 1; a normal left ventricular ejection fraction of at least 55%; adequate bone marrow, hepatic, and renal function; at least one measureable lesion; and known oestrogen and progesterone receptor status. Exclusion criteria included bilateral breast cancer, previous breast cancer treatment, previous anthracycline treatment, and pregnancy or lactation. We randomly allocated patients 1:1 to receive neoadjuvant CT-P6 or reference trastuzumab intravenously (eight cycles, each lasting 3 weeks, for 24 weeks; 8 mg/kg on day 1 of cycle 1 and 6 mg/kg on day 1 of cycles 2–8) in conjunction with neoadjuvant docetaxel (75 mg/m^2 on day 1 of cycles 1–4) and FEC (fluorouracil [500 mg/m^2], epirubicin [75 mg/m^2], and cyclophosphamide [500 mg/m^2]; day 1 of cycles 5–8) therapy. We stratified randomisation by clinical stage, receptor status, and country and used permuted blocks. We did surgery within 3–6 weeks of the final neoadjuvant study drug dose, followed by an adjuvant treatment period of up to 1 year. We monitored long-term safety and efficacy for 3 years after the last patient was enrolled. Participants and investigators were masked to treatment until study completion. The primary efficacy endpoint, analysed in the per-protocol population, was pathological complete response, assessed via specimens obtained during surgery, analysed by masked central review of local histopathology reports. The equivalence margin was –0·15 to 0·15. This trial is registered with ClinicalTrials.gov, number NCT02162667, and is ongoing, but no longer recruiting. FINDINGS: Between Aug 7, 2014, and May 6, 2016, we randomly allocated 549 patients (271 [49%] to CT-P6 *vs*. 278 [51%] to reference trastuzumab). A similar proportion of patients achieved pathological complete response with CT-P6 (116 [46·8%; 95% CI 40·4–53·2] of 248 patients) and reference trastuzumab (129 [50·4%; 44·1–56·7] of 256 patients). The 95% CI of the estimated treatment outcome difference (–0·04% [95% CI –0·12 to 0·05]) was within the equivalence margin. 19 (7%) of 271 patients in the CT-P6 group reported serious treatment-emergent adverse events versus 22 (8%) of 278 in the

reference trastuzumab group; frequent (occurring in more than one patient) serious adverse events were febrile neutropenia (four [1%] *vs*. one [<1%]) and neutropenia (one [<1%] *vs*. two [1%]). Grade 3 or worse treatment-related adverse events occurred in 17 (6%) of 271 patients in the CT-P6 group versus 23 (8%) of 278 in the reference trastuzumab group; the most frequently reported adverse event was neutropenia in ten (4%) versus 14 (5%). INTERPRETATION: CT-P6 showed equivalent efficacy to reference trastuzumab and adverse events were similar. Availability of trastuzumab biosimilars could increase access to this targeted therapy for HER2-positive early-stage cancer.

15. Tolaney SM, Ziehr DR, Guo H, Ng MR, Barry WT, Higgins MJ, Isakoff SJ, Brock JE, Ivanova EV, Paweletz CP, Demeo MK, Ramaiya NH, Overmoyer BA, Jain RK, Winer EP, Duda DG. Phase II and Biomarker Study of Cabozantinib in Metastatic Triple-Negative Breast Cancer Patients. Oncologist 2017;22(1):25–32.

■ Currently, no targeted therapies are available for metastatic triplenegative breast cancer (mTNBC). We evaluated the safety, efficacy, and biomarkers of response to cabozantinib, a multikinase inhibitor, in patients with mTNBC. We conducted a single arm phase II and biomarker study that enrolled patients with measurable mTNBC. Patients received cabozantinib (60 mg daily) on a 3-week cycle and were restaged after 6 weeks and then every 9 weeks. The primary endpoint was objective response rate. Predefined secondary endpoints included progression-free survival (PFS), toxicity, and tissue and blood circulating cell and protein biomarkers. Of 35 patients who initiated protocol therapy, 3 (9% [95% confidence interval (CI): 2, 26]) achieved a partial response (PR). Nine patients achieved stable disease (SD) for at least 15 weeks, and thus the clinical benefit rate (PR+SD) was 34% [95% CI: 19, 52]. Median PFS was 2.0 months [95% CI: 1.3, 3.3]. The most common toxicities were fatigue, diarrhea, mucositis, and palmar-plantar erythrodysesthesia. There were no grade 4 toxicities, but 12 patients (34%) required dose reduction. Two patients had TNBCs with MET amplification. During cabozantinib therapy, there were significant and durable increases in plasma placental growth factor, vascular endothelial growth factor (VEGF), VEGF-D, stromal cell-derived factor 1a, and carbonic anhydrase IX, and circulating CD3+cells and CD8+T lymphocytes, and decreases in plasma soluble VEGF receptor 2 and CD14+ monocytes (all $P < .05$). Higher baseline concentrations of soluble MET (sMET) associated with longer PFS ($P = .03$). In conclusion, cabozantinib showed encouraging safety and efficacy signals but did not meet the primary endpoint in pretreated mTNBC. Exploratory analyses of circulating biomarkers showed that cabozantinib induces systemic changes consistent with activation of the immune system and antiangiogenic activity, and that sMET should be further evaluated a potential biomarker of response. IMPLICATIONS FOR PRACTICE: Triple-negative breast cancer (TNBC)-a disease with a dearth of effective therapies-often overexpress MET, which is associated with poor clinical outcomes. However, clinical studies of agents targeting MET and VEGF pathways-alone or in combination-have shown disappointing results. This study of cabozantinib (a dual VEGFR2/MET) in metastatic TNBC, while not meeting its prespecified endpoint, showed that treatment is associated with circulating biomarker changes, and is active in a subset of patients. Furthermore, this study demonstrates that cabozantinib therapy induces a systemic increase in cytotoxic lymphocyte populations and a decrease in immunosuppressive myeloid populations. This supports the testing of combinations of cabozantinib with immunotherapy in future studies in breast cancer patients.

16. Morrow M, Van Zee KJ, Patil S, Petruolo O, Mamtani A, Barrio AV, Capko D, El-Tamer M, Gemignani ML, Heerdt AS, Kirstein L, Pilewskie M, Plitas G, Sacchini VS, Sclafani LM, Ho A, Cody HS. Axillary Dissection and Nodal Irradiation Can Be Avoided for Most Node-positive Z0011-eligible Breast Cancers: A Prospective Validation Study of 793 Patients. Ann Surg 2017;266(3):457–462.

■ OBJECTIVE: To determine rates of axillary dissection (ALND) and nodal recurrence in patients eligible for ACOSOG Z0011. BACKGROUND: Z0011 demonstrated that patients with cT1-2N0 breast cancers and 1 to 2 involved sentinel lymph nodes (SLNs) having breast-conserving therapy had no difference in locoregional recurrence or survival after SLN biopsy alone or ALND. The generalizability of the results and importance of nodal radiotherapy (RT) is unclear. METHODS: Patients eligible for Z0011 had SLN biopsy alone. Prospectively defined indications for ALND were metastases in ≥3 SLNs or gross extracapsular extension. Axillary imaging

was not routine. SLN and ALND groups and radiation fields were compared with chi-square and t tests. Cumulative incidence of recurrences was estimated with competing risk analysis. RESULTS: From August 2010 to December 2016, 793 patients met Z0011 eligibility criteria and had SLN metastases. Among them, 130 (16%) had ALND; ALND did not vary based on age, estrogen receptor, progesterone receptor, or HER2 status. Five-year event-free survival after SLN alone was 93% with no isolated axillary recurrences. Cumulative 5-year rates of breast+nodal and nodal+distant recurrence were each 0.7%. In 484 SLN-only patients with known RT fields (103 prone, 280 supine tangent, 101 breast+nodes) and follow-up ≥12 months, the 5-year cumulative nodal recurrence rate was 1% and did not differ significantly by RT fields. CONCLUSIONS: We confirm that even without preoperative axillary imaging or routine use of nodal RT, ALND can be avoided in a large majority of Z0011-eligible patients with excellent regional control. This approach has the potential to spare substantial numbers of women the morbidity of ALND.

