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ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Clinical Practice Guideline: Update on Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer

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This represents an abridged version of the complete guideline update and contains updated recommendations with a brief discussion of the relevant literature. The complete guideline, with a comprehensive discussion of the literature and additional tables, is available at www.asco.org/guidelines/endocrinebreast.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
To develop evidence-based guidelines, based on a systematic review, for endocrine therapy for postmenopausal women with hormone receptor–positive breast cancer.

Methods
A literature search identified relevant randomized trials. Databases searched included MEDLINE, PREMEDLINE, the Cochrane Collaboration Library, and those for the Annual Meetings of the American Society of Clinical Oncology (ASCO) and the San Antonio Breast Cancer Symposium (SABCS). The primary outcomes of interest were disease-free survival, overall survival, and time to contralateral breast cancer. Secondary outcomes included adverse events and quality of life. An expert panel reviewed the literature, especially 12 major trials, and developed updated recommendations.

Results
An adjuvant treatment strategy incorporating an aromatase inhibitor (AI) as primary (initial endocrine therapy), sequential (using both tamoxifen and an AI in either order), or extended (AI after 5 years of tamoxifen) therapy reduces the risk of breast cancer recurrence compared with 5 years of tamoxifen alone. Data suggest that including an AI as primary monotherapy or as sequential treatment after 2 to 3 years of tamoxifen yields similar outcomes. Tamoxifen and AIs differ in their adverse effect profiles, and these differences may inform treatment preferences.

Conclusion
The Update Committee recommends that postmenopausal women with hormone receptor–positive breast cancer consider incorporating AI therapy at some point during adjuvant treatment, either as up-front therapy or as sequential treatment after tamoxifen. The optimal timing and duration of endocrine treatment remain unresolved. The Update Committee supports careful consideration of adverse effect profiles and patient preferences in deciding whether and when to incorporate AI therapy.

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INTRODUCTION

The first technology assessment for the adjuvant use of aromatase inhibitors (AIs) for women with hormone receptor–positive breast cancer was published by the American Society of Clinical Oncology (ASCO) in 2002.[1] The technology assessment was updated in 2003[2] and 2004.[3] Since then, additional reports from large-scale trials of adjuvant endocrine therapy have been published. These developments warranted an update and systematic review.

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UPDATE METHODOLOGY

Guideline Questions

The Update Committee (Appendix Table A1, online only) focused on the optimal adjuvant endocrine strategy with use of either tamoxifen, AIs, or both in sequence; duration of AI therapy; long-term adverse effects of AI therapy; identification of subpopulations who might derive selective benefit from either AIs or tamoxifen-based treatments; efficacy of AIs among premenopausal women; and similarities or differences among commercially available third-generation AIs.

Literature Review and Analysis

Literature search strategy. For this update, ASCO staff evaluated a recent systematic review completed by Cancer Care Ontario (CCO) that included literature through May 2007.[4] MEDLINE, PREMEDLINE, and the Cochrane Collaboration databases were searched from May 2007 through February 2009 (Appendix, online only), as were electronic databases for the San Antonio Breast Cancer Symposium (SABCS) and ASCO Annual Meetings from 2007 to 2009.

Inclusion and exclusion criteria. Articles identified for inclusion in this systematic review met the following criteria: (1) the intervention was for the adjuvant therapy of breast cancer, (2) participants were randomly assigned to any of the treatments described previously, and (3) reports included at least one of the following primary outcomes of interest: overall survival, disease-free survival, or breast cancer–specific survival. Three different treatment strategies were identified on the basis of the timing of AI therapy: initial endocrine therapy (hereafter referred to as a *primary* adjuvant strategy), *sequential* therapy with treatment divergence if the patient was disease free following 1 to 4 years of initial treatment with adjuvant endocrine agents (most often tamoxifen), or *extended* therapy with random assignment if the patient was disease free following 5 years of treatment with adjuvant tamoxifen.

Twelve prospective, randomized clinical trials originally identified by the co-chairs were the focus of this systematic review. These same trials were identified in the CCO systematic review, as well as in a systematic review completed by the National Institute for Health Research (NIHR) in the United Kingdom.[5]

Several important limitations of the existing literature were identified. Of particular note is the timing of randomization (Fig 1). Most sequential trials and all of the extended trials randomly assigned women who were free of recurrence through multiple years of tamoxifen therapy, effectively excluding women with early recurrence. For this reason, the patient populations in the sequential and extended trials may differ importantly from one another and from patients in the primary therapy studies. Another limitation is the relatively short follow-up; disease recurrence decades after diagnosis is not uncommon. The longest available median follow-up in the present trials is

Table 1. Summary of 2010 Recommendations

Clinical Question	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 to 3 years of tamoxifen. Duration of AI therapy should not exceed 5 years.
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 incorporating tamoxifen for a total of 5 years of adjuvant endocrine therapy.
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 to 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 to 3 years is recommended, but switching at 5 years is also supported by available data.
2. Are there specific patient populations that derive differing degrees of benefit from an AI in comparison to 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.
3. What are the toxicities and risks of adjuvant endocrine therapy?	Clinicians should consider adverse effect profiles, patient preferences, and pre-existing conditions when discussing adjuvant endocrine strategies. Adverse effect profiles should be discussed with patients when presenting available treatment options. Clinicians may recommend that patients change treatments if adverse effects are intolerable or patients are persistently noncompliant with therapy.
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.
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.

Abbreviation: AI, aromatase inhibitor.

slightly more than 8 years; most studies have considerably shorter follow-up. For the majority of the efficacy outcomes across all studies, the median time to event has yet to be reached. The relatively modest number of events may also limit study conclusions.

The number of actual events was modest because of the generally favorable prognosis among patients. Owing to the vagaries of data collection and patient participation, as well as the distribution of clinical subsets, subgroup evaluations are hindered by relatively small sample sizes. Small sample size is also a limitation in analyzing available quality-of-life data. Finally, comparisons between trials are hindered because of different definitions of study end points.[6]

Consensus Development Based on Evidence

The Update Committee was charged with reviewing evidence from the systematic review and drafting new recommendations (Table 1). Per standard ASCO practice, the guideline was submitted to the *Journal of Clinical Oncology* for peer review. The content of the guideline was reviewed and approved by both the ASCO Clinical Practice Guideline Committee and the Board of Directors before publication.

Guideline and Conflicts of Interest

The Update Committee was assembled in accordance with ASCO's Conflict of Interest Management Procedures for Clinical Practice Guidelines ("Procedures," summarized at www.asco.org/guidelinescoi). Members completed ASCO's disclosure form, which requires disclosure of financial and other interests relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Update Committee did not disclose any such relationships.

