ASCO special article

Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update

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PURPOSE To update the ASCO clinical practice guideline on adjuvant endocrine therapy based on emerging data about the optimal duration of aromatase inhibitor (AI) treatment.

METHODS ASCO conducted a systematic review of randomized clinical trials from 2012 to 2018. Guideline recommendations were based on the Panel's review of the evidence from six trials.

RESULTS The six included studies of AI treatment beyond 5 years of therapy demonstrated that extension of AI treatment was not associated with an overall survival advantage but was significantly associated with lower risks of breast cancer recurrence and contralateral breast cancer compared with placebo. Bone-related toxic effects were more common with extended AI treatment.

RECOMMENDATIONS The Panel recommends that women with node-positive breast cancer receive extended therapy, including an AI, for up to a total of 10 years of adjuvant endocrine treatment. Many women with node-negative breast cancer should consider extended therapy for up to a total of 10 years of adjuvant endocrine treatment based on considerations of recurrence risk using established prognostic factors. The Panel noted that the benefits in absolute risk of reduction were modest and that, for lower-risk node-negative or limited node-positive cancers, an individualized approach to treatment duration that is based on considerations of risk reduction and tolerability was appropriate. A substantial portion of the benefit for extended adjuvant AI therapy was derived from prevention of second breast cancers. Shared decision making between clinicians and patients is appropriate for decisions about extended adjuvant endocrine treatment, including discussions about the absolute benefits in the reduction of breast cancer recurrence, the prevention of second breast cancers, and the impact of adverse effects of treatment.

Additional information can be found at www.asco.org/breast-cancer-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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

INTRODUCTION

The ASCO Clinical Practice Guideline on Adjuvant Endocrine Therapy for Women with Hormone Receptor–Positive Breast Cancer was most recently updated and published in January 2016. 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 produced this 2018 Focused Update in response to new peer-reviewed publications of six randomized clinical trials (RCTs) on extension of aromatase inhibitor (AI) treatment published since the literature search date cutoff for the 2014 update.

Focused Updates for Clinical Practice Guidelines are approved by the Clinical Practice Guidelines Committee, and this Update reflects new evidence regarding the recommendation on duration of adjuvant endocrine treatment in previous versions of this guideline, which have focused on the first 5 years of treatment,[1] or the duration of therapy for women who receive tamoxifen monotherapy.[2] This summarizes an updated literature search and reviews and analyzes new data regarding this recommendation available since the systematic review for the previous update in 2014, with a specific focus on duration of endocrine therapy for postmenopausal women who may have AI treatment as part of their initial adjuvant regimens and AI treatment as extended adjuvant endocrine therapy.

This 2018 Update does not address the other clinical questions posed in the 2010 guideline or in the 2013 and 2016 updates. Appendix Table A1 (online only) provides a summary of those previous recommendations, which remain current.

GUIDELINE QUESTIONS

As this Focused Update addresses solely one Clinical Question, the Guideline Questions for the full guideline are available in the Appendix (online only).

THE BOTTOM LINE

Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update

Guideline Question Does extended adjuvant therapy, including aromatase inhibitors (AIs), after 5 years of sequential endocrine therapy improve clinically meaningful outcomes (disease-free survival, overall survival, quality of life, and toxicity) in postmenopausal women with hormone receptor–positive early breast cancer?

Target Population Postmenopausal women with stages I to III hormone receptor–positive breast cancer.

Target Audience Medical, surgical, and radiation oncologists; oncology nurses and physician assistants; general practitioners; and women with stages I to III hormone receptor–positive breast cancer.

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

Focused Update Recommendations

Recommendation 1. Many women with node-negative breast cancer are potential candidates for and may be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine treatment based on considerations of recurrence risk using established prognostic factors. However, as the recurrence risk is lower, the benefits are likely narrower for such patients. Women with low-risk node-negative tumors should not routinely be offered extended therapy.

Recommendation 2. Women with node-positive breast cancer should be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine treatment.

Recommendation 3. Women who receive extended adjuvant endocrine therapy should receive no more than 10 years of total treatment.

Recommendation 4. As prevention of secondary or contralateral breast cancers is a major benefit of extended AI therapy, the risk of second breast cancers (or not) based on prior therapy should inform the decision to pursue extended treatment.

Recommendation 5. Extended therapy carries ongoing risks and side effects, which should be weighed against the potential absolute benefits of longer treatment in a shared decision-making process between the clinical team and the patient.

Qualifying Statement. To date, none of the studies have shown improvement in overall survival with longer-duration AI therapy. As such, the recommendations on extended adjuvant AI therapy are based on benefits that include prevention of distant recurrence and prevention of second breast cancers.

Refer to Appendix Table A1 for the full list of recommendations.

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

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

METHODS

This ASCO Clinical Practice Guideline Focused Update provides revised recommendations with a comprehensive discussion of the relevant literature (2012 to 2018) for this specific recommendation. The full guideline to which this revision applies and additional information are available at www.asco.org/breast-cancer-guidelines. The complete list of recommendations, including the updated recommendation(s), is in Appendix Table A1.

The recommendations for this update were developed by a multidisciplinary group of experts (Appendix Table A2, online only), which included a patient representative and an ASCO Guidelines staff with health research methodology expertise, using evidence from phase III, RCTs and clinical experience as a guide. Clinical Practice Guideline Updates are approved by the ASCO Clinical Practice Guidelines Committee. A systematic review in PubMed was conducted from 2012 through 2018 and for meeting abstracts through 2017.

Articles were selected for inclusion in the systematic review of the evidence if they met the following criteria:

- Published journal articles from the medical literature
- Phase III RCTs
- Meeting abstracts, if presentations/posters were available
- Written language, English only

- Systematic reviews with or without meta-analyses
- Study population of postmenopausal women

Articles were excluded from the systematic review if they were (1) other reviews (consensus, narrative, expert panel, guidelines); (2) editorials, commentaries, letters, news articles, case reports; or (3) published in a non-English language. Ratings for the type of recommendation and strength of the evidence and potential bias are provided with each recommendation (see the Methodology Supplement for rating definitions).

Detailed information about the methods used to develop this guideline is available in the Methodology Supplement at www.asco.org/breast-cancer-guidelines, including an overview (eg, Expert Panel composition, development process); literature search and data extraction; and recommendation development and quality assessment processes. All funding for the administration of the project was provided by ASCO.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the 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

Study Characteristics

Six phase III RCTs met the eligibility criteria of the updated systematic review and comprise the evidentiary basis for the guideline recommendations on duration of AI therapy.[3-8] As seen in Figure 1 and Table 1, each of these studies investigated the benefit of extended adjuvant therapy with AIs beyond 5 years in postmenopausal women with stage I to III, hormone receptor–positive breast cancer. The trial, Letrozole in Treating Women With Primary Breast Cancer Who Have Received 5 Years of Aromatase Inhibitor Therapy (MA.17R)[3] compared letrozole 2.5 mg daily of letrozole with placebo for 5 years in 1,918 women who had already received 4.5 to 6 years of adjuvant therapy with an AI, preceded in most women by treatment with tamoxifen. Eligible women had to be disease free, had to have an Eastern Cooperative Oncology Group performance status of less than 3, and had a minimum life expectancy of at least 5 years. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-42 study[7] also compared letrozole 2.5 mg daily with placebo in 3,923 women who had completed 5 years of endocrine therapy that consisted of either 5 years of an AI or up to 3 years of tamoxifen followed by an AI for a total of 5 years. The Different Durations of Adjuvant Anastrozole Therapy (DATA) trial[5] compared 6 years of adjuvant anastrozole (1 mg daily) with 3 years of adjuvant anastrozole, in 1,660 women, after 2 to 3 years of adjuvant tamoxifen. To be eligible, women had to be free of signs of locoregional recurrence or distant metastases. The Investigation on the Duration of Extended Adjuvant Letrozole (IDEAL) trial[4] randomly assigned 1,824 women who were disease free to letrozole for either 2.5 or 5 years. Eligibility included WHO performance status less than or equal to 1 and completion of 5 years adjuvant endocrine