Hot Topics

Seth A. Wander; Erica L. Mayer, and Harold J. Burstein

Blocking the Cycle: Cyclin-Dependent Kinase 4/6 Inhibitors in Metastatic, Hormone Receptor–Positive Breast Cancer

(J Clin Oncol 2017;35(25):2866–2870.)

Abstract: A 68-year-old postmenopausal woman was diagnosed with breast cancer 6 years ago when she presented with a stage II (T2N1), right-sided, invasive ductal carcinoma considered grade 2 of 3 on core biopsy, with a positive fine-needle aspiration of a palpable, ipsilateral axillary lymph node. Immunohisto-chemical analysis was positive for estrogen and progesterone receptor expression and negative for human epidermal growth factor receptor 2 (HER2) overexpression. She received neoadjuvant dose-dense doxorubicin, cyclophosphamide, and paclitaxel chemotherapy, followed by breast-conserving surgery and axillary lymph node dissection, which revealed residual disease in three of 11 nodes. She received adjuvant radiation therapy and initiated letrozole, with excellent compliance during the interval 6-year period. While receiving adjuvant letrozole therapy, she reported 3 months of worsening back pain. Skeletal scintigraphy and cross-sectional imaging confirmed widespread osseous metastatic disease and right supraclavicular lymph node enlargement (Figure 1). Core biopsy of the involved lymph node confirmed estrogen receptor (ER)–positive (90%), progesterone receptor–negative, HER2-negative recurrent metastatic breast cancer. The patient reported mild pain that was adequately controlled with over-the-counter anti-inflammatory medications. She has remained active with an excellent performance status.

Challenges in diagnosis and management

The selective ER degrader (SERD), fulvestrant, which was US Food and Drug Administration (FDA)–approved for treatment of advanced breast cancer in 2002, has been the standard of care for postmenopausal women with hormone receptor (HR)–positive, HER2-negative metastatic breast cancer that developed while receiving adjuvant aromatase inhibitor (AI) therapy or after first-line endocrine therapy with an AI. Recently, a trio of new kinase inhibitors that target cyclin-dependent kinases 4 and 6 (CDK4/6) have ushered in a new class of drugs for oncology and new treatment para in HR-positive, HER2-negative metastatic breast cancer.

The recent emergence of the CDK4/6 inhibitor class of therapy has prompted important questions about how best to add these agents to standard endocrine therapies, how to manage the specific adverse effects of CDK4/6 inhibitors, whether there are specific biomarkers that could inform patient selection for treatment, and whether these agents provide important value in cancer care.

Summary of the relevant literature

In ER-positive breast cancer, estrogen drives production of cyclin D1, which binds to and activates CDK4/6.[1] These active cyclin–CDK complexes phosphorylate the retinoblastoma (Rb) tumor suppressor, thereby releasing the critical eukaryotic transcriptional activator, E2 factor.[2] E2 factor is responsible for driving the transcription of multiple genes that are involved in the G1-S cell-cycle transition point, a key

Key points

- *The selective ER degrader (SERD), fulvestrant, which was US Food and Drug Administration (FDA)–approved for treatment of advanced breast cancer in 2002.*
- *Recently, a trio of new kinase inhibitors that target cyclin-dependent kinases 4 and 6 (CDK4/6) have ushered in a new class of drugs for oncology and new treatment para in HR-positive, HER2-negative metastatic breast cancer.*

Key points

- *CDK4/6 inhibitors also seem to have preferential activity in ER-positive luminal breast cancer cell lines and in a subset of HER2-positive cell lines, but had limited efficacy in triple-negative, nonluminal cells.*
- *Preclinical observations set the stage for the rational development of CDK4/6 inhibitors as therapies for ER-positive metastatic breast cancer.*
- *Three CDK4/6 inhibitors—palbociclib (Ibrance; Pfizer, New York, New York), ribociclib (Kisqali; Novartis, Basel, Switzerland), and abemaciclib (Lilly, Indianapolis, Indiana)—have undergone extensive clinical exploration along nearly identical development pathways.*
- *The PALOMA-1 study demonstrated a significant improvement in PFS favoring combination therapy (20.2 months vs. 10.2 months; hazard ratio, 0.488).*
- *The US FDA granted palbociclib accelerated approval in early 2015 as initial therapy for postmenopausal women with HR-positive, HER2-negative advanced breast cancer in combination with letrozole.*

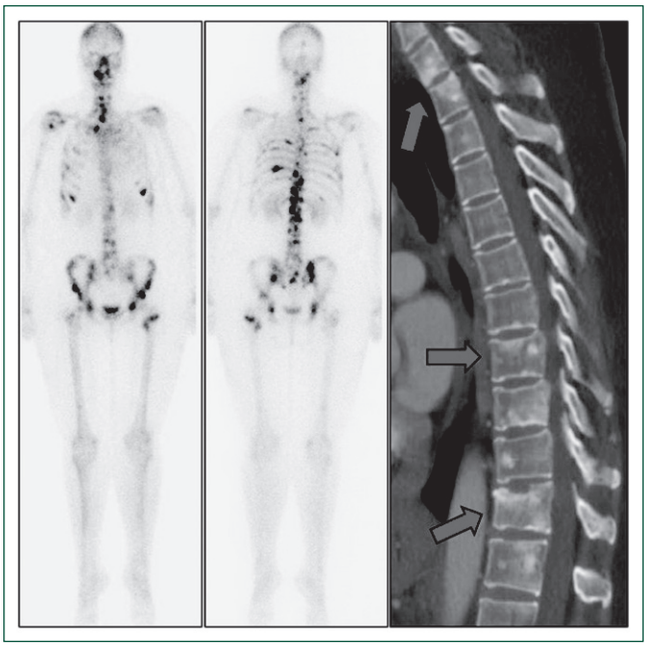

FIGURE 1 ■ Representative imaging. Nuclear medicine bone scan and computed tomography cross-sectional imaging study revealing widespread osseous metastatic disease in this patient with recurrent estrogen receptor–positive, human epidermal growth factor receptor 2–negative breast cancer. Arrows indicate areas of osseous metastatic disease.

checkpoint in promoting cellular proliferation. Preclinical work in both cell lines and xenograft models of ER-positive breast cancer revealed potential synergy when CDK4/6 inhibitors were combined with antiestrogen therapy.[3,4] CDK4/6 inhibitors also seem to have preferential activity in ER-positive luminal breast cancer cell lines and in a subset of HER2-positive cell lines, but had limited efficacy in triple-negative, nonluminal cells.[3]