RESULTS

Summary of the Literature Review Results

Since the last ASCO update, 442 published articles and 42 presentations, posters, or abstracts were identified (Appendix Fig A1). Of these, 49 reported either findings from one of 12 trials[7-49] or were systematic reviews or meta-analyses of this same set of landmark trials for adjuvant endocrine therapy.[4,50-54] Thirteen articles with primary data were retrieved to complement extraction. Five reports available after completion of the initial search were also considered.[55,56]

Table 2. Disease-Free Survival

Trial	Arm	Median Follow-Up (months)	Range (months)	No. of Patients Observed		Disease-Free Survival Events				HR	95% CI	*P*
						AI		Comparator				
				AI	Comparator	No.	%	No.	%			
Primary												
ATAC[20]	ANA *v* TAM ITT	100	0-126	3,125	3,116	817	26.1	887	28.5	0.90	0.82 to 0.99	.025
BIG 1-98[41]	LET *v* TAM ITT	76		2,463	2,459	509	20.7	565	23.0	0.88	0.78 to 0.99[a]	.03
ABCSG-12[22]	ANA *v* TAM	47.8		903	900	72	8.0	65	7.2	1.10	0.78 to 1.53	.59
Sequential												
BIG 1-98[41]	TAM/LET *v* LET	71		1,548	1,546	259	16.7	248	16.0	1.05	0.84 to 1.32[b]	NR
	LET/TAM *v* LET	71		1,540	1,546	236	15.3	248	16.0	0.96	0.76 to 1.21[b]	NR
ABCSG-8[29]	TAM/ANA *v* TAM ITT	72		1,865	1,849	227	12.2	261	14.1	0.85	0.71 to 1.01[c,d]	.067
ITA[9]	ITT	64	12-93	223	225	39	17.5	63	28	0.57	0.38 to 0.85[e]	.005
TEAM[56]	TAM/EXE *v* EXE ITT	61		4,868	4,898	714		712		0.97	0.88 to 1.08	.604
IES[13]	ITT	55.7	0-89.7	2,352	2,372	354		455		0.76	0.66 to 0.88	< .001
N-SAS BC-03[8]		42	3.2-60	347	349	26	7.5	37	10.6	0.69	0.42 to 1.14	.14[f]
ARNO 95[33]		30.1	< 12 to ≥ 84	489	490	38	7.8	56	11.4	0.66	0.44 to 1.00	.049
Extended												
MA.17[25]	ITT[g]	64	16-95	2,583	2,587	164	6.3	235	9.1	0.68	0.55 to 0.83	< .001
ABCSG-6a[30]		62.3		386	466	30	7.8	57	12.2	0.62	0.40 to 0.96[h]	.031
NSABP B-33[36]		30		783	779	37	4.7	52	6.7	0.68		.07

NOTE. Percent calculated as number of events divided by number of patients observed.

Abbreviations: AI, aromatase inhibitor; HR, hazard ratio; ATAC, Arimidex, Tamoxifen, Alone or in Combination (trial); ANA, anastrozole; TAM, tamoxifen; ITT, intent to treat; BIG, Breast International Group; LET, letrozole; ABCSG, Austrian Breast and Colorectal Cancer Study Group; NR, not reported; ITA, Italian Tamoxifen Anastrozole (trial); TEAM, Tamoxifen Exemestane Adjuvant Multinational (trial); EXE, exemestane; IES, Intergroup Exemestane Study; N-SAS, National Surgical Adjuvant Study (Group); ARNO, Arimidex-Nolvadex (trial); NSABP, National Surgical Adjuvant Breast and Bowel Project.

[a]Analysis includes only patients from monotherapy arms; crossovers not censored.

[b]99% CIs used to account for multiple comparisons.

[c]Relapse-free survival includes local and distant recurrence, contralateral breast cancer, and death without recurrence.

[d]Patients who crossed over were censored at time of crossover.

[e]Event-free survival includes locoregional or distant recurrence, second primary (including contralateral breast cancer), and deaths without recurrence.

[f]Two different *P* values reported (*P* = .06 in abstract, *P* = .14 on poster).

[g]Seventeen patients omitted from ITT analysis.

[h]Recurrence-free survival.

Table 3. Contralateral Breast Cancer

Trial	Arm	Median Follow-Up (months)	Range (months)	No. of Patients Observed		Contralateral Breast Cancer Events				HR	95% CI	*P*
						AI		Comparator				
				AI	Comparator	No.	%	No.	%			
Primary												
ATAC[20]	ANA *v* TAM ITT	100		3,125	3,116	61	1.9	87	2.8	0.68	0.49 to 0.94	.02
BIG 1-98[5]	LET *v* TAM	68		4,003	4,007	16	0.4	27	0.7	NR	NR	NR
TEAM[32]	EXE *v* TAM ITT*	33†		4,898	4,868	21	0.4	17	0.3	NR	NR	NR
Sequential												
ABCSG-8[29]	TAM/ANA *v* TAM ITT	72		1,865	1,849	19	1.0	29	1.6	0.64	0.36 to 1.13	NR
IES[13]	ITT	55.7	0-89.7	2,352	2,372	18	0.76	35	1.5	0.57	0.33 to 0.98	.04
ARNO 95[33]		30.1	< 12 to ≥ 84	489	490	7	1.4	5	1	NR	NR	NR
Extended												
MA.17[28]		64		2,583	2,587	30	1.16	49	1.89	0.61	0.39 to 0.97	.033
ABCSG-6a[30]		62.3		386	466	6	1.6	11	2.4	0.67	0.25 to 1.80‡	.422

NOTE. Percent calculated as number of events divided by number of patients observed.
Abbreviations: AI, aromatase inhibitor; HR, hazard ratio; ATAC, Arimidex, Tamoxifen, Alone or in Combination (trial); ITT, intent to treat; BIG, Breast International Group; LET, letrozole; TAM, tamoxifen; NR, not reported; TEAM, Tamoxifen Exemestane Adjuvant Multinational (trial); EXE, exemestane; ABCSG, Austrian Breast and Colorectal Cancer Study Group; ANA, anastrozole; IES, Intergroup Exemestane Study; ARNO, Arimidex-Nolvadex (trial).
*Data for contralateral risk in the TEAM trial have been reported for comparison of initial therapy of TAM *v* EXE but not for TAM/EXE *v* EXE at this time.
†Follow-up for all TEAM patients is 33 months (data beyond that censored).
‡Risk of contralateral breast cancer.

GUIDELINE RECOMMENDATIONS

Clinical question 1a. What adjuvant endocrine treatments should be offered to postmenopausal women with hormone receptor–positive breast cancer?