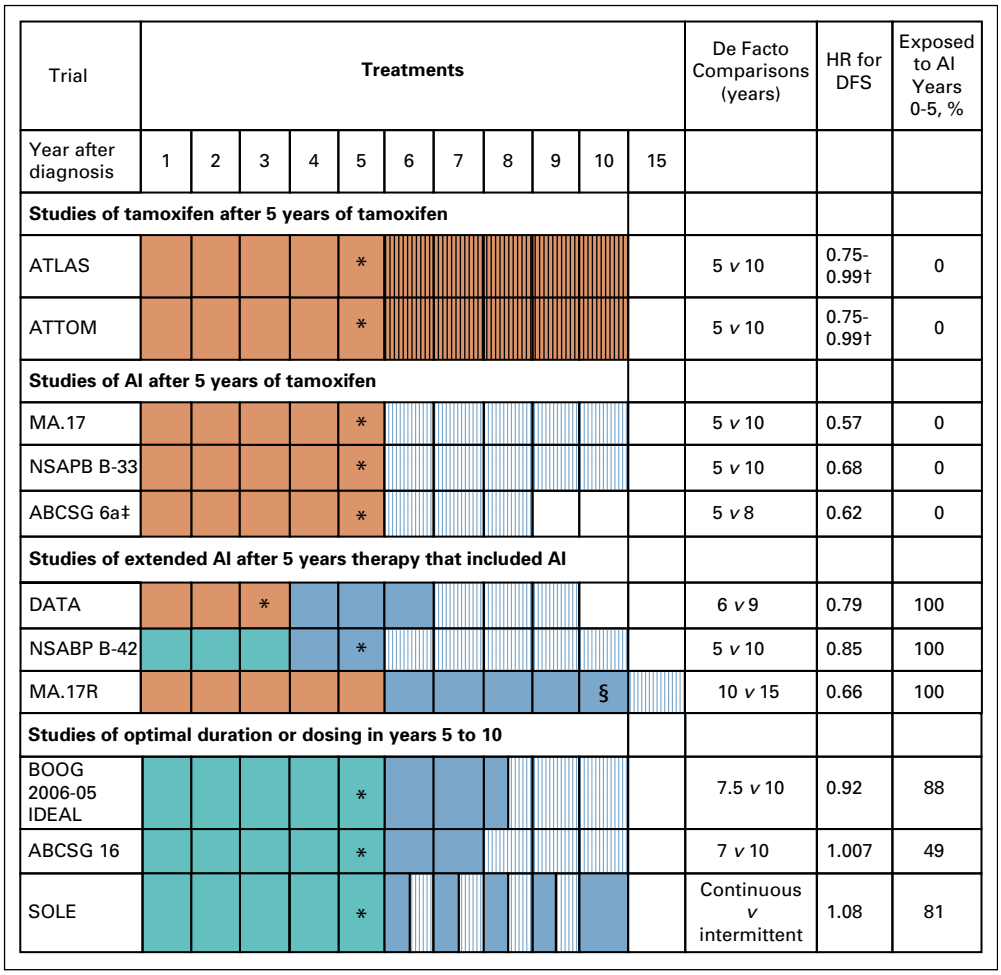

FIG 1. Schema for trials of extended adjuvant endocrine therapy. ABCSG, Austrian Breast Cancer Study Group; AI, aromatase inhibitor; ATLAS, Adjuvant Tamoxifen Longer Against Shorter; ATTOM, Adjuvant Tamoxifen—To Offer More; BOOG, Borstkanker Onderzoek Groep; DATA, Different Durations of Adjuvant Anastrozole Therapy; DFS, disease-free survival; HR, hazard ratio; IDEAL, Investigation on the Duration of Extended Adjuvant Letrozole; MA.17, Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years; MA.17R, Extending Aromatase-Inhibitor Adjuvant Therapy to 10 years; NSABP, National Surgical Adjuvant Breast and Bowel Project; SOLE, Study of Letrozole Extension. (*) Time of random assignment. (†) The trials of extended tamoxifen therapy showed a time-dependent HR. After 10 years (ie, 5 years after random assignment), the HR was 0.75, but it was lower in earlier years of follow-up. (‡) Some patients in ABCSG 6 received tamoxifen ± aminoglutethimide, a first-generation AI. (§) Patients in MA.17R were randomly assigned after 5 years of letrozole with or without having received 5 years of tamoxifen. Dark orange, tamoxifen; teal, AI or tamoxifen; blue, AI. Striped years denote timing of randomized intervention versus no treatment or placebo.

therapy with either tamoxifen for 5 years, an AI for 5 years, or a sequence of both. The Austrian Breast Cancer Study Group trial 16 (ABCSG 16)[8] randomly assigned 3,484 women free of cancer recurrence after 4 to 6 years of adjuvant therapy with tamoxifen, an AI, or a sequence of tamoxifen and then an AI to either 2 or 5 years of anastrozole as extended therapy. The Study of Letrozole Extension (SOLE) trial[6] included 4,884 women with node-positive breast cancer who were randomly assigned after 5 years of adjuvant endocrine therapy to either continuous letrozole for 5 years or to 5 years of an intermittent schedule of letrozole given 9 months on and 3 months off in years 1 through 4 and then on throughout year 5. The primary outcome for all studies was disease-free survival (DFS), whereas overall survival (OS) and adverse events (AEs) were secondary outcomes.

Study Quality

Study quality was formally assessed for the six included studies. Design aspects related to the individual study quality were assessed by one reviewer and independently audited by another for factors such as blinding, allocation concealment, placebo control, intention to treat, and funding sources. The risk of bias was assessed as low to intermediate for the included trials. Refer to the Methodology in the Data Supplement for the detailed quality assessment and definitions of ratings for overall potential risk of bias.

RECOMMENDATIONS

Does extended adjuvant AI therapy after 5 years of sequential endocrine therapy improve clinically meaningful outcomes (DFS, OS, quality of life, and toxicity) in

TABLE 1. Summary of Trials

Trial or Patient Characteristic	Study											
	MA.17R[3]		NRG Oncology/ NSABP B-42[7]		DATA[5]		IDEAL[4]		ABCSG 16[8]		SOLE[6]	
	Letrozole 2.5 mg (n = 959)	Placebo (n = 959)	Letrozole 2.5 mg (n = 1,959)	Placebo (n = 1,964)	Anastrozole 3 year 1 mg (n = 833)	Anastrozole 6 year 1 mg (n = 827)	Letrozole 2.5 year (n = 908)	Letrozole 5 year (n = 913)	Anastrozole 2 year 1 mg (n = 833)	Anastrozole 5 year 1 mg (n = 827)	Continuous Letrozole (n = 2,426)	Intermittent Letrozole (n = 2,425)
Trial characteristic												
Duration of treatment	5 years		5 years		3 years	6 years	2.5 years	5 years	2 years	5 years	5 years	
Eligibility criteria	Postmenopausal status		Postmenopausal status		Postmenopausal status		Postmenopausal status		Postmenopausal status		Postmenopausal status	
	Disease free after having completed 4.5-6 years of AI therapy		ER positive and/or PR positive		ER positive and/or PR positive		Histologically proven invasive breast cancer adequately treated at time of diagnosis		Histologically confirmed, local radically treated invasive or minimal-invasive breast cancer with or without previous chemotherapy and/or radiotherapy		Operable, unilateral breast cancer for which they had undergone local treatment (surgery ± radiotherapy) with no known clinical residual locoregional disease	
	HR positive (unknown HR status was permitted only for patients who had participated in MA.17)		Stage I, II, or IIIa invasive breast cancer at diagnosis		Already received 2-3 years of adjuvant tamoxifen		ER positive and/or PR positive		No distant metastasis or relapse at random assignment		No distant metastasis or relapse at random assignment	
	PS < 3 on ECOG scale		Completed 5 years of hormonal therapy consisting of either 5 years of an AI or up to 3 years of tamoxifen followed by an AI (for a total of 5 years)		Never had signs of locoregional recurrences or distant metastasis		Completed 5 years (± 3 months) adjuvant endocrine therapy with either tamoxifen for 5 years, AIs for 5 years, or a sequence of both (provided tamoxifen was given upfront for 2-3 years)		TNM classification at time of diagnosis: T1-3, N0 and N+, M0		Lymph node positive	
	Minimum life expectancy of ≥ 5 years						No evidence of breast cancer recurrence at time of random assignment		ER positive and PR positive before the beginning of primary endocrine therapy		ER positive and/or PR positive	
							WHO PS 0 or 1				Completed 4-6 years of adjuvant endocrine therapy	
							Adjuvant endocrine treatment completed for no longer than 2 years		Endocrine therapy for 5 years (maximum deviation ± 12 months)			
							Accessible for follow up for the duration of the trial		Therapy break (from the preliminary therapy) maximum 12 months			
Median time between initial diagnosis and random assignment	10.6 years		NR		NR		NR		NR		NR	
Median duration of prior treatment with tamoxifen	5 years; 68.5% received tamoxifen for 4.5-5.5 years; 20.7% received no tamoxifen		NR		2.3 years (IQR, 2.1-2.5 years) for both groups		NR		NR		Median duration of previous endocrine therapy	

(continued on following page)

TABLE 1. Summary of Trials (continued)