■ First-line metastatic setting

These preclinical observations set the stage for the rational development of CDK4/6 inhibitors as therapies for ER-positive metastatic breast cancer. Three CDK4/6 inhibitors—palbociclib (Ibrance; Pfizer, New York, New York), ribociclib (Kisqali; Novartis, Basel, Switzerland), and abemaciclib (Lilly, Indianapolis, Indiana)—have undergone extensive clinical exploration along nearly identical development pathways. Each has been evaluated in randomized clinical trials as either first- or second-line treatments in combination with standard endocrine therapy for postmenopausal women with ER-positive, HER2-negative metastatic breast cancer, with a primary end point of progression-free survival (PFS; Table 1). Palbociclib was initially explored in a randomized, phase II, open-label study, PALOMA-1,[5] in which 165 patients were randomly assigned to receive letrozole alone or in combination with palbociclib as first-line therapy. Patients could have received prior adjuvant AI; however, discontinuation must have occurred at least 1 year before enrollment. The PALOMA-1 study demonstrated a significant improvement in PFS favoring combination therapy (20.2 months *vs*. 10.2 months; hazard ratio, 0.488). On the basis of these results, the US FDA granted palbociclib accelerated approval in early 2015 as initial therapy for postmenopausal women with HR-positive, HER2-negative advanced breast cancer in combination with letrozole. Results from PALOMA-1 were subsequently validated in the larger, randomized,

TABLE 1 - Select randomized clinical studies of endocrine therapy plus CDK4/6-directed therapy in estrogen receptor–positive metastatic breast cancer

Study	Regimen	Phase	No.	PFS, endocrine alone (months)	PFS, + CDK4/6 inhibitor (months)	Hazard ratio (95% CI)
First line						
PALOMA-1	Letrozole with or without palbociclib	II	165	10.2	20.2	0.488 (0.319 to 0.748)
PALOMA-2	Letrozole with or without palbociclib	III	666	14.5	24.8	0.58 (0.46 to 0.72)
MONALEESA-2	Letrozole with or without ribociclib	III	668	14.7	NR	0.56 (0.43 to 0.72)
MONARCH-3	NSAI with or without abemaciclib	III	493		NCT02246621*	
Second line						
PALOMA-3	Fulvestrant with or without palbociclib	III	521	4.6	9.5	0.46 (0.36 to 0.59)
MONARCH-2	Fulvestrant with or without abemaciclib	III	669	9.3	16.4	0.553 (0.449 to 0.681)
MONALEESA-3	Fulvestrant with or without ribociclib	III	725		NCT02422615	

*Interim analysis reportedly met primary end point of improved PFS in the combination arm.[8]
CDK4/6, cyclin-dependent kinase 4/6; PFS, progression-free survival; NSAI, nonsteroidal aromatase inhibitor.

placebo-controlled, phase III PALOMA-2 study.[6] In PALOMA-2, 666 postmenopausal patients with treatment-naïve metastatic HR-positive, HER2-negative breast cancer were randomly assigned to receive letrozole and placebo or letrozole and palbociclib. Palbociclib was associated with significant improvement in PFS among patients who received combination therapy (24.8 months *vs*. 14.5 months; hazard ratio, 0.58).

Nearly identical results have recently been reported for the combination of ribociclib and letrozole as first-line therapy. In the phase III, placebo-controlled MONALEESA-2 study, 668 patients were randomly assigned to receive ribociclib and letrozole versus letrozole and placebo.[7] Again, patients were allowed to have received prior AI therapy if the treatment interval exceeded 12 months. Median PFS for the ribociclib-based arm exceeded 24 months, whereas letrozole alone yielded a median PFS of 14.7 (hazard ratio, 0.56). On the basis of these results, ribociclib was recently granted US FDA approval in combination with an AI as initial therapy for postmenopausal women with HR-positive, HER2-negative metastatic breast cancer.

Abemaciclib has also been evaluated as a first-line treatment in combination with a nonsteroidal AI as part of the randomized, double-blind, placebo-controlled phase III MONARCH-3 trial that accrued 493 women (NCT02246621). A press release from Lilly on April 24, 2017, stated that MONARCH-3 also demonstrated an improvement in PFS with the addition of CDK4/6 inhibitor to AI therapy.[8]

Second-line and refractory metastatic setting

All three CDK4/6 inhibitors have also been assessed in randomized trials with the shared study design of fulvestrant with or without CKD4/6 inhibitor as second-line therapy for metastatic cancer after AI treatment in postmenopausal women (Table 1). The randomized,

Key points

- *Nearly identical results have recently been reported for the combination of ribociclib and letrozole as first-line therapy.*
- *In the phase III, placebo-controlled MONALEESA-2 study, 668 patients were randomly assigned to receive ribociclib and letrozole versus letrozole and placebo.*
- *Median PFS for the ribociclib-based arm exceeded 24 months, whereas letrozole alone yielded a median PFS of 14.7 (hazard ratio, 0.56).*

Key points

- *Palbociclib-based therapy improved PFS compared with fulvestrant alone (9.5 months vs. 4.6 months) with a hazard ratio of 0.46 (95% CI, 0.36 to 0.59).*
- *On the basis of these results, in early 2016, palbociclib was granted approval by the US FDA in combination with fulvestrant for women with HR-positive, HER2-negative metastatic breast cancer with disease progression after endocrine therapy.*
- *Double-blind, placebo-controlled, phase III study included postmenopausal women who had experienced progression either on first-line endocrine therapy for metastatic disease, on neoadjuvant or adjuvant endocrine therapy, or within 12 months of the end of adjuvant endocrine therapy.*
- *A total of 669 patients were randomly assigned to receive abemaciclib and fulvestrant or fulvestrant and placebo.*
- *Of note, despite the significant improvements observed in PFS in both the first-line and second-line metastatic setting, mature overall survival results have not yet been published from any of the large randomized studies outlined.*

placebo-controlled PALOMA-3 study explored the utility of palbociclib with fulvestrant in HR-positive, HER2-negative metastatic breast cancer.[9,10] In this trial, patients were required to have experienced progression with prior endocrine therapy for advanced breast cancer or developed recurrence within 12 months of adjuvant endocrine therapy, and 521 patients were randomly assigned to receive palbociclib with fulvestrant versus fulvestrant and placebo. Palbociclib-based therapy improved PFS compared with fulvestrant alone (9.5 months *vs*. 4.6 months) with a hazard ratio of 0.46 (95% CI, 0.36 to 0.59). Neither the degree of prior endocrine sensitivity, nor a patient's menopausal status—premenopausal women could initiate concurrent ovarian suppression—seemed to impact the response to combination therapy. On the basis of these results, in early 2016, palbociclib was granted approval by the US FDA in combination with fulvestrant for women with HR-positive, HER2-negative metastatic breast cancer with disease progression after endocrine therapy.

The study by Sledge et al,[11] which accompanies this article, provides data from the MONARCH-2 trial, which explored the efficacy of abemaciclib with fulvestrant in HR-positive, HER2-negative advanced breast cancer. This double-blind, placebo-controlled, phase III study included postmenopausal women who had experienced progression either on first-line endocrine therapy for metastatic disease, on neoadjuvant or adjuvant endocrine therapy, or within 12 months of the end of adjuvant endocrine therapy. A total of 669 patients were randomly assigned to receive abemaciclib and fulvestrant or fulvestrant and placebo. Combination therapy significantly improved PFS compared with fulvestrant alone (16.4 months *vs*. 9.3 months), with a hazard ratio of 0.553 (95% CI, 0.449 to 0.681). Different durations of PFS for the fulvestrant control arm in PALOMA-3 and MONARCH-2 may suggest underlying differences in the patient population and the sensitivity of tumors to fulvestrant therapy; the hazard ratio for relative benefit from the CDK4/6 inhibitors is essentially the same between the two trials.

Of note, despite the significant improvements observed in PFS in both the first-line and second-line metastatic setting, mature overall survival results have not yet been published from any of the large randomized studies outlined above. Similarly, with proven activity in either the first or second line of treatment, it is not known which timepoint would yield the optimal use or value of a CDK4/6 inhibitor.