Recommendation 1a. The Update Committee recommends, on the basis of data from randomized, controlled trials, that most postmenopausal women consider taking an AI during the course of adjuvant treatment to lower recurrence risk, either as primary therapy or after 2 to 3 years of tamoxifen—strategies that yield

Table 4. Overall Survival

Trial	Arm	Median Follow-Up (months)	Range (months)	No. of Patients Observed		Overall Survival Deaths				HR	95% CI	*P*
						AI		Comparator				
				AI	Comparator	No.	%	No.	%			
Primary												
ATAC[20]	ANA *v* TAM ITT	100		3,125	3,116	629	20.1	624	20.0	1.00	0.89 to 1.12	.99
BIG 1-98[41]	LET *v* TAM ITT	76		2,463	2,459	303	12.3	343	14.0	0.81	0.69 to 0.94*	.08
ABCSG-12[22]	ANA *v* TAM	47.8		903	900	27	3.0	15	1.7	1.8	0.95 to 3.38	.70
Sequential												
ABCSG-8[29]	TAM/ANA *v* TAM ITT	72		1,865	1,849	138	7.4	165	9.0	0.78	0.62 to 0.98†	.032
BIG 1-98[41]	TAM/LET *v* LET	71		1,548	1,546	154	9.9	137	8.9	1.13	0.83 to 1.53‡	NR
	LET/TAM *v* LET	71		1,540	1,546	123	8.0	137	8.9	0.90	0.65 to 1.24‡	NR
ITA[9]	ITT	64	12-93	223	225	12	5.4	21	9.3	0.56	0.28 to 1.15	.1
TEAM[56]	TAM/EXE *v* EXE ITT	61		4,868	4,898	NR (90.6% survival)		NR (90.5% survival)		1.00	0.89 to 1.14	.999
IES[13]	ITT	55.7	0-89.7	2,352	2,372	222	9.4	261	11.0	0.85	0.71 to 1.02	.08
N-SAS BC-03[8]		42	3.2-60	347	349	NR		NR		NR		.59
ARNO 95[33]		30.1	< 12 to ≥ 84	489	490	15	3.1	28	5.7	0.53	0.28 to 0.99	.045
Extended												
MA.17[25]	ITT§	64	16-95	2,583	2,587	154	6.0	155	6.0	0.98	0.78 to 1.22	.853
ABCSG-6a[30]		62.3		386	466	40	10.4	55	11.8	0.89	0.59 to 1.34	.570
NSABP B-33[36]		30		783	779	16	2.0	13	1.7	NR		NR

NOTE. Percent calculated as number of events divided by number of patients observed.
Abbreviations: AI, aromatase inhibitor; HR, hazard ratio; ATAC, Arimidex, Tamoxifen, Alone or in Combination (trial); ANA, anastrozole; TAM, tamoxifen; ITT, intent to treat; BIG, Breast International Group; LET, letrozole; ABCSG, Austrian Breast and Colorectal Cancer Study Group; NR, not reported; ITA, Italian Tamoxifen Anastrozole (trial); TEAM, Tamoxifen Exemestane Adjuvant Multinational (trial); EXE, exemestane; IES, Intergroup Exemestane Study; N-SAS, National Surgical Adjuvant Study (Group); ARNO, Arimidex-Nolvadex (trial); NSABP, National Surgical Adjuvant Breast and Bowel Project.
*Analysis includes only patients from monotherapy arms; crossovers not censored.
†Patients who crossed over were censored.
‡99% CIs used to account for multiple comparisons.
§Seventeen patients omitted from ITT analysis.