Trial or Patient Characteristic	Study											
	MA.17R[3]		NRG Oncology/ NSABP B-42[7]		DATA[5]		IDEAL[4]		ABCSG 16[8]		SOLE[6]	
	Letrozole 2.5 mg (n = 959)	Placebo (n = 959)	Letrozole 2.5 mg (n = 1,959)	Placebo (n = 1,964)	Anastrozole 3 year 1 mg (n = 833)	Anastrozole 6 year 1 mg (n = 827)	Letrozole 2.5 year (n = 908)	Letrozole 5 year (n = 913)	Anastrozole 2 year 1 mg (n = 833)	Anastrozole 5 year 1 mg (n = 827)	Continuous Letrozole (n = 2,426)	Intermittent Letrozole (n = 2,425)
Median duration of prior treatment with an AI	5 years; 95.4% received AI for 4.5-5.5 years		NR		NR		NR		NR		5.0 years (IQR, 4.7-5.1 years)	
Median interval between last dose of AI and random assignment	< 6 months for 90% of patients		NR		NR		NR		NR		72% ended prior endocrine therapy ≤ 1 month	70% ended prior endocrine therapy ≤ 1 month
Rate of adherence, %	62.5	62.3	NR	62.5	NR		73.5	57.5	75.7	59.4	NR, but rates were similar for both groups	
Median follow-up	6.25 years (75 months)		6.9 years		4.2 years		6.6 years		8.85 years (106.2 months)		5 years	
Primary outcome measure	DFS		DFS (defined as local, regional, distant recurrence, contralateral breast cancer, second nonbreast primary cancer, and death as a result of any cause)		Adapted DFS (defined as the DFS starting as of 3 years after random assignment and including as event: breast cancer recurrences (local, regional, distant); second primary cancers, including contralateral breast cancer and cancers other than basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix; death as a result of any cause)		DFS		DFS		DFS	
Secondary outcome measure	OS, incidence of contralateral breast cancer, QOL, long-term safety		OS, BCFI, distant recurrence, osteoporotic fractures, arterial thrombotic events		Incidence of contralateral breast cancer, OS, and toxicity		OS, distant metastasis–free interval, second primary breast cancer, safety		OS, time to contralateral breast cancer, time to second primary cancer, time to first clinical fracture		OS, BCFI, distant recurrence–free interval, sites of first DFS event, second (nonbreast) malignancies, deaths without prior cancer event, and AEs	
Patient characteristic, %												
Node positive	53.5	53.2	42-43		66.2	67.8	73.9	74.3	31.8	30.1	99	99
Node negative	46.5	46.7	57-58		33.8	32.2	26.1	25.7	65.8	66.9	1	1
Prior adjuvant tamoxifen	79.3		39		NR		71.3	71.2	51.1	50.6	18*	18*
Age < 60 years	NR		34-35		58.6	58.4	70 (< 65 years)	69.6 (< 65 years)	31.8		49.1	48.1
HER2 negative	NR		78 (8 unknown)		89.8 (7.6 unknown)	90.1 (7.7 unknown)	79.3	81.1	NR		74 (7 unknown)	76 (9 unknown)

Abbreviations: ABCSG, Austrian Breast Cancer Study Group; AE, adverse event; AI, aromatase inhibitor; BCFI, breast cancer–free interval; DATA, Different Durations of Adjuvant Anastrozole Therapy; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HR, hormone receptor; IDEAL, Investigation on the Duration of Extended Adjuvant Letrozole; IQR, interquartile range; MA.17R, Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years; NR, not reported; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival; PR, progesterone receptor; PS, performance status; QOL, quality of life; SOLE, Study of Letrozole Extension.

*SERMs only.

postmenopausal women with hormone receptor–positive early breast cancer? If so, which patients should be advised to receive such therapy, and how should treatment optimally be administered?

Focused Update Recommendations

Recommendation 1. Many women with node-negative breast cancer are potential candidates for and may be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine treatment based on considerations of recurrence risk using established prognostic factors. However, as the recurrence risk is lower, the benefits are likely narrower for such patients. Women with low-risk node-negative tumors should not routinely be offered extended therapy.

Recommendation 2. Women with node-positive breast cancer should be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine treatment.

Recommendation 3. Women who receive extended adjuvant endocrine therapy should receive no more than 10 years of total treatment.

Recommendation 4. As prevention of secondary or contralateral breast cancers is a major benefit of extended AI therapy, the risk of second breast cancers (or not) based on prior therapy should inform the decision to pursue extended treatment.

Recommendation 5. Extended therapy carries ongoing risks and side effects, which should be weighed against the potential absolute benefits of longer treatment in a shared decision-making process between the clinical team and the patient.

Qualifying statement. To date, none of the studies have shown improvement in overall survival with longer-duration AI therapy. As such, the recommendations on extended adjuvant AI therapy are based on benefits that include prevention of distant recurrence and prevention of second breast cancers.

Literature review and analysis. This section summarizes the results of the six trials included in the 2018 updated systematic review. Data on outcomes of interest are reported in Table 2 and Table 3.

DFS

DFS was considered the primary outcome in all trials although the definition of this varied. The MA.17R trial[3] reported statistically significantly higher 5-year rates of DFS, defined as the time from random assignment to recurrence of breast cancer (local, regional, or distant) or the development of new primary breast cancer in women who received extended AI therapy compared with those who received placebo. Multivariable analyses that adjusted for stratification factors, including lymph node status, prior receipt of adjuvant chemotherapy, the interval between the last dose of AI and random assignment, and the duration of prior tamoxifen and AI received before the trial, showed that the risk for disease recurrence, occurrence of contralateral breast cancer, or death was reduced by 21% with extended AI therapy (hazard ratio, 0.79; 95% CI, 0.63 to 1.00; $P = .05$). The NSABP,[7] DATA,[5] and IDEAL[4] trials showed a trend toward higher DFS with extended AI therapy, but statistical significance was not reached. There was no difference in DFS observed in the ABCSG 16 trial[8] of 10 versus 7 years of therapy. The SOLE study[6] did not show a difference in DFS for intermittent compared with continuous extended AI therapy through a total of 10 years of treatment.

Contralateral/Second Primary/Breast Cancer–Free Interval/OS

The MA.17R trial[3] reported that the risk of breast cancer recurrence and contralateral breast cancer was reduced by 34% among women who continued AI therapy for 10 years compared with those who received placebo after initial AI therapy ($P = .01$). When the annual incidence rate of contralateral breast cancer alone was considered, a reduction of 58% was reported in women on extended AI therapy compared with those randomly assigned to placebo. Extended AI therapy resulted in a statistically significant improvement in breast cancer–free interval, as seen in the 29% reduction in the risk of breast cancer recurrence or contralateral breast cancer reported in the NSABP B-42 trial.[7] This trial also reported a 28% statistically significant reduction in the cumulative incidence of distant recurrence. The IDEAL trial[4] found a statistically significant but modest 1% absolute risk reduction in second primary breast cancers. There was no difference in distant metastasis–free interval found in the IDEAL trial. Neither the ABCSG 16 trial[8] nor the SOLE trial[6] showed a significant reduction in risk of contralateral breast cancer. Extended AI therapy has not as yet been shown to improve OS in any of the six trials.

Quality of Life

The MA.17R trial[3] reported on quality-of-life outcomes and found no significant between-group differences in the 36-Item Short Form Survey (SF-36) summary scores, in the majority of SF-36 subscale scores, or in The Menopause-Specific Quality of Life Questionnaire (MENQOL) symptom subscales. However, when the role-physical subscale of the SF-36 was considered, a significantly worse quality-of-life score was seen among women in the letrozole group compared with the placebo group ($P = .009$). Patient-reported outcomes during the first 2 years of treatment in the SOLE trial[6] suggested that intermittent AI therapy was associated with significantly less worsening in physical well-being, mood and sleep disturbances than continuous therapy; however, longer-term health-related quality-of-life data are not available yet.

AEs

Extended AI therapy resulted in an increase in well-described AEs across all six trials. Bone-related AEs occurred significantly more frequently in women who received extended AI therapy than in those randomly assigned to placebo in the MA.17R trial.[3] The other trials reported a

TABLE 2. Efficacy Outcomes

Study	Intervention/ Comparison	Disease-Free Survival at 5 Years	Overall Survival at 5 Years	Second Primary Breast Cancer, Including Contralateral	Recurrence	QOL
MA.17R[3]	Letrozole (n = 959) for an additional 5 years *v* placebo (n = 959)	Letrozole: 95% (95% CI, 93% to 96%)	Letrozole: 93% (95% CI, 92% to 95%)	Letrozole: 13/959 (1.4%)	Letrozole: 55/959 (5.7%)	SF-36 summary score *P* = NS
		Placebo: 91% (95% CI, 89% to 93%)	Placebo: 94% (95% CI, 92% to 95%)	Placebo: 31/959 (3.2%)	Placebo: 68/959 (7.1%)	SF-36 role-physical subscale: between-group difference in change (worsening) in score *P* = .009
		HR, 0.79 (0.63 to 1.00)*	HR, 0.97 (95% CI, 0.73 to 1.28)	HR, 0.66 (95% CI, 0.48 to 0.91)†	HR, NR	MENQOL score *P* = NS
		P = .05	*P* = .83	*P* = .01		
NSABP B-42[7]	Letrozole (n = 1,959) for an additional 5 years *v* placebo (n = 1,964)	Letrozole: 84.7%	Letrozole: 91.8%	Cumulative incidence of breast cancer–free interval:	Cumulative incidence of distant recurrence	NR
		Placebo: 81.3%	Placebo: 92.3%	Letrozole: 6.7%	Letrozole: 3.9%	
		HR, 0.85 (95% CI, 0.73 to 0.999)	HR, 1.15 (95% CI, 0.92 to 1.44)	Placebo: 10.0%	Placebo: 5.8%	
		P = .048	*P* = .22	HR, 0.71 (95% CI, 0.56 to 0.89)	HR, 0.72 (95% CI, 0.53 to 0.97)	
				P = .003	*P* = .03	
DATA[5]	Anastrozole 6 years *v* 3 years	Adapted DFS‡	Adapted OS	Adapted cumulative 5-year incidence of second breast cancer:	NR	NR
		Anastrozole 6 years: 83.1%	Anastrozole 6 years: 90.8%	Anastrozole 6 years: 1.5% (95% CI, 0.5% to 2.4%)		
		Anastrozole 3 years: 79.4%	Anastrozole 3 years: 90.4%	Anastrozole 3 years: 3.3% (95% CI, 1.7% to 4.9%)		
		HR, 0.79 (0.62 to 1.02)	HR, 0.91 (0.65 to 1.29)	HR, 0.50 (95% CI, 0.23 to 1.07)		
		P = .07	*P* = .60	*P* = .068		
			Note: The median adapted follow-up was only 4.1 years at the time of presentation.			
IDEAL[4]	Letrozole 2.5 years *v* 5 years	Letrozole 2.5 years: 82.0%	Letrozole 2.5 years: 93.5%	Letrozole 2.5 years: 3.1%	DMFI:	NR
		Letrozole 5 years: 83.4%	Letrozole 5 years: 92.6%	Letrozole 5 years: 1.1%	Letrozole 2.5 years: 6.1%	
		HR, 0.92 (95% CI, 0.74 to 1.16)	HR, 1.04 (95% CI, 0.78 to 1.38)	HR, 0.39 (95% CI, 0.19 ro 0.81)	Letrozole 5 years: 7.1%	
		P = .49	*P* = .79	*P* = .01	HR, 1.06 (95% CI, 0.78 to 1.45)	
					P = .71	