Toxicity

All three CDK4/6 inhibitors are available in oral form and are reasonably well tolerated (Table 2). Both palbociclib and ribociclib are daily medications, administered intermittently on a 3-week on/1-week off schedule. Abemaciclib, in contrast, is administered continuously as a twice-per-day medication. Abemaciclib has demonstrated appreciable concentrations in the CSF, which may prove to be a clinical advantage, though there currently are no data to suggest the value of this pharmacologic property.[12] The toxicity profiles of palbociclib and ribociclib are similar. Because of the cytostatic effects of these agents on bone marrow progenitor cells, ribociclib and palbociclib cause frequent neutropenia (Table 2; > 74% all-grade toxicity; 54% to 67% grade 3 or 4 toxicity); however, despite the frequency of neutropenia, febrile neutropenia and other serious infections are exceedingly rare with palbociclib and ribociclib as a result of the rapid neutrophil maturation upon drug withdrawal.[13] Because of the high rates of neutropenia, a CBC with differential should be obtained on day 1 of each cycle and on day 14 of cycles 1 and 2. Palbociclib dose reductions to 100 mg or 75 mg for persistent neutropenia are common. Reassuringly, a detailed safety analysis from the PALOMA-3 trial demonstrated no detrimental impact on efficacy from the protocol-specified dose reduction.[14] Both agents may also cause occasional low-grade fatigue, nausea, and hair thinning.

■ **TABLE 2 - Dosing and toxicity for cyclin-dependent kinase 4/6 inhibitors**

Common adverse event*	Palbociclib (125 mg per day [3 weeks on, 1 week off])		Ribociclib (600 mg per day [3 weeks on, 1 week off])		Abemaciclib (200 mg twice per day [continuous])	
	All grades	Grade 3 and 4	All grades	Grade 3 and 4	All grades	Grade 3 and 4
Neutropenia	74–81	54–67	74	59	46	27
Thrombocytopenia	16–22	2–3	NR	NR	16	3
Fatigue	37–40	2–4	37	2	40	3
Diarrhea	21–26	1–4	35	1	86	13
Nausea	25–35	0–2	52	2	45	3
QTc prolongation	NR	NR	3	NR	NR	NR

Data are given as percent.
*Common adverse events in phase III trials in the metastatic setting.
NR, not reported; QTc, corrected QT interval.

Ribociclib causes occasional low-grade diarrhea, and patients on ribociclib require laboratory and ECG monitoring for rare instances of liver function test elevations and QT prolongation, respectively.

In the MONARCH-2 trial of fulvestrant with or without abemaciclib, serious adverse events that were possibly related to the study drug occurred at a low rate: 8.8% of all patients who received abemaciclib versus 1.3% of patients who received placebo. Compared with the other agents, abemaciclib had lower rates of neutropenia but greater degrees of diarrhea (Table 2; diarrhea, 86.4% all grade, 13.4% grade 3, and 0% grade 4 toxicity). Diarrhea was effectively managed with antidiarrheal medications, and the majority of patients did not require treatment modification. Less than 3% of patients discontinued the study drug as a result of diarrhea.

■ Biomarkers

Variability noted in response to CDK4/6-directed therapy underscores the critical need to establish tumor attributes that might serve as predictive biomarkers of response or resistance. Characterization of primary breast tumors as part of the effort of The Cancer Genome Atlas revealed high rates of cyclin D1 amplification in luminal tumors,[15] which is consistent with older findings on the basis of immunohistochemical analysis.[16] Rb loss or mutation, which would, in theory, render CDK4/6 inhibition ineffective as cell division has become independent of Rb control, seems to be an exceedingly rare event in primary luminal/ER-positive breast tumors.[15] Early preclinical characterization of palbociclib revealed that high levels of cyclin D1 and Rb, as well as low levels of the cell-cycle inhibitory molecule p16, were predictors of sensitivity,[3] whereas cell lines with loss of Rb were resistant in vitro.[17] Given these findings, components of the cyclin D1–CDK4/6–Rb pathway have been studied as potential biomarkers in patient populations. PALOMA-1 originally enrolled two distinct cohorts. Cohort 1 included any patient with HR-positive, HER2-negative disease, whereas cohort 2 restricted eligibility to include cyclin D1 amplification or *CDKN2A* (p16) loss.[5] Final analysis of the PALOMA-1 data set did not demonstrate a relationship between cyclin expression and palbociclib activity.

Circulating tumor DNA that was obtained via routine blood sampling—so called liquid biopsies[18]—have been used to explore other biomarkers that could predict outcomes with CDK4/6 inhibitors. To date,

Key points

- *Ribociclib causes occasional low-grade diarrhea, and patients on ribociclib require laboratory and ECG monitoring for rare instances of liver function test elevations and QT prolongation, respectively.*
- *Characterization of primary breast tumors as part of the effort of The Cancer Genome Atlas revealed high rates of cyclin D1 amplification in luminal tumors, which is consistent with older findings on the basis of immunohistochemical analysis.*
- *Early preclinical characterization of palbociclib revealed that high levels of cyclin D1 and Rb, as well as low levels of the cell-cycle inhibitory molecule p16, were predictors of sensitivity, whereas cell lines with loss of Rb were resistant in vitro.*

Key points

- *In PALOMA-3,* PIK3CA *mutations were overall an adverse prognostic marker, but did not predict benefit of palbociclib.*
- *Activating mutations in the ER (*ESR1*) arise in 30% to 40% of tumors that are resistant to AI therapy, but* ESR1 *mutations were not predictive of clinical benefit from fulvestrant plus palbociclib in PALOMA-3.*
- *Exploratory analysis of a diverse spectrum of biomarkers that were collected during the MONALEESA-2 study was recently presented.*
- *The success of CDK4/6 inhibitors in the treatment of advanced breast cancer has naturally prompted interest in the role of these agents as adjuvant therapy for early-stage breast cancer.*
- *The PALLAS study (NCT02513394) is a randomized, open-label, phase III study evaluating the outcome of adding 2 years of adjuvant palbociclib to standard endocrine therapy in HR-positive, HER2-negative early breast cancer.*
- *The PENELOPE-B study (NCT01864746) is a double-blind, placebo-controlled study exploring the combination of 1 year of adjuvant palbociclib and standard endocrine therapy in patients with residual disease after receiving preoperative chemotherapy.*

studies have not identified a specific biomarker that is associated with clear benefit or lack of benefit for CDK4/6 inhibition when administered with endocrine therapy. In PALOMA-3, *PIK3CA* mutations were overall an adverse prognostic marker, but did not predict benefit of palbociclib.[9,19] Activating mutations in the ER (*ESR1*) arise in 30% to 40% of tumors that are resistant to AI therapy,[20] but *ESR1* mutations were not predictive of clinical benefit from fulvestrant plus palbociclib in PALOMA-3.[21] Exploratory analysis of a diverse spectrum of biomarkers that were collected during the MONALEESA-2 study was recently presented.[22] Low versus high characterization of Rb, p16, and Ki-67 levels as evaluated by immunohistochemistry or cyclin D1, p16, and ESR1 levels as measured by RNA expression failed to predict patient response to the combination therapy of ribociclib and letrozole. In addition, circulating tumor DNA for *PIK3CA* was assessed and, as in PALOMA-3, failed to correlate with response to the combination therapy arm. Mechanisms of resistance to CDK4/6 inhibitors are under active study at this time and may include a compensatory increase in CDK6 expression.