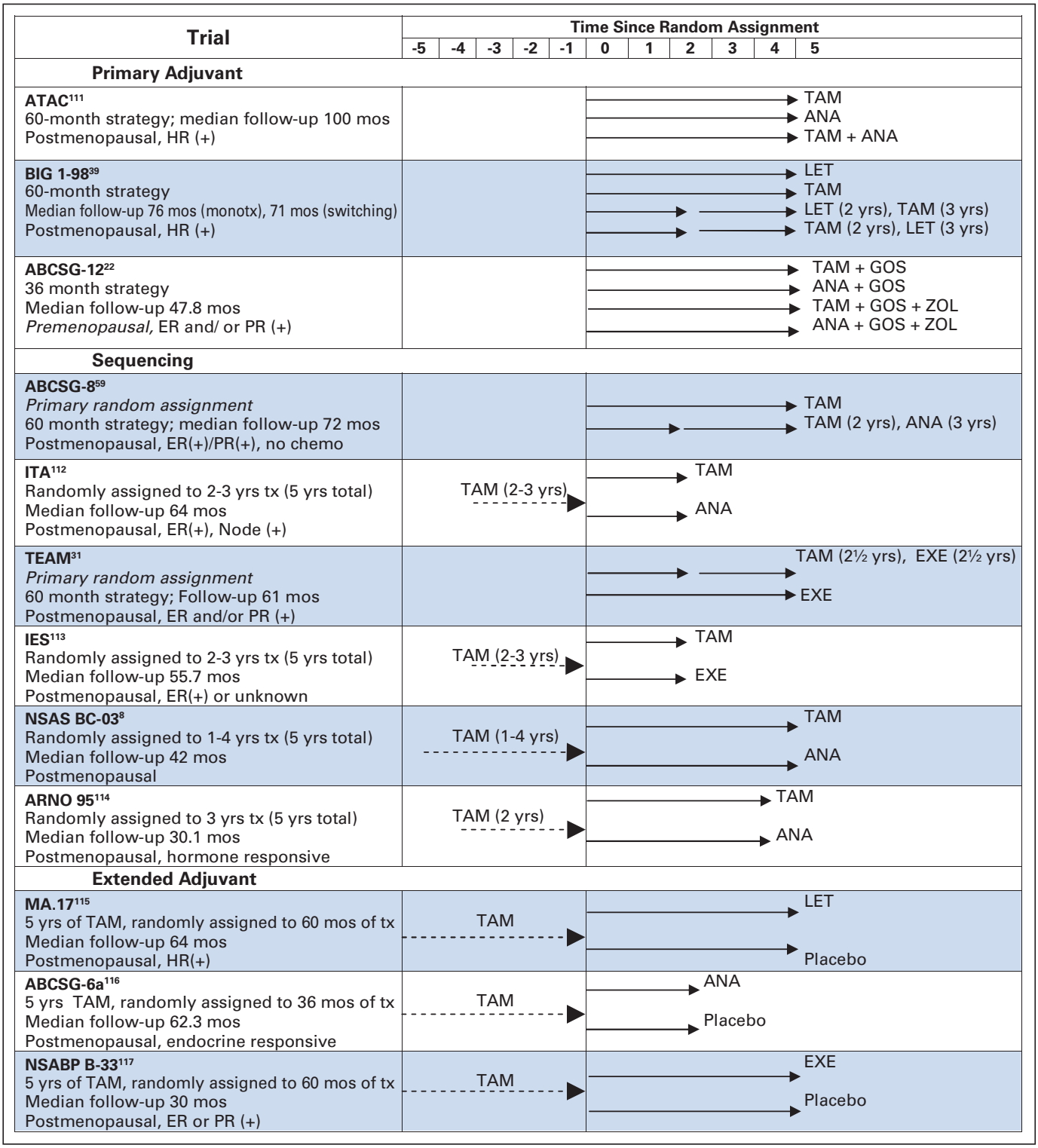

Fig 1. Schema of included trials. ATAC, Arimidex, Tamoxifen, Alone or in Combination (trial); mos, months; HR (+), hormone receptor–positive; TAM, tamoxifen; ANA, anastrozole; BIG, Breast International Group; FU, follow-up; monotx, monotherapy; LET, letrozole; yrs, years; ABCSG, Austrian Breast and Colorectal Cancer Study Group; ER (+), estrogen receptor–positive; PR (+), progesterone receptor–positive; GOS, goserelin; ZOL, zoledronic acid; ABCSG, Austrian Breast and Colorectal Cancer Study Group; Chemo, chemotherapy; ITA, Italian Tamoxifen Anastrozole (trial); tx, therapy; TEAM, Tamoxifen Exemestane Adjuvant Multinational (trial); EXE, exemestane; IES, Intergroup Exemestane Study; Unk, unknown; N-SAS, National Surgical Adjuvant Study (Group); ARNO, Arimidex-Nolvadex (trial); NSABP, National Surgical Adjuvant Breast and Bowel Project.

equivalent outcomes in prospective studies. Duration of AI therapy should not exceed 5 years.

Literature update and discussion 1a. In comparison to 5 years of tamoxifen alone, use of an AI in either primary, sequential, or extended treatment improves disease-free survival and reduces the risk of breast cancer events, including distant recurrence, locoregional recurrence, and contralateral breast cancer (Tables 2 and 3; Fig 1). In absolute terms, the reduction in risk of recurrence associated with AI-based therapy compared with tamoxifen is modest, typically amounting to $< 5\%$ through multiple years of follow-up (Table 2). Tamoxifen and AI-based therapy are equivalent in terms of overall survival when used as either a primary or extended treatment strategy (Table 4). Two of the six trials of sequential treatment strategies yielded statistically significant improvements in overall survival compared with tamoxifen alone, although the absolute difference in overall survival is modest (Table 4).

Breast cancer events such as locoregional recurrence, contralateral breast cancer, and early distant metastatic recurrence are clinically important to patients. For this reason, the Update Committee recommended consideration of AI therapy at some time during adjuvant endocrine therapy even though few trials demonstrated statistically significant differences in overall survival.

Sequential therapy. Two trials directly compared primary monotherapy with sequential therapy as an initial 5-year adjuvant endocrine regimen. The Breast International Group 1-98 (BIG 1-98) trial compared primary tamoxifen or AI monotherapy against sequences of tamoxifen followed by an AI or an AI followed by tamoxifen.[39] The Tamoxifen Exemestane Adjuvant Multicenter (TEAM) trial compared a sequential treatment of tamoxifen followed by an AI against an AI alone.[56,57] Neither study demonstrated clinical or statistically significant differences between patients who received an AI alone, tamoxifen sequenced with an AI, or in the case of BIG 1-98, an AI sequenced with tamoxifen, with respect to disease-free or overall survival. In BIG 1-98, however, each AI-based therapy was superior to tamoxifen monotherapy with respect to disease-free survival (Table 2).[39] These data support the recommendation to incorporate AI therapy at some point during the first 5 years of adjuvant endocrine therapy, either as primary therapy or in sequence with tamoxifen.

Clinical question 1b. What is the appropriate duration of adjuvant endocrine therapy?

Recommendation 1b. Therapy with an AI should not extend beyond 5 years in either the primary or extended adjuvant settings, outside of clinical trials. In the sequential setting, the Update Committee recommends, on the basis of available evidence from randomized, controlled trials, that patients receive an AI after 2 or 3 years of tamoxifen for a total of 5 years of adjuvant endocrine therapy. The Update Committee recommends that patients who are initially treated with an AI but discontinue treatment before 5 years of therapy consider taking tamoxifen for a total of 5 years of adjuvant endocrine therapy.

Literature update and discussion 1b. Importantly, no trials directly compared sequential or extended adjuvant strategies against one another or primary against extended strategies. Studies used different durations of total endocrine therapy and different durations of AI and tamoxifen treatment. It is not known whether these differences in duration of therapy are clinically significant. Optimal duration of therapy in the extended setting is unclear at this time. Safety and efficacy data from the primary trials support up to 5 years of AI therapy as a primary adjuvant strategy, a duration used in two trials of extended therapy after 5 years of tamoxifen.

The treatment regimen for patients in the sequencing trials spanned 5 years. No data support clinical benefits for durations of AIs longer than 2 or 3 years in a sequencing strategy. Data from randomized, controlled trials demonstrate that women who receive primary AI therapy should be treated for a total of 5 years; women who initially receive tamoxifen and switch to an AI should also receive at least five total years of endocrine therapy. Women who receive extended adjuvant therapy should receive 8 to 10 years of total endocrine treatment—5 years of tamoxifen followed by 3 to 5 years of an AI.

The Update Committee acknowledges that these recommendations yield an unfamiliar pattern of different durations of adjuvant endocrine treatment based on the treatment strategy used. This is a function of offering an AI at a different time point in accordance with each strategy. The recommended limit on AI treatment is 5 years total, across strategies. Two trials—MA.17R and National Surgical Adjuvant Breast and Bowel Project B-42 (NSABP B-42)—are evaluating whether longer durations of AI therapy improve outcomes, but results are not yet available.

Clinical question 1c. If tamoxifen is administered first, how long should it be continued before the switch to an AI?

Recommendation 1c. The Update Committee recommends that, on the basis of available evidence from randomized, controlled trials, patients who initially receive tamoxifen as adjuvant therapy may be offered an AI after 2 to 3 years (sequential) or after 5 years (extended) of therapy. The time to switch from an AI to tamoxifen (or the converse) that maximally improves outcomes is not known from available direct evidence. The Update Committee recommends switching at 2 to 3 years on the basis of data from sequential trials that used this strategy. Switching at 5 years is also a strategy supported by the extended adjuvant randomized trials.