(continued on following page)

TABLE 2. Efficacy Outcomes (continued)

Study	Intervention/ Comparison	Disease-Free Survival at 5 Years	Overall Survival at 5 Years	Second Primary Breast Cancer, Including Contralateral	Recurrence	QOL
ABCSG 16[8]	Anastrozole 2 years vs 5 years	At 10 years:	At 10 years:	Contralateral:	NR	NR
		Anastrozole 2 years: 71.1%	Anastrozole 2 years: 85.3%	Anastrozole 2 years: 3.5%		
		Anastrozole 5 years: 70.3%	Anastrozole 5 years: 84.9%	Anastrozole 5 years: 3.9%		
		HR (*v* 2 years), 1.007 (0.87 to 1.16)	HR (*v* 2 years), 1.01 (0.82 to 1.23)	HR (*v* 2 years), 1.13 (0.74 to 1.73)		
		P = .93	*P* = .95	*P* = .56		
				Second primary cancer:		
				Anastrozole 2 years: 9.4%		
				Anastrozole 5 years: 10.5%		
				HR (*v* 2 years), 1.09 (0.85 to 1.40)		
				P = .48		
SOLE[6]	Continuous letrozole *v* intermittent letrozole§	Intermittent letrozole: 85.8%	Intermittent anastrozole: 94.3%	Breast cancer events:	Intermittent anastrozole: 6.6%	Intermittent letrozole significantly less worsening than continuous letrozole:
		Continuous letrozole: 87.5%	Continuous anastrozole: 93.7%	Intermittent anastrozole: 8.8%	Continuous anastrozole: 7.4%	Vaginal problems (*P* = .017)
		HR, 1.08 (0.93 to 1.26)	HR, 0.85 (0.68 to 1.06)	Continuous anastrozole: 8.9%	HR, 0.88 (0.71 to 1.09)	Musculoskeletal pain (*P* = .023)
		P = .31	*P* = .16	HR, 0.98 (0.81 to 1.18)	*P* = .25	Sleep disturbance (*P* = .0073)
				P = .84		Physical well-being (*P* = .0080)
						Mood (*P* = .026)
						At 24 months, compared with continuous, intermittent letrozole greater improvement in hot flushes (*P* = .025)

Abbreviations: ABCSG, Austrian Breast Cancer Study Group; AI, aromatase inhibitor; DATA, Different Durations of Adjuvant Anastrozole Therapy; DFS, disease-free survival; DMFI, distant metastasis–free survival; HR, hazard ratio; IDEAL, Investigation on the Duration of Extended Adjuvant Letrozole; MA.17R, Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years; MENQOL, Menopause-Specific Quality of Life Questionnaire; NR, not reported; NS, not significant; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival; QOL, quality of life; SF-36, 36-Item Short Form Survey; SOLE, Study of Letrozole Extension.

*HR for disease recurrence, the occurrence of contralateral breast cancer, or death; multivariable analysis was adjusted for stratification factors (lymph node status, prior receipt of adjuvant chemotherapy, the interval between the last dose of AI and random assignment, and the duration of prior receipt of tamoxifen), and the duration of AI therapy received before the trial.

†HR for disease recurrence or the occurrence of contralateral breast cancer.

‡Adapted DFS end point events included breast cancer recurrence (local, regional, or distant); a second primary cancer, including contralateral breast cancer and cancers other than basal-cell or squamous-cell carcinoma of the skin, or carcinoma in situ of the cervix; and death as a result of any cause.

§Continuous: 2.5 mg/day for 5 years; intermittent: 2.5 mg/day during the first 9 months of years 1-4, followed by a 3-month break in each of these years, and then 2.5 mg/day during all 12 months of year 5.

TABLE 3. Adverse Events

Trial and Arm	No. (%) of Events							
	Hot Flashes	Fatigue	Arthritis	Arthralgia	Myalgia	Cardiovascular Event	New Osteoporosis	Bone Fracture*
MA.17R[3]								
Letrozole (n = 959)	360 (38)	346 (36)	317 (33)	513 (53)	268 (28)	116 (12)	109 (11)	133 (14)
Placebo (n = 959)	354 (37)	355 (37)	288 (30)	475 (50)	240 (25)	98 (10)	54 (6)	88 (9)
P	.84	.61	.18	.1	.31	.21	< .001	.001
NSABP B-42[7]								
Letrozole (n = 1,959)	—	—	—	—	—	(4.0)	—	91 (5.4)
Placebo (n = 1,964)	—	—	—	—	—	(3.4)	—	78 (4.8)
HR (95% CI);	—	—	—	—	—	1.21 (0.85 to 1.70); .29	—	1.19† (0.88 to 1.60); .27
P								
DATA[5]								
Anastrozole 6 years (n = 827)	—	—	—	478 (57.8)		119 (14.4)	173 (20.9)	83 (10.0)
Anastrozole 3 years (n = 833)	—	—	—	438 (52.6)		116 (13.9)	137 (16.4)	63 (7.6)
P								
IDEAL[4]								
Letrozole 2.5 years (n = 908)	96 (10.5)	68 (7.5)	—	119 (13.2)	—	—	68 (7.5)	25 (2.8)
Letrozole 5 years (n = 913)	118 (13.1)	89 (9.7)	—	133 (14.7)	—	—	116 (12.7)	45 (5.0)
P	—	—	—	—	—	—	—	—
ABCSG 16[8]								
Anastrozole 2 years (n = 1,731)	—	—	—	—	—	—	—	71 (4.7)
Anastrozole 5 years (n = 1,738)	—	—	—	—	—	—	—	98 (6.3)
HR (95% CI); *P*	—	—	—	—	—	—	—	1.35 (1.00 to 1.84); .053
SOLE[6]								
Intermittent letrozole (n = 2,425)	1,276 (53)	1,002 (42)	NR	1,589 (66)	870 (36)	42‡ (1.7)	1,146§ (47)	198 (8)
Continuous letrozole (n = 2,426)	1,310 (54)	1,083 (45)	NR	1,657 (69)	895 (37)	36‡ (1.5)	1,130§ (47)	214 (9)
P	—	—	—	—	—	—	—	—

Abbreviations: ABCSG, Austrian Breast Cancer Study Group; DATA, Different Durations of Adjuvant Anastrozole Therapy; HR, hazard ratio; IDEAL, Investigation on the Duration of Extended Adjuvant Letrozole; MA.17R, Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years; NR, not reported; NSABP, National Surgical Adjuvant Breast and Bowel Project; SOLE, Study of Letrozole Extension.

*Each patient may have had more than one fracture.

†Cumulative incidence of osteoporotic fractures.

‡Cardiac ischemia.

§Any evidence of osteopenia or osteoporosis (T score less than −1).

trend toward higher osteoporotic fractures with use of extended AI therapy[4,5,7,8] that ranged from an absolute risk increase of 0.6% to 2.4% but did not reach statistical significance. The risk of arterial thrombotic events also showed a trend toward increased risk with extended AI but again did not reach statistical significance in any of the trials. No other statistically significant differences in AEs were reported in the trials.