Emerging applications

The success of CDK4/6 inhibitors in the treatment of advanced breast cancer has naturally prompted interest in the role of these agents as adjuvant therapy for early-stage breast cancer. The PALLAS study (NCT02513394) is a randomized, open-label, phase III study evaluating the outcome of adding 2 years of adjuvant palbociclib to standard endocrine therapy in HR-positive, HER2-negative early breast cancer. Ribociclib is being assessed in the adjuvant setting for women with high-risk HR-positive, HER2-negative disease as part of the randomized, placebo-controlled EarLEE-1 study (NCT03078751). The PENELOPE-B study (NCT01864746) is a double-blind, placebo-controlled study exploring the combination of 1 year of adjuvant palbociclib and standard endocrine therapy in patients with residual disease after receiving preoperative chemotherapy.

A practical question raised by the introduction of CDK4/6 inhibitors to routine clinical practice is whether there is clinical benefit for the continuation of CDK4/6-directed therapy beyond progression in the metastatic setting. The PACE study (NCT03147287) is an upcoming multicenter, randomized, phase II study that aims to determine whether there is activity for palbociclib in combination with fulvestrant after progression on a prior combination of CDK4/6 therapy with endocrine therapy. As CDK4/6 inhibitors continue to permeate standard clinical practice, the next generation of trials in metastatic HR-positive breast cancer must be designed to address potential issues related to cross-resistance and sequential therapy.

Suggested approaches to management

The goals of care for metastatic breast cancer include prolonging survival, reducing or preventing cancer-related symptoms, and maintaining quality of life for women who may live for many years with ongoing treatment. For patients with metastatic HR-positive, HER2-negative breast cancer, international guidelines support a strong preference to select endocrine therapy over chemotherapy as a first-line approach, except in circumstances of complete endocrine resistance or impending visceral crisis.[23,24] Indeed, an important goal of endocrine-based therapy is the delay of the introduction of chemotherapy and its attendant adverse effects.

The patient described in this summary developed metastatic HR-positive, HER2-negative breast cancer while receiving adjuvant treatment with an AI. She has a moderate disease burden, excellent performance status, no evidence of organ dysfunction, and lacks pre-existing comorbidities that might limit consideration of targeted agents.

We recommended the initiation of first-line fulvestrant in combination with a CDK4/6 inhibitor. We believe that these agents are sufficiently well tolerated that the opportunity to nearly double the effective time of endocrine treatment and thus delay the need for chemotherapy makes them valuable agents for the treatment of advanced breast cancer. With the caveat that head-to-head data are not yet available, we interpret the current, collective experience from randomized trials as showing broad similarities between each of the three CDK4/6 inhibitors with respect to efficacy and note the variations in their toxicity profiles. We initiated treatment with high-dose, monthly fulvestrant and palbociclib 125 mg per day on the standard 3-weeks on/1-week off dosing schedule. She also began bisphosphonate therapy for bone metastases. During laboratory monitoring, she was twice found to have asymptomatic grade 3 neutropenia (absolute neutrophil count < 1,000/mm^3), with recovery after a short drug hold, that prompted a dose reduction to 100 mg per day, which she has tolerated for 6 months without further incident. The patient has experienced minor hair thinning as a consequence of treatment. Her exam disclosed an interval decrease in the right supraclavicular lymph node, and imaging studies have shown sclerotic changes in her widespread osseous metastases consistent with treatment effect. She remains on treatment at this time.

Key points

- *We recommended the initiation of first-line fulvestrant in combination with a CDK4/6 inhibitor.*
- *We believe that these agents are sufficiently well tolerated that the opportunity to nearly double the effective time of endocrine treatment and thus delay the need for chemotherapy makes them valuable agents for the treatment of advanced breast cancer.*

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Genetic Testing in Patients With Newly Diagnosed Breast Cancer: Room for Improvement

(J Clin Oncol 2017;35(20):2221–2223.)

Inherited mutations in the tumor suppressor genes *BRCA1* and *BRCA2* confer high lifetime risks for breast and ovarian cancer. Although the incidence of pathogenic variants in these genes is only 0.1% to 0.2% in the general population, they account for up to 5% of all breast cancers and 50% of hereditary breast cancers.[1–3] Genetic testing to detect *BRCA* mutations has been available since 1996, but not until recently has testing become more widely used. Development of new massively parallel sequencing technology and the US Supreme Court ruling of Association for Molecular Pathology *vs*. Myriad Genetics, which invalidated the patents that restricted *BRCA1/2* testing, resulted in decreased costs for genetic testing and more widespread accessibility.[1,4] Public disclosures from some high-profile celebrities have also increased awareness of the importance of genetic testing in those with a significant family history of breast or ovarian cancer, which has led to patient-initiated testing. A Canadian retrospective study that evaluated the impact of the actress Angelina Jolie's story of undergoing risk-reducing bilateral mastectomy for being a *BRCA1* mutation carrier revealed that referral for genetic counseling rose by 90% in the first 6 months after the release of the story and that the number of *BRCA1/2* carriers identified increased by 110%.[3]

As more individuals with a significant family history and high pretest probability for mutation positivity undergo testing, more mutation carriers will be identified. However, some studies have suggested that a significant number of mutation carriers may not meet the criteria for testing because of a paucity of family history or underestimation from standard risk assessments. For example, an Ashkenazi Jewish population study that estimated breast and ovarian cancer risks in *BRCA1/2* mutation carriers reported that 51% of families who harbor the mutations had little or no family history of relevant cancer.[5] These families were small, with few females with mutations who had reached the ages of highest cancer risk; thus, young women in these families would not have been tested in the absence of a general screening program or study protocol.

The knowledge of having a clinically actionable genetic mutation can have a significant impact on one's life, and efforts should be made to identify all individuals who may benefit from genetic testing. Unaffected carriers of *BRCA1/2* mutations may opt to undergo risk-reducing surgical procedures or choose enhanced breast cancer surveillance by adding yearly magnetic resonance imaging. Patients with breast cancer with mutations may be offered more-aggressive surgical treatment, and targeted therapies, such as platinum agents and poly (ADP-ribose) polymerase inhibitors, may be included in the plan for systemic treatment.[6] However, despite improvements in accessibility and more widespread public awareness with regard to the role of genetic testing, utilization,

Key points

- *Genetic testing to detect* BRCA *mutations has been available since 1996, but not until recently has testing become more widely used.*
- *Development of new massively parallel sequencing technology and the US Supreme Court ruling of Association for Molecular Pathology* vs. *Myriad Genetics, which invalidated the patents that restricted* BRCA1/2 *testing, resulted in decreased costs for genetic testing and more widespread accessibility.*
- *The knowledge of having a clinically actionable genetic mutation can have a significant impact on one's life, and efforts should be made to identify all individuals who may benefit from genetic testing.*
- *Unaffected carriers of* BRCA1/2 *mutations may opt to undergo risk-reducing surgical procedures or choose enhanced breast cancer surveillance by adding yearly magnetic resonance imaging.*

Key points

- *The authors reported that only approximately one half of patients with breast cancer with a high pretest mutation risk underwent genetic testing.*
- *Determination of the proper timing of genetic testing is particularly important for patients with a new diagnosis of breast cancer who have not yet had breast surgery because the test result may influence surgical decision making.*
- *The most salient considerations include the probability of a positive result and the patient's desire and eligibility for breast-conserving therapy independent of genetic testing results.*
- *Patients at either average or high risk of* BRCA *positivity who prefer bilateral mastectomy regardless of genetic test results may proceed with surgery without waiting for the results because plans for surgical management will not be influenced.*
- *Although many patients with newly diagnosed breast cancer are eager to undergo surgery as soon as possible, the physician should explain and advise about the benefits of waiting for the genetic test results in certain situations.*

and implementation of genetic screening, counseling and testing remain inadequate, even among individuals with clear risk factors as evidence by a large population-based study that investigated patients' use and perspectives of genetic counseling and testing.[7] The authors reported that only approximately one half of patients with breast cancer with a high pretest mutation risk underwent genetic testing, and more than one half of those who did not have genetic testing were never recommended to be tested by the physician.