Literature update and discussion 1c. Most trials of sequential therapy switched patients from tamoxifen to an AI after 2 to 3 years of therapy. Some specified an exact cross-over point while others permitted switching within a broad window. Trials of extended therapy enrolled patients who already received an average of 5 years of tamoxifen (Fig 1). Of the trials of sequencing or switching, only BIG 1-98,[58] TEAM,[31] and Austrian Breast and Colorectal Cancer Study Group ABCSG-8[59] enrolled patients before commencement of adjuvant endocrine therapy. The other sequencing and all the extended trials randomly assigned patients free of recurrence after multiple years of tamoxifen. Data are lacking to establish the best duration of tamoxifen therapy before switching to an AI.

Three trials of extended adjuvant therapy that used AI treatment for 3 to 5 years after 5 years of tamoxifen demonstrated that extended therapy can lower the risk of breast cancer recurrence (Table 2 and Appendix Table A2, online only) and contralateral breast cancer (Table 3) but does not improve overall survival (Table 4). The Update Committee recommends extended therapy with an AI for postmenopausal patients who complete 5 years of tamoxifen.

For a newly diagnosed patient or a patient who has taken tamoxifen for 2 to 5 years, it is not known whether switching from tamoxifen to an AI earlier or later is more effective for long-term disease-free survival. Lacking direct comparative data, the Update Committee recommends considering a switch to an AI after 2 or 3 years of tamoxifen therapy. This recommendation is informed by several observations. First, both the Arimidex-Nolvadex (ARNO) 95 and

ABCSG-8 trials, which transitioned patients from tamoxifen to an AI after 2 or 3 years, demonstrated survival advantages, as did a meta-analysis of sequential trials[29,33,60] (Table 3). Second, each AI-based arm of BIG 1-98, including those with switching at 2 years, had improved disease-free survival relative to 5 years of tamoxifen[39] (Table 2). Incorporating an AI into the adjuvant treatment regimen at some point during the first 5 years of endocrine therapy yields clinical improvements.

Clinical question 2. Are there specific patient populations that derive differing degrees of benefit from an AI in comparison to tamoxifen?

Recommendation 2. Direct evidence from randomized trials does not identify a specific marker or clinical subset that predicted which adjuvant treatment strategy, tamoxifen or AI monotherapy or sequential therapy, would maximally improve outcomes for a given patient. Among men with breast cancer, tamoxifen remains the standard adjuvant endocrine treatment. The Update Committee recommends against using CYP2D6 genotype to select adjuvant endocrine therapy. The Update Committee encourages caution with concurrent use of CYP2D6 inhibitors (such as bupropion, paroxetine, or fluoxetine; Table 5) and tamoxifen because of the known drug-drug interactions.

Literature update and discussion 2. Endocrine therapy is effective only among patients with tumors that express hormone receptors such as estrogen receptor (ER) and/or progesterone receptor.[61,62] Tumor size, nodal status, grade, quantitative levels of hormone receptor expression, HER2 overexpression, markers of proliferation, and the 21-gene recurrence score[63] are prognostic factors among patients receiving endocrine therapy.[37] These prognostic markers help to define relative risk of recurrence in the first 5 to 10 years after diagnosis.

The major trials of adjuvant AI therapy included patients with hormone receptor–positive tumors, generally irrespective of other markers or staging. Retrospective subset analyses from some trials considered a variety of prognostic factors among patients receiving tamoxifen or AI therapy. In these retrospective studies, tumor size, nodal status, age, quantitative ER and progesterone receptor levels, HER2 expression,[44,60] grade, Ki-67,[49] and the 21-gene recurrence score[64] seem to serve as prognostic factors for risk of breast cancer recurrence among patients receiving either tamoxifen or AI therapy (Appendix Table A3, online only).

Traditional assumptions about proportionate risk reduction achieved with adjuvant therapy suggest that differences in clinical outcome between various treatments are likely to be of greater absolute magnitude among patients with higher-risk breast cancers. Conversely, among women with lower-risk tumors, differences in outcomes between AI-based therapies and tamoxifen or between primary or sequential use of AIs are likely to be smaller if present at all. Emerging data from BIG 1-98 seem to validate these assumptions.[37,65] However, available retrospective subset analyses are constrained by missing data on some patients, technical limitations in the performance of correlative marker testing, multiple hypothesis testing, varying assays used by different trials, and lack of prospective, corroborative data.

On the basis of evidence from randomized clinical trials and consistent with the recommendation, the Update Committee recommended treatment with either upfront use of an AI or sequential therapy with tamoxifen, followed by an AI, irrespective of any specific clinical subset or prognostic marker.

Male breast cancer. There is no evidence to evaluate the efficacy of adjuvant AI therapy in men. Tamoxifen remains the standard adjuvant endocrine therapy for male breast cancer.[66]

CYP2D6 genotype. Accumulating data suggest that variability in tamoxifen metabolism may affect serum levels of the tamoxifen metabolite endoxifen, which may in turn affect the likelihood of cancer recurrence in tamoxifen-treated patients.[66-73] Factors that contribute to this variability include concurrent use of other drugs that inhibit the CYP2D6 isoenzyme (which converts tamoxifen to endoxifen) and pharmacogenetic variation (polymorphisms) in CYP2D6 alleles. It is not known whether variations in CYP2D6 genotype account for differences in outcomes among patients treated with tamoxifen. Available data on CYP2D6 pharmacogenetics are insufficient to recommend testing as a tool to determine an adjuvant endocrine strategy.

The Update Committee recognized the accumulating evidence on drug-drug interactions between tamoxifen and other drugs that inhibit CYP2D6 (such as buproprion, paroxetine, or fluoxetine; Table 5). Evidence linking such interactions to breast cancer outcomes remains limited and indirect. Patients clearly benefiting from known CYP2D6 inhibitors might avoid tamoxifen because of potential pharmacologic interactions. Conversely, women taking tamoxifen may prefer to avoid concurrent use of known CYP2D6 inhibitors if suitable alternatives are available.

Clinical question 3. What are the toxicities and risks of adjuvant endocrine therapy?

Recommendation 3. The Update Committee recommends that clinicians consider adverse effect profiles, patient preferences, and pre-existing conditions when recommending an adjuvant endocrine strategy for postmenopausal women. Clinicians should discuss adverse effect profiles when presenting available treatment options. The Update Committee suggests that clinicians consider recommending that patients change treatment if adverse effects are intolerable or if patients are persistently noncompliant with therapy.