A recent meta-analysis calculated the odds of AEs between patients who were randomly assigned to prolonged treatment with AIs and those randomly assigned to placebo or no treatment in phase III RCTs.[9] Longer treatment with AIs was associated with an increased odds of cardiovascular events (odds ratio [OR], 1.18; 95% CI, 1.00 to 1.40; $P = .05$; number needed to harm [NNH], 122), bone fractures (OR, 1.34; 95% CI, 1.16 to 1.55; $P < .001$; NNH, 72), and

treatment discontinuation for AEs (OR, 1.45; 95% CI, 1.25 to 1.68; $P < .001$; NNH, 21). Longer treatment with AIs did not influence the odds of either second malignancy (OR, 0.93; 95% CI, 0.73 to 1.18; $P = .56$) or death without breast cancer recurrence (OR, 1.11; 95% CI, 0.90 to 1.36; $P = .34$).[9]

DISCUSSION

Adjuvant endocrine therapy is the cornerstone of systemic treatment of estrogen receptor (ER)–positive breast cancers. However, despite 5 years of adjuvant endocrine therapy, ER-positive tumors retain a substantial risk of late recurrence; indeed, even in contemporary series, there are more recurrences after 5 years than in the first 5 years after diagnosis.[10] This clinical situation has led to multiple trials of extended (beyond 5 years) endocrine treatment. The prognostic factors for late recurrence are well established (Table 4),[11-21] and include anatomic stage (tumor size and, in particular, nodal status) and certain pathologic features. Higher-grade tumors pose a higher risk for late recurrence, as do tumors with lower levels of ER expression, compared with low-grade tumors and those with strong levels of ER expression. Higher-risk scores on genomic assays have also been shown to be prognostic for late recurrence. Luminal A tumor subtypes are less likely to recur than luminal B; tumors with lower 21-gene recurrence scores or lower measures on a variety of other commercial genomic assays (Table 4) are also at lower risk for late recurrence. Interestingly, these are the same risk factors for early recurrence of ER-positive breast cancer during endocrine therapy in the years immediately after diagnosis.[22,23] That is, higher-risk tumors carry higher risk across the full arc of time after diagnosis, and there is no unique marker for early versus late patterns of recurrence.

TABLE 4. Prognostic Factors for Recurrence After 5 Years of Adjuvant Endocrine Therapy

Factor	Relationship
Anatomic stage	
Nodal status	N+ > N−[11]
Tumor size	Risk increase with increased T
Tumor pathology	
Higher grade	Higher grade > lower grade[11,12]
Lower levels of ER expression	Higher ER < lower ER
Genomic assay	
Intrinsic subtype	Luminal A < B[13]
21-gene recurrence score	Lower < higher[14]
PAM 50 ROR score	Lower < higher[15-17]
Breast cancer index score	Lower < higher[18-20]
EndoPredict clinical score	Lower < higher[21]

Abbreviations: ER, estrogen receptor; PAM, prediction analysis of microarray; ROR, risk of recurrence.

Appreciation of risks for late recurrence beyond 5 years of treatment does not necessarily imply that longer durations of adjuvant endocrine therapy would reduce recurrence risk or otherwise improve breast cancer outcomes. Randomized studies have shown, however, that extended endocrine therapy can reduce recurrence among women who received an initial 5 years of tamoxifen treatment. The strategies of either continuing tamoxifen for a total of 10 years or extending therapy by switching to an AI are both associated with a reduced risk of breast cancer recurrence (Fig 1). Based on these findings, the Expert Panel has in previous guidelines recommended either of these approaches for women who have proven tolerant of adjuvant endocrine therapy and are at substantial residual risk for late recurrence.[2]

An unresolved clinical question has been whether women who receive AI-based adjuvant endocrine therapy in their first 5 years after diagnosis would also benefit from extended duration treatment, and, if so, how such treatment should optimally be administered.[1] Clinical practice evolved such that AIs are frequently a routine component of early adjuvant therapy for postmenopausal women, either instead of tamoxifen or in sequence with tamoxifen. This clinical shift meant that new data from clinical trials have been needed to address the question of extended duration of therapy in an era when many women received AI treatment within the first 5 years. In the Expert Panel's previous guideline update, there were insufficient data to address this management question.

There are now multiple randomized trials (Fig 1) that address the question: In women who have received AI-based therapy as part of their initial 5 years of adjuvant treatment, does extended therapy with ongoing AI treatment reduce the risk of recurrence? The NSABP B-42,[7] MA.17R,[3] and DATA[5] trials all included women who had previous AI exposure and were offered additional ongoing AI therapy. In each of these trials, there was a relative reduction in recurrence risk on the order of 15% to 20% (hazard ratios, 0.79 to 0.85), which translated into a 2% to 4% improvement in DFS for average-risk patients included in these studies. These are measurable but modest differences. By traditional inference, and supported by subset analyses, women at greater risk of late recurrence based on clinical stage derived larger benefit in risk reduction, whereas lower-risk patients—typically those with stage I disease—garnered less benefit on average.

These trials support the more general finding, observed with 10 years of tamoxifen compared with 5 years, or with 5 years of tamoxifen followed by 5 years of AI therapy, that longer duration of treatment is associated with a lower risk of breast cancer recurrence. Based on indirect comparisons between the various trials (Fig 1), Panelists noted that the relative benefits for extended endocrine therapy appear most pronounced in women who switch from tamoxifen to an AI. In contrast, those who continued with tamoxifen

monotherapy, or those who had AI exposure in years 0 to 5 and then continued with AI treatment, appeared to derive proportionally less benefit from extended therapy to 10 years. The true significance of these indirect comparisons is unknown. However, they may be the result of the modest but reproducible benefits of AI-based treatment compared with tamoxifen-alone–based treatment, both within the first 5 years or as extended therapy. Based on these findings, the Expert Panel reiterated its recommendation that postmenopausal women should incorporate AI-based therapy during their course of adjuvant endocrine treatment, though the best time to start such therapy remains unclear. Patients who prove intolerant of AI therapy should receive tamoxifen.

A substantial fraction of improvement in DFS relates to secondary prevention of contralateral breast cancer. Thus, the measurable benefits of extended AI therapy are more pronounced among women with intact breasts. By contrast, women who have undergone bilateral mastectomy and are not at jeopardy for second breast cancers would derive less numerical benefit from extended AI therapy.

Survival benefits for extended therapy have been observed for women with received 10 years of tamoxifen compared with 5 years and for women who receive 5 years of AI therapy after 5 years of tamoxifen. To date, none of the studies has noted a survival benefit for extended AI therapy, although this could still reflect the relatively low event rates and limited follow-up. In the studies of extended duration of tamoxifen treatment, there was a time dependence on the realized benefits of extended therapy, in which reductions in recurrence and mortality emerged more clearly with longer follow-up periods. This same nonproportionality of hazards was observed in trials of extended AI therapy[24] and underscores the need for long-term follow-up to measure fully the benefits of extended treatment. Nonetheless, lack of reported survival benefit for extended AI therapy should be part of the discussion of the risks and benefits when engaged in shared decision making about extended treatment.

The studies note the persistence of familiar but ongoing treatment-related AEs with AI therapy. These include symptoms of estrogen deprivation (Table 3), such as hot flashes/night sweats, arthralgias/myalgias, and sexual dysfunction. Over the years, many studies have shown that these symptoms have a detrimental impact on quality of life in breast cancer survivors and are associated with higher rates of nonadherence with treatment. Bone health, in particular, is a concern with longer AI exposure. Multiple trials reported significant differences in the rates of new onset osteoporosis or of bone fracture with extended duration of AI therapy (Table 3). In absolute terms, the excess risk of bone fracture nearly approximates the diminished risk of breast cancer recurrence in low- or average-risk patients. Interventions such as bone density monitoring and initiation of bone-modifying therapy may reduce the incidence of osteoporosis or fracture among women who receive AI therapy. Yet, the studies of extended AI treatment were conducted at a time and in populations when such interventions were widely available; despite those resources, the higher rate of fractures and osteoporosis was observed.

There are additional trials (Fig 1) that ask the question: In patients who receive extended AI therapy, how should such treatment optimally be administered? The ABCSG 16[8] and IDEAL[4] studies compared a total of 7 to 7.5 years against a duration of 10 years. The SOLE trial[6] had a total duration of 10 years but compared intermittent treatment, which omitted 3 months of therapy each year in years 5 through 9, against continuous treatment. None of these trials showed a statistically significant difference in recurrence events or in contralateral breast cancer events. These data suggest that durations of AI treatment longer than 5 years are of potential clinical benefit, though the marginal benefits of treatment longer than 7 or 8 years may be narrow. Patients at low or average risk for recurrence who opt to forego the final year or two of extended therapy are unlikely to substantially compromise their long-term outcomes.

The Expert Panel reviewed the benefits and risks of extended AI therapy as adjuvant treatment and made the following recommendations. These recommendations are for postmenopausal women who have received AI therapy either upfront or as part of their treatment during the initial 5 years of therapy and thus correspond to the population studied in trials of extended treatment. As previously mentioned, the Expert Panel has recommended that patients who have had an initial 5 years of tamoxifen should receive extended endocrine therapy with either tamoxifen or an AI.