Determination of the proper timing of genetic testing is particularly important for patients with a new diagnosis of breast cancer who have not yet had breast surgery because the test result may influence surgical decision making. Some variables should be considered when deciding the timing of genetic testing related to surgery. The most salient considerations include the probability of a positive result and the patient's desire and eligibility for breast-conserving therapy independent of genetic testing results. Thus, the timing of testing and surgical management should be influenced by these variables, among others, in different common clinical scenarios.

Patients at high risk for *BRCA* positivity who desire breast-conserving surgery

Patients with a high likelihood for testing positive but who prefer and are eligible for breast-conserving therapy should be tested as soon as possible after diagnosis and are recommended to wait until test results are available, typically 2 to 3 weeks. If genetic test results prove positive, the patient should be informed of the elevated risk of contralateral breast cancer as well as the elevated recurrence risk in the affected breast with breast-conservation therapy only. Furthermore, patients should be counseled that for those who opt for lumpectomy coupled with radiation (deferment of mastectomy until if and when recurrence develops), there is the additional potential consequence of more-limited options for reconstruction in the future and a potential increased risk of complications after reconstruction related to having had radiation. As such, bilateral mastectomy in *BRCA* mutation carriers with breast cancer, particularly those who are diagnosed at a young age, should strongly be considered.

Patients at average risk who desire breast-conserving surgery

Although always reasonable to wait for genetic test results before proceeding with surgery, patients at average risk may elect to proceed with surgery with the understanding that if results come back positive after lumpectomy, consideration might be given to undergo more-extensive surgery.

Patients who prefer bilateral mastectomy regardless of genetic test results

Patients at either average or high risk of *BRCA* positivity who prefer bilateral mastectomy regardless of genetic test results may proceed with surgery without waiting for the results because plans for surgical management will not be influenced. However, if any doubt about undergoing more-extensive surgery is expressed or it is perceived that genetic test results will factor into surgical decision making, patients should be encouraged to wait for results.

Although many patients with newly diagnosed breast cancer are eager to undergo surgery as soon as possible, the physician should explain and advise about the benefits of waiting for the genetic test results in certain situations, such as those mentioned previously. Also important is that patients are reassured that a delay of surgery for a few weeks will in no way affect survival or risk of recurrence.

In the article accompanying this editorial, Kurian et al[8] reported that disappointingly, 27% of patients with breast cancer at high risk of mutation and 33% of those at average risk had genetic testing after surgery, and a substantial proportion of surgeons never delayed surgery for test results.

Even more alarming was the number of surgeons who admitted to managing patients with a variant of uncertain significance (VUS) the same way as *BRCA* mutation carriers, which likely led to 51% of average-risk patients with a VUS who underwent bilateral mastectomy. Because *BRCA1* and *BRCA2* are very large genes, different types of variations can occur. In 5% to 10% of patients, genetic test results will yield a VUS, which represents a variant of the gene where a change to the expected sequence is observed that has not been observed with any frequency in the testing laboratory to be clearly classified as pathogenic or nonpathogenic.[9,10] Currently, no internationally accepted standard for *BRCA* test reporting or a consistently agreed upon classification system exists, which has led some laboratories to report variants without interpretation.[9] Ordering providers who are not well versed in VUS literature may have difficulty with fully understanding the implications of a VUS result and misguide the patient. Because most VUSs are ultimately reclassified as benign, the management of an individual who carries a VUS should be based on personal and family history and not on the presence or absence of the variant itself.[11,12] Therefore, a patient with breast cancer without a significant family history or personal risk factors should not be recommended to undergo bilateral mastectomy solely on the basis of a VUS result. There is no question that when patients receive a VUS result, the word they often hear above all is "uncertain." As such, they often opt for more-extensive surgery, even when the meaning of VUS results are appropriately reviewed and discussed. Confounding their decision is that often, patients who undergo genetic testing to begin with have a family history of breast cancer and may be inclined toward more-extensive surgery irrespective of genetic test results. Our job as breast surgeons is to provide appropriate and accurate information in concert with our genetic counselors to convey that more-extensive surgery is no better than lumpectomy with respect to overall breast cancer survival and systemic recurrence and that a VUS has the potential to be reclassified as benign. Then it is our patients' decision.

In the study by Kurian et al,[8] VUS status was determined on the basis of patient survey. As with all survey studies, one limitation is that the results are subject to patient recall and ability to understand complex concepts, such as VUS, which can be fraught with inaccuracy.

Genetic testing has become an integral part of breast cancer treatment planning, and proper genetic counseling is critical to make informed decisions on the basis of the test result. Kurian et al[8] underscore some of the significant shortcomings of current patterns for integrating genetic testing into clinical practice. Counseling services by a trained professional often are lacking, in part because of the limited availability of genetic counselors. In addition, review of an individual's three-generation family tree and in-depth pretest risk assessment can be time consuming and may not be feasible in a busy physician's practice. Having a genetic counselor embedded within a breast clinic with the availability to counsel and initiate testing in appropriately selected patients on the same day as surgical consultation for a breast cancer diagnosis is optimal but not realistic in many, if not most, places. For example, Kurian et al point out that low-volume surgeons refer less frequently to genetic counselors. Might it be possible that low-volume surgeons represent less-populated areas where genetic counseling services are less readily available? Of interest is to ascertain the relationship between referral patterns to genetic counselors and geography of surgeons surveyed along with availability of genetic counseling services in that area. Furthermore, in the Kurian et al study, 39% of patients who underwent testing were considered to be at average risk for harboring a mutation. How in fact testing was actually achieved in these patients is unclear given restrictive criteria for coverage of testing by insurance companies and

Key points

- *Currently, no internationally accepted standard for BRCA test reporting or a consistently agreed upon classification system exists, which has led some laboratories to report variants without interpretation.*
- *A patient with breast cancer without a significant family history or personal risk factors should not be recommended to undergo bilateral mastectomy solely on the basis of a VUS result.*
- *There is no question that when patients receive a VUS result, the word they often hear above all is "uncertain."*
- *Confounding their decision is that often, patients who undergo genetic testing to begin with have a family history of breast cancer and may be inclined toward more-extensive surgery irrespective of genetic test results.*
- *Genetic testing has become an integral part of breast cancer treatment planning, and proper genetic counseling is critical to make informed decisions on the basis of the test result.*
- *Kurian et al underscore some of the significant shortcomings of current patterns for integrating genetic testing into clinical practice.*
- *Counseling services by a trained professional often are lacking, in part because of the limited availability of genetic counselors.*

Key points

- *Optimization of testing implementation and accurate interpretation should be paramount to the surgeon who cares for women with breast cancer.*

recent changes that deny coverage for testing without actual genetic counseling first.

In an ideal world, all facilities where patients with breast cancer are treated would at least have the ability to make a timely referral to a qualified health professional who can give proper counseling and administer genetic testing with the goal of providing accurate risk assessment and devising the best treatment plan for the patient. Genetic testing represents one of the most significant advances in personalizing breast cancer treatment and individualizing care. Optimization of testing implementation and accurate interpretation should be paramount to the surgeon who cares for women with breast cancer. As Kurian et al[8] demonstrate, on this front, there is much room for improvement.