Literature update and discussion 3. Tamoxifen and AIs are generally well tolerated but are associated with specific toxicities including effects on bone, cardiovascular, and gynecologic health. The differing adverse effect profiles are functions of differing mechanisms of action. Tamoxifen is a selective ER modulator with mixed pro- and antiestrogenic activities, while AIs achieve near complete estrogen deprivation in postmenopausal women. The Update Committee did not find

Table 5. Commonly Used CYP2D6 Inhibitors

Strong inhibitors
Bupropion
Fluoxetine
Paroxetine
Quinidine
Moderate inhibitors
Duloxetine
Terbinafine
Weak inhibitors
Amiodarone
Cimetidine
Sertraline

Flockhart DA: http://medicine.iupui.edu/clinpharm/ddis/table.asz.

evidence that AI therapy is less toxic or better tolerated than tamoxifen. Both drug classes have distinct adverse effect profiles that are relevant to individualizing therapy for patients.

Substudies from the large, randomized trials show generally well-maintained and similar quality of life scores in women receiving any of the adjuvant endocrine therapies.[18,36,43,48,74-77] The severity of the most common adverse effects is mild to moderate for the majority of patients; serious adverse effects are rare. The long-term adverse effect profiles for tamoxifen-treated patients are established from historical literature.[78] Late effects of AI therapy remain to be fully characterized.

Appendix Tables A4 through A8 (online only) include an abbreviated list of the adverse effects tabulated from the therapies evaluated in the prospective, randomized trials discussed herein. Tamoxifen and AIs have differing effects on cardiovascular health. Data suggest that AIs are associated with increased cardiovascular disease, possibly including ischemic cardiac disease, though in absolute terms, at present, any differences are believed to be small.[40,51] In comparison to tamoxifen, AI therapy is associated with an increased risk of both hypercholesterolemia and hypertension. Data are insufficient to exclude clinically significant differences in cardiovascular disease associated with the AIs. Tamoxifen is associated with an increased risk of venous thromboembolic events, giving rise to a 1% to 2% greater risk of deep vein thrombosis compared with women taking AIs (Appendix Table A5).[51] Data on the relative incidence of stroke with either tamoxifen or an AI are inconclusive. Longer follow-up is required to better characterize the potential cardiac toxicity of AI therapy.

Tamoxifen and AIs have differing effects on musculoskeletal health and symptoms. In comparison to tamoxifen, AIs are associated with greater loss of bone mineral density[17] and fractures (Appendix Table A6). The incidence of osteoporosis and bone fractures[79] differs by approximately 2% to 4% in trials of primary adjuvant endocrine therapy comparing tamoxifen with an AI[11,19,21]; risk is increased with AI therapy. Randomized clinical trials suggest that bisphosphonate therapy can mitigate AI-associated loss of bone density.[21,80-82] The long-term impact of AI treatment on osteoporosis risk and fracture risk has not been characterized.

With maturation of clinical data and accumulating clinical experience, it is clear that AIs cause a musculoskeletal/arthralgia syndrome. This syndrome is characterized by bone and joint symptoms, frequently described by patients as pain, stiffness, or achiness that is symmetric and not associated with other signs of rheumatologic disorders.[46,83-86] The prevalence of this syndrome is unclear, though it seems to be widespread; most patients have mild to moderate symptoms. There are no known interventions of proven value for AI-associated musculoskeletal symptoms. Discontinuation of AI therapy usually relieves symptoms within 8 to 10 weeks.

Tamoxifen and AIs have differing effects on gynecologic health; adverse events are more common among women receiving tamoxifen. In general, tamoxifen is associated with an increased risk of uterine cancer (approximately 1% of patients), benign endometrial pathology (including bleeding, polyps, and hyperplasia), hysterectomy, and vaginal discharge (Appendix Table A7). AIs seem to be less frequently associated with hot flashes than tamoxifen is (Appendix Table A8). The Arimidex, Tamoxifen, Alone or in Combination (ATAC) and MA.17 trials both reported a lower incidence of vaginal dryness among patients treated with tamoxifen.[74,77] Alternatively, the Intergroup Exemestane Study (IES) documented similar rates of vaginal dryness among both treatment arms,[18] and the TEAM trial reported a statistically higher rate of vaginal dryness in patients who received sequential tamoxifen and exemestane compared with exemestane alone.[56] Findings were mixed with respect to loss of libido: MA.17 and IES noted similar rates, while AI-treated patients had higher rates in the ATAC trial (Appendix Table A8).[31,75,76]

Clinical question 4. Are AIs effective adjuvant therapy for women who are premenopausal at the time of diagnosis?

Recommendation 4. The Update Committee recommends that women who are pre- or perimenopausal at the time of breast cancer diagnosis be treated with 5 years of tamoxifen.

Additional considerations. The Update Committee recommends that clinicians use caution in evaluating menopausal status of patients who were pre- or perimenopausal at diagnosis. Unequivocal determination of menopausal status may be challenging to prove. Even among women who have not experienced menses for more than 1 year, laboratory testing is inadequate because patients may recover ovarian function. This particularly applies to those patients who experience chemotherapy- or tamoxifen-induced amenorrhea.

Literature update and discussion 4. AI therapy has been shown to be effective only in postmenopausal women and is contraindicated in patients with residual ovarian function. Patients accrued to ABCSG-12, the only trial to include premenopausal women, were all treated with gonadotropin-releasing hormone agonist therapy to achieve a postmenopausal state.[22] Eligible patients had favorable prognosis and low-grade breast cancer, and none received adjuvant chemotherapy, though 5% did receive neoadjuvant chemotherapy. These patients are not necessarily representative of younger women with early-stage breast cancer. ABCSG-12 demonstrated equivalence with respect to time to recurrence, disease-free survival, and overall survival between tamoxifen and AI therapy in premenopausal women given ovarian suppression.[22] Because of tamoxifen equivalence with AI therapy in that setting and the occasional failure to achieve menopausal status with ovarian suppression, the Update Committee strongly recommends tamoxifen as primary adjuvant endocrine therapy for all pre- or perimenopausal women and women with treatment-induced amenorrhea.

Some women who were pre- or perimenopausal at the time of diagnosis may become unequivocally postmenopausal in subsequent years. For these patients, the Update Committee suggests incorporating AIs as either sequential or extended adjuvant endocrine therapy. Relatively few women in the studies of sequential or extended therapy met this description. Thus, the magnitude of benefit for introducing an AI in the subsequent treatment of such women is not well characterized.[87]

Both chemotherapy and tamoxifen can contribute to amenorrhea. This effect may be transient or permanent, depending on the patient's age and therapies received. Multiple reports document late clinical recovery of ovarian function among women with treatment-induced amenorrhea, which could render AI therapy ineffective.[88,89] Cessation of menses for 1 year is the clinical hallmark of menopause. However, this clinical definition applies only to women without health conditions, surgery, or medications that contribute to amenorrhea, such as chemotherapy or tamoxifen and, thus, may not apply to many breast cancer patients.