1. Many women with node-negative breast cancer are potential candidates for and may be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine treatment based on considerations of recurrence risk using established prognostic factors. The use of the word “many” underscores that not all women with node-negative breast cancer will benefit from extended AI therapy. In women with node-negative breast cancers, T stage, grade, and genomic signature are all known to serve as prognostic markers for risk of recurrence after 5 years of endocrine therapy. The Expert Panel favored extended AI treatment among higher-risk, node-negative patients, including women with stage T2/T3 tumors and T1c tumors with higher-risk prognostic factors based on the assumption that a higher residual risk of recurrence will translate into a larger clinical benefit with extended therapy. Options for extended treatment are listed in the Bottom Line Box.
2. In contrast, the Expert Panel believed that 5 years of therapy that included an AI was sufficient for women with T1a/T1b tumors or T1c tumors with lower-risk prognostic factors on the assumption that the lower risk of late recurrence would translate into narrower

benefit for extended therapy. For women with low-risk, T1ab tumors, the Expert Panel reiterated that either tamoxifen or an AI-based approach for 5 years was an option.

The Expert Panel acknowledged that none of the studies of extended adjuvant therapy stratified patients by grade or genomic markers and that, to date, only one study has examined use of a genomic assay as a prognostic marker during extended adjuvant treatment with any regimen.[18] However, the Expert Panel believed that retrospective findings on the importance of established prognostic factors, including stage, grade, and genomic signatures (Table 4), for both early and late recurrence have become sufficiently robust that a clinical risk stratification that reflected these prognostic factors could reasonably be used to inform the clinical decision about extended therapy with AI treatment. In part, this decision reflects a clinical situation in which the treatment benefits are modest for lower-stage cancers and for which there has been no survival benefit observed to date. The Expert Panel anticipates that data will be forthcoming in the future to clarify the role of grade and genomic assays as predictors of benefit from extended adjuvant treatment.

3. Women with node-positive breast cancer should be offered extended AI-based therapy for up to a total of 10 years of adjuvant endocrine treatment. Extended therapy in the setting of higher-risk node-positive breast cancers provides a substantial reduction in risk of recurrence that, in the opinion of the Expert Panel, warrants the ongoing AEs and risks of treatment. The Expert Panel acknowledged that the prognosis in cases of limited nodal involvement (eg, one or two affected nodes) may be sufficiently favorable that clinicians and patients might reasonably opt to forego extended therapy based on individualized assessment of the AEs/tolerability of therapy and additional prognostic factors, as noted in Table 4. Preferred options for extended therapy include an AI for up to a total of 10 years or a sequence of tamoxifen for 2 to 3 years followed by 7 to 8 years of an AI or a sequence of tamoxifen for 5 years followed by an AI for 5 years. As in previous guidelines, the Expert Panel recommends 10 years of tamoxifen therapy for premenopausal women or for postmenopausal women who have not tolerated or prefer not to take AI-based treatment.
4. Women who receive extended adjuvant endocrine therapy should receive no more than 10 years of total treatment; data for durations of therapy beyond 10 years suggest sufficiently minimal benefit that they are not recommended. There are now multiple trials that have explored a total duration of 10 years of therapy, either with tamoxifen or AI monotherapy or based on a sequence of tamoxifen followed by AI treatment. These studies provide a solid evidence base to aim for 10 years of treatment. The only study to date that explored longer durations of treatment was the MA.17R trial,[3] in which 70% patients received treatment beyond 10 years of therapy. For patients who embark on AI treatment at time of diagnosis, in particular, the Expert Panel noted that there were no data for use of AI therapy longer than 10 years. Given those limitations and the narrow clinical benefits of treatment beyond 10 years, the Expert Panel recommended that ordinary care consist of a total of 10 years of therapy.

Two trials[4,8] have compared shorter extended treatment durations versus longer durations; in these studies, women received either 2 to 2.5 or 5 years of extended treatment with an AI after an initial 5 years of adjuvant endocrine therapy. No difference was seen in disease recurrence rates in these trials, although the IDEAL[4] study showed a numerically lower risk of recurrence after the separation of treatment arms at 2.5 years. The SOLE trial[6] compared an intermittent versus continuous dosing schedule for extended AI therapy and reported no difference in DFS, although, again, there was a numerically lower risk in the continuous treatment arm. Given these findings and the potential clinical benefits of treatment to 10 years, the Expert Panel generally favored a total duration of 10 years. However, the Expert Panel also acknowledged that these prospective studies suggest that women who foreshorten the total duration of therapy from 10 years to 8 years appear not to forfeit substantial benefits of therapy. The Expert Panel believed that these data offer reassurance to patients and clinicians that treatment on the order of 7 to 8 years instead of 10 years, or that treatment interruptions of several months with subsequent resumption of therapy, do not appear to significantly compromise long-term outcomes in average-risk patients.

Adherence with adjuvant endocrine therapy has been widely studied. It is known that a substantial fraction of patients will be nonadherent with adjuvant endocrine treatment because of AEs, personal preferences, and access to medication. The Expert Panel encourages clinicians to be aware of issues related to nonadherence and to mitigate symptoms or barriers that affect adherence and encourages patients to use medicines as prescribed by their providers and as used in clinical trials. However, the results from the SOLE,[6] IDEAL,[4] and ABCSG 16[8] trials suggest that there may be few clinical consequences to minor degrees of nonadherence during the course of extended adjuvant therapy. This may be reassuring to patients and clinicians alike.

5. The Expert Panel emphasized that the decision about extended AI therapy required discussion with the individual patient and shared decision making based on an understanding of the individual patient's risk factors for recurrence, treatment experience, and tolerability during the first 5 years of therapy as well as the likely benefits of prevention of second, contralateral, or ipsilateral breast cancers and the lack of known survival advantage for extended AI monotherapy. The Expert

Panel noted that, as all women considering extended AI therapy have already had several years of antiestrogen treatments, they are uniquely positioned to understand the impact of these treatments on their symptoms and quality of life. AI-based therapy is associated with both well-documented medical concerns, such as osteoporosis and bone fracture, and substantial symptoms, including menopausal symptoms, sexual dysfunction, hair thinning, and arthralgias that often have a profound effect on well-being. Women for whom these treatments have proven burdensome or have caused a markedly negative impact on quality of life may understandably weigh differently the inherent trade-offs between risk reduction and ongoing AEs. Women at greater risk for osteoporosis/fracture may also reach different decisions about extended AI therapy based on these trade-offs. Women with cancers that harbor substantial residual risk despite 5 years of treatment are likely to have greater numerical benefit from extended therapy. The benefits of extended duration treatment emerge slowly and during a long arc of time; most trials suggest that measurable differences are only seen after 4 years or longer of extended therapy. For that reason, patients with comorbid conditions of life expectancies that do not realistically include that timeframe are unlikely to benefit from extended endocrine treatment.

6. Women at jeopardy for contralateral or second breast cancers are more likely to see secondary benefits from extended AI therapy (Fig 1), and the Expert Panel recommended that women may consider extended treatment of that purpose irrespective of initial stage. Multiple studies of extended AI therapy[3-5,7] show that extended treatment lowers the relative risk of a second breast cancer by at least 50%, which translates to a 1% to 2% numerical reduction in risk through approximately 5 years of follow-up. These benefits are consistent with the historical risk reduction for antiestrogen therapy seen in the prevention trials that used tamoxifen or AI treatments and in older studies of adjuvant endocrine therapy. Conversely, women who have undergone mastectomy, in particular bilateral mastectomy, as part of their treatment program would not be expected to realize the benefit of secondary prevention with extended AI treatment. This individualized assessment of benefit/risk should inform treatment preference.

SUMMARY

ER-positive breast cancers carry substantial risk of late recurrence despite 5 years of adjuvant endocrine therapy. Multiple strategies of extended (beyond 5 years) treatment have been shown to reduce recurrence risk and offer additional benefit in reduction of the risk of contralateral breast cancer. Based on data from prospective, randomized clinical trials, the ASCO adjuvant endocrine therapy Expert Panel recommends extended duration with any one of the following strategies:

AI for up to a total of 10 years; or
tamoxifen for 2 to 3 years followed by AI for 7 to 8 years; or
tamoxifen for 5 years followed by AI for 5 years; or
tamoxifen for 10 years.

Extended duration therapy is associated with ongoing AEs of treatment that may affect quality of life or increase the risk of other health problems. For these reasons, and because the absolute benefits of risk reduction with extended therapy are modest in average-risk patients, clinicians and women with breast cancer must individualize treatment decisions based on cancer stage and risk of late recurrence and based on the tolerability and AEs of treatment that have been experienced to date by the patient. Women with greater risk of recurrence based on well-known prognostic factors (nodal involvement, larger tumors, and other adverse prognostic features in the cancer) are more likely to realize substantial clinical benefits from treatment and thus should receive extended endocrine therapy up to a total of 10 years of treatment. Women with lower risk of late recurrence, typically stage I disease with lower-risk features, may reasonably stop therapy after 5 years unless there is strong motivation for prevention of late recurrence and/or contralateral/second breast cancers. Patient preferences, identified through a shared decision-making process and informed by the magnitude of potential benefit and the associated risks of treatment, are critical to decide whether to continue therapy beyond 5 years. Clinical teams should mitigate symptoms of extended therapy and ensure access to therapy in women who pursue adjuvant endocrine treatment.

ADDITIONAL RESOURCES

Additional information, including data supplements, evidence tables, and clinical tools and resources, can be found at www.asco.org/breast-cancer-guidelines. Patient information is available there and at www.cancer.net.