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Landmark Clinical Trials

Efficacy and safety of anti-Trop-2 antibody drug conjugate sacituzumab govitecan (IMMU-132) in heavily pretreated patients with metastatic triple-negative breast cancer

AUTHORS
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PURPOSE
Trop-2, expressed in most triple-negative breast cancers (TNBCs), may be a potential target for antibody-drug conjugates. Sacituzumab govitecan, an antibody-drug conjugate, targets Trop-2 for the selective delivery of SN-38, the active metabolite of irinotecan.

PATIENTS AND METHODS
We evaluated sacituzumab govitecan in a single-arm, multicenter trial in patients with relapsed/refractory metastatic TNBC who received a 10 mg/kg starting dose on days 1 and 8 of 21-day repeated cycles. The primary end points were safety and objective response rate; secondary end points were progression-free survival and overall survival.

RESULTS
In 69 patients who received a median of five prior therapies (range, one to 12) since diagnosis, the confirmed objective response rate was 30% (partial response, n = 19; complete response, n = 2), the median response duration was 8.9 (95% CI, 6.1 to 11.3) months, and the clinical benefit rate (complete response + partial response + stable disease ≥ 6 months) was 46%. These responses occurred early, with a median onset of 1.9 months. Median progression-free survival was 6.0 (95% CI, 5.0 to 7.3) months, and median overall survival was 16.6 (95% CI, 11.1 to 20.6) months. Grade ≥ 3 adverse events included neutropenia (39%), leukopenia (16%), anemia (14%), and diarrhea (13%); the incidence of febrile neutropenia was 7%. The majority of archival tumor specimens (88%) were moderately to strongly positive for Trop-2 by immunohistochemistry. No neutralizing antibodies to the ADC or antibody were detected, despite repeated cycles developed.

CONCLUSION
Sacituzumab govitecan was well tolerated and induced early and durable responses in heavily pretreated patients with metastatic TNBC. As a therapeutic target and predictive biomarker, Trop-2 warrants further research.

REFERENCE
J Clin Oncol 2017;35(19):2141–2148.

Phase I study and biomarker analysis of pyrotinib, a novel Irreversible Pan-ErbB receptor tyrosine kinase inhibitor, in patients with human epidermal growth factor receptor 2-Positive metastatic breast cancer

AUTHORS
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PURPOSE
This phase I study assessed the safety, tolerability, pharmacokinetics, antitumor activity, and predictive biomarkers of pyrotinib, an irreversible pan-ErbB inhibitor, in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer. Patients and Methods Pyrotinib was administered continuously, orally, once per day to patients who did not have prior exposure to tyrosine kinase inhibitors of HER2. Planned dose escalation was 80, 160, 240, 320, 400, and 480 mg. For pharmacokinetic analysis, timed blood samples were collected on day 1 and day 28. Next-generation sequencing was performed on circulating tumor DNA and genomic DNA from tumor samples.

RESULTS
Thirty-eight patients were enrolled. The dose-limiting toxicity was grade 3 diarrhea, which occurred in two patients administered 480 mg of pyrotinib; thus, the maximum tolerated dose was 400 mg. Common pyrotinib-related adverse events included diarrhea (44.7% [17 of 38]), nausea (13.2% [five of 38]), oral ulceration (13.2% [five of 38]), asthenia (10.5% [four of 38]),

and leukopenia (10.5% [four of 38]). The only grade 3 adverse event was diarrhea. Pharmacokinetic analyses indicated that pyrotinib exposure was dose dependent. The overall response rate was 50.0% (18 of 36), and the clinical benefit rate (complete response + partial response + stable disease ≥ 24 weeks) was 61.1% (22 of 36). The median progression-free survival was 35.4 weeks (95% CI, 23.3 to 40.0 weeks). The overall response rate was 83.3% (10 of 12) in trastuzumab-naive patients and 33.3% (eight of 24) in trastuzumab-pretreated patients. Preliminary results suggest that PIK3CA and TP53 mutations in circulating tumor DNA (P = .013) rather than in archival tumor tissues (P = .474) may predict the efficacy of pyrotinib.

CONCLUSION

Continuous once-per-day pyrotinib was well tolerated and demonstrated promising antitumor activity in HER2-positive patients with metastatic breast cancer. The maximum tolerated dose was established as 400 mg. Diarrhea was the dose-limiting toxicity. The promising antitumor activity and acceptable tolerability of pyrotinib warrant its further evaluation in a phase II study.

REFERENCE

J Clin Oncol. 2017;35(27):3105–3112.

■ Hypofractionated postmastectomy radiation therapy Is safe and effective: first results from a prospective Phase II Trial

AUTHORS

Khan AJ, Poppe MM, Goyal S, Kokeny KE, Kearney T, Kirstein L, Toppmeyer D, Moore DF, Chen C, Gaffney DK, Haffty BG.

PURPOSE

Conventionally fractionated postmastectomy radiation therapy (PMRT) takes approximately 5 to 6 weeks. Data supporting hypofractionated PMRT is limited. We prospectively evaluated a short course of hypofractionated PMRT, in which therapy was completed in 15 treatment days. Patients and Methods We delivered PMRT at a dose of 36.63 Gy in 11 fractions of 3.33 Gy over 11 days to the chest wall and the draining regional lymph nodes, followed by an optional mastectomy scar boost of four fractions of 3.33 Gy. Our primary end point was freedom from any grade 3 or higher toxicities. We incorporated early stopping criteria on the basis of predefined toxicity thresholds.

RESULTS

We enrolled 69 women with stage II to IIIa breast cancer, of whom 67 were eligible for analysis. After a median follow-up of 32 months, there were no grade 3 toxicities. There were 29 reported grade 2 toxicities, with grade 2 skin toxicities being the most frequent (16 of 67; 24%). There were two patients with isolated ipsilateral chest wall tumor recurrences (2 of 67; crude rate, 3%). Three-year estimated local recurrence-free survival was 89.2% (95% CI, 0.748 to 0.956). The 3-year estimated distant recurrence-free survival was 90.3% (95% CI, 0.797 to 0.956). Forty-one patients had chest wall reconstructions; three had expanders removed for infection before radiation therapy. The total rate of implant loss or failure was 24% (9 of 38), and the unplanned surgical correction rate was 8% (3 of 38), for a total complication rate of 32%.

CONCLUSION

To our knowledge, our phase II prospective study offers one of the shortest courses of PMRT reported, delivered in 11 fractions to the chest wall and nodes and 15 fractions inclusive of a boost. We demonstrated low toxicity and high local control with this schedule. On the basis of our data, we have designed a cooperative group phase III prospective, randomized trial of conventional versus hypofractionated PMRT that will activate soon.

REFERENCE

J Clin Oncol 2017;35(18):2037–2043.

■ MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer

AUTHORS

Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, Park IH, Trédan O, Chen SC, Manso L, Freedman OC, Garnica Jaliffe G, Forrester T, Frenzel M, Barriga S, Smith IC, Bourayou N, Di Leo A.

PURPOSE

Abemaciclib, a cyclin-dependent kinase 4 and 6 inhibitor, demonstrated efficacy as monotherapy and in com-

bination with fulvestrant in women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer previously treated with endocrine therapy.

METHODS
MONARCH 3 is a double-blind, randomized phase III study of abemaciclib or placebo plus a nonsteroidal aromatase inhibitor in 493 postmenopausal women with HR-positive, HER2-negative advanced breast cancer who had no prior systemic therapy in the advanced setting. Patients received abemaciclib or placebo (150 mg twice daily continuous schedule) plus either 1 mg anastrozole or 2.5 mg letrozole, daily. The primary objective was investigator-assessed progression-free survival. Secondary objectives included response evaluation and safety. A planned interim analysis occurred after 189 events.