At present, the role of ovarian suppression in addition to tamoxifen for premenopausal patients is not known. The Suppression of Ovarian Function Trial (SOFT) is comparing tamoxifen, tamoxifen plus ovarian suppression, and exemestane plus ovarian suppression,

and it continues to accrue patients. Findings from this trial will further define best practices for premenopausal patients as well as those patients who experience treatment-induced menopause.

Clinical question 5. Can the third-generation AIs be used interchangeably?

Recommendation 5. In the absence of direct comparisons, the Update Committee interprets available data as suggesting that benefits of AI therapy represent a "class effect." Meaningful clinical differences between the commercially available third-generation AIs have not been demonstrated to date. In the clinical opinion of the Update Committee (rather than direct evidence from randomized trials), postmenopausal patients intolerant of one AI but who are still candidates for adjuvant endocrine therapy may be advised to consider tamoxifen or a different AI.

Literature update and discussion 5. Previous results were limited to reports for principal use of a single AI in each of the clinical settings of primary, sequential, or extended adjuvant therapy. There are still no data from head-to-head comparisons of AIs. However, there are data from randomized trials for each of the commercially available third-generation AIs for all of the adjuvant treatment strategies (primary, sequential, and extended; Fig 1). The Update Committee interprets the existing data comparing the AIs with tamoxifen as qualitatively similar with respect to efficacy and tolerability. Toxicity reports (Appendix Tables A4 through A8) have not suggested obvious clinical advantages of one AI over another with respect to compliance, constitutional or menopausal symptoms, bone health, cardiovascular disease, or quality of life. Anecdotal experience suggests that patients may tolerate one AI better than another, but patterns are neither predictable nor consistent. Two trials—MA.27 and Femara versus Anastrozole Clinical Evaluation (FACE)—are directly comparing one AI against another as primary adjuvant therapy. However, data are not yet available from either trial.

PATIENT COMMUNICATION

The purpose of this section is to address aspects of patient-provider communication that play a role in decision making about the use of adjuvant endocrine therapy, the selection of agent, and the barriers to adherence to treatment regimens (taking medication as prescribed) and persistence with the medication schedule (taking medication for the full duration prescribed). Separate literature searches and Update Committee members' suggestions, rather than the systematic review, were used to prepare this section.

Patients need to be informed about risk factors for tumor recurrence, the role of residual subclinical (ie, microscopic) disease in causing recurrence, and the potential benefit of adjuvant endocrine therapy. Clinicians can base risk estimates in women with hormone receptor–positive disease on well-established prognostic markers such as stage, HER2 status, and grade. Emerging molecular diagnostic assays such as the 21-gene recurrence score also seem to serve as prognostic markers in ER-positive, node-negative breast cancer.[90,91] Decision tools such as Adjuvant! Online[92] quantify and communicate, in broad terms, both the risk of cancer recurrence and the benefit of various adjuvant endocrine treatment strategies on the basis of a patient's tumor characteristics, comorbidity, age, and receipt of chemotherapy.[93]

Rates of nonpersistence (early discontinuation of medications) in women who start taking tamoxifen are as high as 30% at 3 years after filling a first prescription. For example, a study of 2,816 women identified a 22% rate of nonpersistence 12 months after starting tamoxifen.[94] In another study of 392 patients, 32% of women discontinued adjuvant tamoxifen at 2 years and 39% at 3 years.[95] Similarly, in a sample of 961 women 65 years of age or older, 24% discontinued tamoxifen after 2 years of treatment, 33% discontinued tamoxifen after 3 years of treatment, and 50% discontinued tamoxifen before 5 years; discontinuation was not due to recurrent disease.[96]

Data from clinical trials[97] and claims-based research[98] indicate that persistence is no better with AIs. Physicians may underestimate rates of nonadherence and nonpersistence, and patients may be reluctant to disclose problems with adherence and persistence. Patient beliefs about the benefits and risks of medications are associated with adherence and persistence; thus, discussing and addressing such beliefs is warranted.[99]

Adverse effects are particularly important in precipitating early discontinuation of therapy. Patients who experience treatment-related adverse effects are more likely to discontinue adjuvant endocrine therapy, particularly during the first years.[100,101] Adverse effects were the most common reason for discontinuation, particularly during the first year according to one study. Among those who stopped tamoxifen in the first year, 70% stopped because of adverse effects.[96] Patients who experience adverse effects for which they were not prepared seem to be at particularly high risk for nonpersistence.[101] Similarly, musculoskeletal adverse effects of the AIs have been shown to prompt discontinuation in more than 10% of patients who start an AI.[85] Information support for patients about anticipated adverse effects and management of those adverse effects may increase persistence.[91]

Financial constraints are another reported cause of nonpersistence with therapy. One study of patients taking tamoxifen noted that 60% of patients who discontinued therapy early reported this issue as a key factor.[96] It is likely that the out-of-pocket costs of AIs (Table 6) pose an even greater barrier to patients. Although physicians are generally reluctant to discuss costs of cancer therapies,[102] inquiring about patients' cost concerns may help direct patients to assistance programs and create opportunities to stress the benefits of persistence with adjuvant endocrine therapy. ASCO supports the development of resources to facilitate patient-provider communication about costs of cancer care.[103]

In summary, optimal adjuvant endocrine therapy includes careful consideration of tumor risk, treatment benefits and adverse effects, and patient adherence. Clinicians should discuss realistic, quantitative

Table 6. Cost of Therapies

Drug	Cost ($)	
	Per Unit	30-Day Supply
Anastrozole (Arimidex), 1 mg	12.66	379.80
Exemestane (Aromasin), 25 mg	11.38	341.40
Letrozole (Femara), 2.5 mg	13.91	417.30
Tamoxifen (Nolvadex), 20 mg	3.67	110.10
Tamoxifen, 20 mg	0.73	21.90

NOTE. US dollars; www.drugstore.com.

risks of cancer recurrence and death and benefits from cancer therapy as part of the adjuvant therapy decision-making process. Clinicians should alert patients to common adverse effects of therapy and serially inquire about treatment-related toxicities, patient adherence, and factors that may affect adherence and persistence.