RELATED ASCO GUIDELINES

- Breast Cancer Survivorship Care Guideline[17] (http://ascopubs.org/doi/10.1200/JCO.2015.64.3809)
- Integrative Therapies During and After Breast Cancer[19] (http://ascopubs.org/doi/10.1200/JCO.2018.79.2721)
- Fertility Preservation in Patients with Cancer[20] (http://ascopubs.org/doi/10.1200/JCO.2018.78.1914)
- Interventions to Address Sexual Problems in People with Cancer[21] (http://ascopubs.org/doi/10.1200/JCO.2017.75.8995)

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABLITY STATEMENT

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REFERENCES

1. Burstein HJ, Prestrud AA, Seidenfeld J, et al: American Society of Clinical Oncology clinical practice guideline: Update on adjuvant endocrine therapy for women with hormone receptor–positive breast cancer. J Clin Oncol 28:3784-3796, 2010
2. Burstein HJ, Temin S, Anderson H, et al: Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. J Clin Oncol 32:2255-2269, 2014
3. Goss PE, Ingle JN, Pritchard KI, et al: Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med 375:209-219, 2016
4. Blok EJ KJ, Kroep JR, Meershoek-Klein Kranenbarg E, et al: Optimal duration of extended adjuvant endocrine therapy for early breast cancer: Results of the IDEAL trial (BOOG 2006-05). J Natl Cancer Inst doi: 10.1093/jnci/djx134 [epub on January 1, 2018]
5. Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM, et al: Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): A randomised, phase 3 trial. Lancet Oncol 18:1502-1511, 2017
6. Colleoni M, Luo W, Karlsson P, et al: Extended adjuvant intermittent letrozole versus continuous letrozole in postmenopausal women with breast cancer (SOLE): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 19:127-138, 2018
7. Mamounas E, Bandos H, Lembersky B, et al: A randomized, double-blinded, placebo-controlled clinical trial of extended adjuvant endocrine therapy (tx) with letrozole (L) in postmenopausal women with hormone-receptor (+) breast cancer (BC) who have completed previous adjuvant tx with an aromatase inhibitor (AI): Results from NRG Oncology/NSABP B-42. Cancer Res 77, 2017 (suppl; abstr S1-05)
8. Gnant M SG, Greil R, et al: A prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years of anastrozole after initial 5 years of adjuvant endocrine therapy: Results from 3,484 postmenopausal women in the ABCSG 16 trial. San Antonio Breast Cancer Symposium San Antonio, TX 2017
9. Goldvaser H, Barnes TA, Šeruga B, et al: Toxicity of extended adjuvant therapy with aromatase inhibitors in early breast cancer: A systematic review and meta-analysis. J Natl Cancer Inst 110:31-39, 2018
10. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365:1687-1717, 2005
11. Filipits M, Nielsen TO, Rudas M, et al: The PAM50 risk-of-recurrence score predicts risk for late distant recurrence after endocrine therapy in postmenopausal women with endocrine-responsive early breast cancer. Clin Cancer Res 20:1298-1305, 2014
12. Lænkholm AV, Jensen MB, Eriksen JO, et al: PAM50 risk of recurrence score predicts 10-year distant recurrence in a comprehensive Danish cohort of postmenopausal women allocated to 5 years of endocrine therapy for hormone receptor–positive early breast cancer. J Clin Oncol 36:735-740, 2018
13. Sestak I, Cuzick J, Dowsett M, et al: Prediction of late distant recurrence after 5 years of endocrine treatment: A combined analysis of patients from the Austrian breast and colorectal cancer study group 8 and arimidex, tamoxifen alone or in combination randomized trials using the PAM50 risk of recurrence score. J Clin Oncol 33:916-922, 2015
14. Sgroi DC, Sestak I, Cuzick J, et al: Prediction of late distant recurrence in patients with oestrogen-receptor–positive breast cancer: A prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population. Lancet Oncol 14:1067-1076, 2013
15. Zhang Y, Schroeder BE, Jerevall PL, et al: A novel breast cancer index for prediction of distant recurrence in HR+ early-stage breast cancer with one to three positive nodes. Clin Cancer Res 23:7217-7224, 2017
16. Dubsky P, Brase JC, Jakesz R, et al: The EndoPredict score provides prognostic information on late distant metastases in ER+/HER2- breast cancer patients. Br J Cancer 109:2959-2964, 2013
17. Runowicz CD, Leach CR, Henry NL, et al: American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. J Clin Oncol 34:611-635, 2016
18. Sgroi DC, Carney E, Zarrella E, et al: Prediction of late disease recurrence and extended adjuvant letrozole benefit by the HOXB13/IL17BR biomarker. J Natl Cancer Inst 105:1036-1042, 2013
19. Lyman GH, Greenlee H, Bohlke K, et al: Integrative therapies during and after breast cancer treatment: ASCO endorsement of the SIO clinical practice guideline. J Clin Oncol 36: 2647-2655, 2018
20. Oktay K, Harvey BE, Partridge AH, et al: Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol 36:1994-2001, 2018
21. Carter J, Lacchetti C, Andersen BL, et al: Interventions to address sexual problems in people with cancer: American Society of Clinical Oncology clinical practice guideline adaptation of Cancer Care Ontario guideline. J Clin Oncol 36:492-511, 2018
22. Kennecke H, McArthur H, Olivotto IA, et al: Risk of early recurrence among postmenopausal women with estrogen receptor–positive early breast cancer treated with adjuvant tamoxifen. Cancer 112:1437-1444, 2008

23. Mauriac L, Keshaviah A, Debled M, et al: Predictors of early relapse in postmenopausal women with hormone receptor–positive breast cancer in the BIG 1-98 trial. Ann Oncol 18:859-867, 2007

24. Mamounas EP, Lembersky B, Jeong JH, et al: NSABP B-42: A clinical trial to determine the efficacy of five years of letrozole compared with placebo in patients completing five years of hormonal therapy consisting of an aromatase inhibitor (AI) or tamoxifen followed by an AI in prolonging disease-free survival in postmenopausal women with hormone receptor–positive breast cancer. Clin Breast Cancer 7:416-421, 2006

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Adjuvant Endocrine Therapy for Women with Hormone Receptor–Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update

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Consulting or Advisory Role: Patient Resource, Breakthrough Chronic Care
Patents, Royalties, Other Intellectual Property: I am named on a patent held by MD Anderson Cancer Center as a co-inventor on a method of radiation cancer patients with magnetically optimized high energy electron radiation

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APPENDIX

TABLE A1. Summary of All Recommendations (Original Recommendations and Focused Update Recommendations)

No.	Clinical Question	2010 Recommendation	2013 Recommendation	2016 Recommendation	2018 Recommendation
1a	What adjuvant endocrine treatments should be offered to postmenopausal women with hormone receptor–positive breast cancer?	Postmenopausal women should consider taking an AI during the course of adjuvant treatment to lower recurrence risk, either as primary therapy or after 2-3 years of tamoxifen. Duration of AI therapy should not exceed 5 years.	II. Women diagnosed with hormone receptor–positive breast cancer who are postmenopausal should be offered adjuvant endocrine therapy with one of the following initial options:	No change	No change
1b	What is the appropriate duration of adjuvant endocrine therapy?	Therapy with an AI should not extend beyond 5 years in either the primary or extended adjuvant settings outside the clinical trials setting. In the sequential setting, patients should receive an AI after 2 or 3 years of tamoxifen for a total of 5 years of adjuvant endocrine therapy. Patients initially treated with an AI but who discontinue treatment before 5 years of therapy should consider incorporation of tamoxifen for a total of 5 years of adjuvant endocrine therapy.	IIA. Tamoxifen for a duration of 10 years. (Evidence Quality: High, Strength of Recommendation: Strong); or IIB. An AI for a duration of 5 years. There are insufficient data currently to recommend an AI for a duration of greater than 5 years. (Evidence Quality: High, Strength of Recommendation: Strong); or IIC. Tamoxifen for an initial duration of 5 years, then a switch to an AI for up to 5 years, for a total duration of up to 10 years of adjuvant endocrine therapy. (Evidence Quality: High, Strength of recommendation: Strong) IID. Tamoxifen for a duration of 2-3 years and a switch to an AI for up to 5 years, for a total duration of up to 7-8 years of adjuvant endocrine therapy. (Evidence Quality: High, Strength of Recommendation: Strong)	No change	1. Many women with node-negative breast cancer are potential candidates for and may be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine treatment based on considerations of recurrence risk using established prognostic factors. However, as the recurrence risk is lower, the benefits are likely narrower for such patients. Women with low-risk node-negative tumors should not routinely be offered extended therapy. 2. Women with node-positive breast cancer should be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine treatment. 3. Women who receive extended adjuvant endocrine therapy should receive no more than 10 years of total treatment. 4. As prevention of secondary or contralateral breast cancers is a major benefit of extended AI therapy and overall survival is not, the risk of second breast cancers (or not) based on prior therapy should inform the decision to pursue extended treatment. 5. Extended therapy carries ongoing risks and side effects, which should be weighed against the potential absolute benefits of longer treatment, in a shared decision-making process between the clinical team and the patient. Qualifying statement: To date, none of the studies have shown improvement in overall survival with longer-duration AI therapy. As such, the recommendations on extended adjuvant AI therapy are based on benefits that include prevention of distant recurrence and prevention of second breast cancers.
1c	If tamoxifen is administered first, how long should it be continued before the switch to an AI?	Patients who initially receive tamoxifen as adjuvant therapy may be offered an AI after 2-3 years (sequential) or after 5 years (extended) of therapy. The best time to switch from an AI to tamoxifen (or the converse) is not known. Switching at 2-3 years is recommended, but switching at 5 years is also supported by available data.	IIC. Tamoxifen for an initial duration of 5 years, then a switch to an AI for up to 5 years, for a total duration of up to 10 years of adjuvant endocrine therapy. (Evidence Quality: High, Strength of recommendation: Strong); or IID. Tamoxifen for a duration of 2-3 years and a switch to an AI for up to 5 years, for a total duration of up to 7-8 years of adjuvant endocrine therapy. (Evidence Quality: High, Strength of Recommendation: Strong)	No change	No change