RESULTS
Median progression-free survival was significantly prolonged in the abemaciclib arm (hazard ratio, 0.54; 95% CI, 0.41 to 0.72; P = .000021; median: not reached in the abemaciclib arm, 14.7 months in the placebo arm). In patients with measurable disease, the objective response rate was 59% in the abemaciclib arm and 44% in the placebo arm (P = .004). In the abemaciclib arm, diarrhea was the most frequent adverse effect (81.3%) but was mainly grade 1 (44.6%). Comparing abemaciclib and placebo, the most frequent grade 3 or 4 adverse events were neutropenia (21.1% *vs*. 1.2%), diarrhea (9.5% *vs*. 1.2%), and leukopenia (7.6% *vs*. 0.6%).

CONCLUSION
Abemaciclib plus a nonsteroidal aromatase inhibitor was effective as initial therapy, significantly improving progression-free survival and objective response rate and demonstrating a tolerable safety profile in women with HR-positive, HER2-negative advanced breast cancer.

REFERENCE
J Clin Oncol 2017;35(32):3638–3646.

Trastuzumab emtansine with or without pertuzumab versus trastuzumab plus taxane for human epidermal growth factor receptor 2-positive, advanced breast cancer: primary results from the Phase III MARIANNE study

AUTHORS
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PURPOSE
Trastuzumab and pertuzumab are human epidermal growth factor receptor 2 (HER2) -targeted monoclonal antibodies, and trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that combines the properties of trastuzumab with the cytotoxic activity of DM1. T-DM1 demonstrated encouraging efficacy and safety in a phase II study of patients with previously untreated HER2-positive metastatic breast cancer. Combination T-DM1 and pertuzumab showed synergistic activity in cell culture models and had an acceptable safety profile in a phase Ib and II study.

METHODS
In the MARIANNE study, 1,095 patients with centrally assessed, HER2-positive, advanced breast cancer and no prior therapy for advanced disease were randomly assigned 1:1:1 to control (trastuzumab plus taxane), T-DM1 plus placebo, hereafter T-DM1, or T-DM1 plus pertuzumab at standard doses. Primary end point was progression-free survival (PFS), as assessed by independent review.

RESULTS
T-DM1 and T-DM1 plus pertuzumab showed noninferior PFS compared with trastuzumab plus taxane (median PFS: 13.7 months with trastuzumab plus taxane, 14.1 months with T-DM1, and 15.2 months with T-DM1 plus pertuzumab). Neither experimental arm showed PFS superiority to trastuzumab plus taxane. Response rate was 67.9% in patients who were treated with trastuzumab plus taxane, 59.7% with T-DM1, and 64.2% with T-DM1 plus pertuzumab; median response duration was 12.5 months, 20.7 months, and 21.2 months, respectively. The incidence of grade ≥ 3 adverse events was numerically higher in the control arm (54.1%)

versus the T-DM1 arm (45.4%) and T-DM1 plus pertuzumab arm (46.2%). Numerically fewer patients discontinued treatment because of adverse events in the T-DM1 arms, and health-related quality of life was maintained for longer in the T-DM1 arms.

CONCLUSION
T-DM1 showed noninferior, but not superior, efficacy and better tolerability than did taxane plus trastuzumab for first-line treatment of HER2-positive, advanced breast cancer.

REFERENCE
J Clin Oncol 2017;35(2):141–148.

A Phase I/Ib study of enzalutamide alone and in combination with endocrine therapies in women with advanced breast cancer

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PURPOSE
Several lines of evidence support targeting the androgen signaling pathway in breast cancer. Enzalutamide is a potent inhibitor of androgen receptor signaling. Preclinical data in estrogen-expressing breast cancer models demonstrated activity of enzalutamide monotherapy and enhanced activity when combined with various endocrine therapies (ET). Enzalutamide is a strong cytochrome P450 3A4 (CYP3A4) inducer, and ETs are commonly metabolized by CYP3A4. The pharmacokinetic (PK) interactions, safety, and tolerability of enzalutamide monotherapy and in combination with ETs were assessed in this phase I/Ib study.

EXPERIMENTAL DESIGN
Enzalutamide monotherapy was assessed in dose-escalation and dose-expansion cohorts of patients with advanced breast cancer. Additional cohorts examined effects of enzalutamide on anastrozole, exemestane, and fulvestrant PK in patients with estrogen receptor-positive/progesterone receptor-positive (ER^+/PgR^+) breast cancer.

RESULTS
Enzalutamide monotherapy (n = 29) or in combination with ETs (n = 70) was generally well tolerated. Enzalutamide PK in women was similar to prior data on PK in men with prostate cancer. Enzalutamide decreased plasma exposure to anastrozole by approximately 90% and exemestane by approximately 50%. Enzalutamide did not significantly affect fulvestrant PK. Exposure of exemestane 50 mg/day given with enzalutamide was similar to exemestane 25 mg/day alone.

CONCLUSIONS
These results support a 160 mg/day enzalutamide dose in women with breast cancer. Enzalutamide can be given in combination with fulvestrant without dose modifications. Exemestane should be doubled from 25 mg/day to 50 mg/day when given in combination with enzalutamide; this combination is being investigated in a randomized phase II study in patients with ER^+/PgR^+ breast cancer.

REFERENCE
Clin Cancer Res 2017;23(15):4046–4054.

Response to radiotherapy after breast-conserving surgery in different breast cancer subtypes in the swedish breast cancer Group 91 radiotherapy randomized clinical trial

AUTHORS
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PURPOSE
o evaluate the effect of adjuvant radiotherapy (RT) after breast conservation surgery in different breast cancer subtypes in a large, randomized clinical trial with long-term follow-up.

PATIENTS AND METHODS
Tumor tissue was collected from 1,003 patients with node-negative, stage I and II breast cancer who were randomly assigned in the Swedish Breast Cancer Group 91 Radiotherapy trial between 1991 and 1997 to breast

conservation surgery with or without RT. Systemic adjuvant treatment was sparsely used (8%). Subtyping was performed with immunohistochemistry and in situ hybridization on tissue microarrays for 958 tumors.

RESULTS

RT reduced the cumulative incidence of ipsilateral breast tumor recurrence (IBTR) as a first event within 10 years for luminal A-like tumors (19% *vs*. 9%; P = .001), luminal B-like tumors (24% *vs*. 8%; P < .001), and triple-negative tumors (21% *vs*. 6%; P = .08), but not for human epidermal growth factor receptor 2-positive (luminal and nonluminal) tumors (15% *vs*. 19%; P = .6); however, evidence of an overall difference in RT effect between subtypes was weak (P = .21). RT reduced the rate of death from breast cancer (BCD) for triple-negative tumors (hazard ratio, 0.35; P = .06), but not for other subtypes. Death from any cause was not improved by RT in any subtype. A hypothesized clinical low-risk group did not have a low risk of IBTR without RT, and RT reduced the rate of IBTR as a first event after 10 years (20% *vs*. 6%; P = .008), but had no effect on BCD or death from any cause.

CONCLUSION

Subtype was not predictive of response to RT, although, in our study, human epidermal growth factor receptor 2-positive tumors seemed to be most radioresistant, whereas triple-negative tumors had the largest effect on BCD. The effect of RT in the presumed low-risk luminal A-like tumors was excellent.

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J Clin Oncol. 2017;35(28):3222–3229.