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TABLE A1. Summary of All Recommendations (Original Recommendations and Focused Update Recommendations) (continued)

No.	Clinical Question	2010 Recommendation	2013 Recommendation	2016 Recommendation	2018 Recommendation
2	Are there specific patient populations that derive different degrees of benefit from an AI compared with tamoxifen?	A specific marker or clinical subset that predicts which adjuvant treatment strategy (tamoxifen alone, AI alone, or AI and tamoxifen based) is best has not been identified. Among men with breast cancer, tamoxifen remains the standard adjuvant endocrine treatment. The CYP2D6 genotype is not recommended to select adjuvant endocrine therapy. Caution with concurrent use of CYP2D6 inhibitors (such as bupropion, paroxetine, or fluoxetine) and tamoxifen is recommended because of drug-drug interactions.	No change	No change	No change
3	What are the toxicities and risks of adjuvant endocrine therapy?	Clinicians should consider adverse effect profiles, patient preferences, and pre-existing conditions when they discuss adjuvant endocrine strategies. Adverse effect profiles should be discussed with patients when available treatment options are presented. Clinicians may recommend that patients change treatments if adverse effects are intolerable or patients are persistently noncompliant with therapy.	No change	No change	No change
4	Are AIs effective adjuvant therapy for women who are premenopausal at the time of diagnosis?	Women who are pre- or perimenopausal at diagnosis should be treated with 5 years of tamoxifen.	Women diagnosed with hormone receptor–positive breast cancer who are pre/perimenopausal should be offered adjuvant endocrine therapy as follows: IA. Tamoxifen for an initial duration of 5 years. IB. After 5 years, women should receive additional therapy based on menopausal status: IB1. If women are pre/perimenopausal, or if menopausal status is unknown or cannot be determined, they should be offered continued tamoxifen for a total duration of 10 years. (Evidence Quality: High, Strength of Recommendation: Strong); or IB2. If women have become definitively postmenopausal, they should be offered continued tamoxifen for a total duration of 10 years or should switch to up to 5 years of AI for a total duration of up to 10 years of adjuvant endocrine therapy. (Evidence Quality for tamoxifen: High, Evidence Quality for AI: High; Strength of Recommendation: Strong)	No change	No change

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TABLE A1. Summary of All Recommendations (Original Recommendations and Focused Update Recommendations) (continued)

No.	Clinical Question	2010 Recommendation	2013 Recommendation	2016 Recommendation	2018 Recommendation
5	Can the third-generation AIs be used interchangeably?	Meaningful clinical differences between the commercially available third-generation AIs have not been demonstrated to date. The Update Committee believes that postmenopausal patients intolerant of one AI may be advised to consider tamoxifen or a different AI.	No change III. Women who are postmenopausal and are intolerant of either tamoxifen or an AI should be offered the alternative type of adjuvant endocrine therapy. IIIA. If women have received an AI but discontinued treatment at < 5 years, they may be offered tamoxifen for a total of 5 years. (Type: Informal consensus, Evidence Quality: Low, Strength of Recommendation: Weak) IIIB. If women have received tamoxifen for 2-3 years, they should be offered a switch to an AI for up to 5 years, for a total duration of up to 7-8 years of adjuvant endocrine therapy.	No change	No change
6	What is the appropriate sequence of adjuvant endocrine therapy?		IV. Women who have received 5 years of tamoxifen as adjuvant endocrine therapy should be offered additional adjuvant endocrine treatment. IVA. If women are postmenopausal, they should be offered continued tamoxifen for a total duration of 10 years or should switch to up to 5 years of AI for a total duration of up to 10 years of adjuvant endocrine therapy. (Type: Evidence-Based, Evidence Quality: High, Strength of Recommendation: Strong) IVB. If women are pre/perimenopausal or menopausal status cannot be ascertained, they should be offered 5 additional years of tamoxifen for a total of 10 years of adjuvant endocrine therapy. (Type: Evidence-Based, Evidence Quality: High, Strength of Recommendation: Strong)	No change	No change

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TABLE A1. Summary of All Recommendations (Original Recommendations and Focused Update Recommendations) (continued)

No.	Clinical Question	2010 Recommendation	2013 Recommendation	2016 Recommendation	2018 Recommendation
7	Should premenopausal women with ER-positive tumors receive adjuvant ovarian suppression in addition to standard adjuvant therapy and, if so, in which subsets of patients?			The Panel recommends that higher-risk patients should receive ovarian suppression in addition to adjuvant endocrine therapy, whereas lower-risk patients should not. Qualifying statement: The Panel notes that two prospective studies did not show overall clinical benefit for the addition of ovarian suppression to tamoxifen in premenopausal, ER-positive breast cancer. However, in a large subset of women with higher-risk cancers, nearly all of whom received chemotherapy but remained premenopausal, ovarian suppression added to tamoxifen reduced the risk of breast cancer recurrence. Because of the design of the clinical trials, there are few definitive criteria by which to define risk. Women with stage II or III breast cancers who would ordinarily be advised to receive adjuvant chemotherapy should receive ovarian suppression in addition to endocrine therapy. Women with stage I or II breast cancers at higher risk of recurrence, who might consider chemotherapy, may also be offered ovarian suppression in addition to endocrine therapy. Women with stage I breast cancers that do not warrant chemotherapy should receive endocrine therapy but not ovarian suppression. Women with node-negative cancers ≤ 1 cm (T1a, T1b) should receive endocrine therapy but not ovarian suppression. Qualifying statements: The standard duration of ovarian suppression in the included trials was 5 years. With no comparative data available on alternative durations, the Panel supports ovarian suppression for 5 years. To date, there is no adequate evidence to assess the benefit of adjuvant ovarian suppression in women at sufficient risk to warrant chemotherapy compared with 10 years of tamoxifen. There is no current role for ovarian suppression as adjuvant therapy in ER-negative breast cancers. There are substantial adverse effects to ovarian suppression. Clinicians and patients should consider the tradeoffs of adverse effects when they choose ovarian suppression. The long-term effects of ovarian suppression on breast cancer risk and survival are not yet established.	No change

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TABLE A1. Summary of All Recommendations (Original Recommendations and Focused Update Recommendations) (continued)

No.	Clinical Question	2010 Recommendation	2013 Recommendation	2016 Recommendation	2018 Recommendation
8	If ovarian suppression is recommended, should ovarian suppression be administered in combination with tamoxifen or an AI?			Ovarian suppression may be administered with either tamoxifen or an AI. Qualifying statements: Tamoxifen and AI therapy differ in their adverse effect profiles, which may affect patient preferences. Clinicians should be alert to the possibility of incomplete ovarian suppression with GnRH agonist therapy and should evaluate patients in whom there is concern for residual ovarian function.	No change

Abbreviations: AI, aromatase inhibitor; ER, estrogen receptor; GnRH, gonadotropin-releasing hormone.

TABLE A2. Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update Expert Panel Membership

Name	Affiliation/Institution	Role/Area of Expertise
Harold J. Burstein, MD, PhD	Dana-Farber Cancer Institute, Boston, MA	Medical oncology
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Holly Anderson	Breast Cancer Coalition of Rochester, Rochester, NY	Patient representative
Thomas A. Buchholz, MD	MD Anderson Cancer Center, Houston, TX	Radiation oncology
Nancy E. Davidson, MD	University of Pittsburgh Cancer Institute and UPMC Cancer Center, Pittsburgh, PA	Medical oncology
Karen A. Gelmon, MD	BC Cancer Agency, Vancouver, BC	Medical oncology
Sharon H. Giordano, MD	MD Anderson Cancer Center, Houston, TX	Medical oncology
Clifford A. Hudis, MD	Memorial Sloan Kettering Cancer Center, New York, NY	Medical oncology
Alexander J. Solky, MD	Interlakes Oncology and Hematology PC, Rochester, NY	Community oncology
Vered Stearns, MD	Johns Hopkins School of Medicine, Baltimore, MD	Medical oncology
Eric P. Winer, MD	Dana-Farber Cancer Institute, Boston, MA	Medical oncology
Christina Lacchetti	American Society of Clinical Oncology, Alexandria, VA	Staff/health research methodologist