HEALTH DISPARITIES

ASCO clinical practice guidelines represent expert recommendations derived from high-quality evidence on the best practices in disease management. However, racial, ethnic, and socioeconomic disparities in quality of health care exist and persist in the United States. Members of racial and ethnic minority groups and patients with fewer financial resources tend to have a higher burden of comorbid illness, are more likely to be uninsured or underinsured, face more challenges in accessing care, and are at greater risk of receiving poor-quality care than other Americans.[104-108]

Representation of minorities in clinical trials of adjuvant endocrine therapy is low. To date, no evidence indicates differences in therapeutic benefit between black and white women receiving adjuvant tamoxifen in the clinical trials setting. A few studies suggest that women who belong to minority groups are less likely to receive guideline-concordant endocrine therapy. One study of prescribing patterns[109] indicated that rates of guideline-concordant adjuvant endocrine therapy prescribing were lower in Hispanic (71%) and black (75%) patients compared with non-Hispanic white (85%) patients.

Only small samples of minority patients were included in persistence studies, largely preventing an examination of correlates and mechanisms of optimal therapy in minorities. Hispanics have largely been omitted. In one study,[95] nonwhite patients (who were pooled because they represented only 17% of the sample) were more likely to stop adjuvant endocrine therapy before completing planned treatment. Other studies addressing racial differences in adherence to or persistence with endocrine therapy generated mixed results.[96,101] Race was not associated with adherence or persistence in one recently published claims-based study of low-income patients with Medicaid[110]; 80% of patients who started adjuvant endocrine therapy were persistent with medication at 1 year of follow-up. Awareness of disparities in quality of care should be considered in the context of this clinical practice guideline.

SUMMARY AND FUTURE DIRECTIONS

Incorporation of an AI improves disease-free survival in postmenopausal women with hormone receptor–positive breast cancer compared with tamoxifen alone. Thus, the Update Committee recommends AI therapy at some point during adjuvant treatment, either as upfront therapy or as sequential or extended treatment after tamoxifen. The optimal timing and duration of AI treatment remain unresolved; it is unclear whether sequential treatment strategies yield advantages over monotherapy with AIs. The Update Committee recognizes distinct adverse effect profiles of tamoxifen and AIs and believes that consideration of adverse effect profiles and patient preferences are relevant to deciding whether and when to incorporate AI therapy.

Important and unanswered questions about adjuvant endocrine therapy in postmenopausal women persist. The Update Committee identified the following issues as clinically significant for ongoing research studies and treatment recommendations:

- Long-term follow-up to characterize the lasting clinical effects of AIs and impact on survival, survivorship, and quality of life
- Comparisons of currently available AIs against one another
- Determination of optimal schedules for endocrine therapy, including duration of treatment, interrupted treatment schedules, and sequencing
- Late adverse effects of AI therapy
- Strategies to improve adherence and minimize disparities in access to therapy
- Interventions to minimize treatment-related adverse effects among women receiving adjuvant endocrine therapy
- Comparative effectiveness analyses of adjuvant endocrine strategies based on efficacy, toxicity, and cost
- Development of biomarker(s) for selection of endocrine strategies and for refining risk estimates in postmenopausal, ER-positive breast cancer
- Identification of predictors of late (after 5 or 10 years) recurrence to tailor durations of therapy
- Definitive analyses of the role of drug metabolism and pharmacogenetics as predictors of benefit and/or treatment options in adjuvant endocrine therapy
- Incorporation of novel antiestrogens or other treatments to enhance endocrine therapy and reduce recurrence risk
- Clarification of the role of AI therapy and ovarian suppression among women who are premenopausal at the time of breast cancer diagnosis

The Update Committee anticipates that the results from prospective randomized trials, ongoing correlative science studies, long-term follow-up from major adjuvant studies, and smaller, focused investigations of related scientific and clinical questions regarding endocrine treatment will continue to inform and revise the recommendations for adjuvant endocrine therapy in the years ahead.

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REFERENCES

1. Winer EP, Hudis C, Burstein HJ, et al: American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor-positive breast cancer: Status report 2002. J Clin Oncol 20:3317-3327, 2002

2. Winer EP, Hudis C, Burstein HJ, et al: American Society of Clinical Oncology technology assessment working group update: Use of aromatase inhibitors in the adjuvant setting. J Clin Oncol 21: 2597-2599, 2003

3. Winer EP, Hudis C, Burstein HJ, et al: American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: Status report 2004. J Clin Oncol 23:619-629, 2005

4. Eisen A, Trudeau M, Shelley W, et al: Aromatase inhibitors in adjuvant therapy for hormone receptor positive breast cancer: A systematic review. Cancer Treat Rev 34:157-174, 2008

5. Hind D, Ward S, De Nigris E, et al: Hormonal therapies for early breast cancer: Systematic review and economic evaluation. Health Technol Assess 11:iii-iv, ix-xi, 1-134, 2007

6. Hudis CA, Barlow WE, Costantino JP, et al: Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: The STEEP system. J Clin Oncol 25:2127-2132, 2007

7. Aihara T, Hozumi Y, Suemasu K, et al: The effects of exemestane, anastrozole and tamoxifen on bone mineral density and bone turnover markers in postmenopausal early breast cancer patients: Preliminary results of N-SAS (national surgical adjuvant study) BC04, the TEAM Japan sub-study. Presented at the 30th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 13-16, 2007 (abstr 2086)

8. Aihara T, Takatsuka Y, Osumi S, et al: Phase III randomized adjuvant study of tamoxifen alone versus sequential tamoxifen and anastrozole in postmenopausal women with hormone-responsive breast cancer: N-SAS BC03 study. Presented at the 31st Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 10-14, 2008 (abstr 1138)

9. Boccardo F, Rubagotti A, Guglielmini P, et al: Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: Updated results of the Italian tamoxifen anastrozole (ITA) trial. Ann Oncol 17:vii10-14, 2006 (suppl 7)

10. Chapman JA, Meng D, Shepherd L, et al: Competing causes of death from a randomized trial of extended adjuvant endocrine therapy for breast cancer. J Natl Cancer Inst 100:252-260, 2008

11. Coleman RE: Long-term effects of anastrozole on bone mineral density: Seven-year results from the ATAC trial. J Clin Oncol 26:27s, 2008 (suppl; abstr 587)

12. Coleman RE, Banks LM, Girgis S, et al: Reversal of skeletal effects of endocrine treatments in the intergroup exemestane study. Presented at the 31st Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 10-14, 2008 (abstr 1128)

13. Coombes RC, Kilburn LS, Snowdon CF, et al: Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): A randomised controlled trial. Lancet 369:559-570, 2007

14. Crivellari D, Sun Z, Coates AS, et al: Letrozole compared with tamoxifen for elderly patients with endocrine-responsive early breast cancer: The BIG 1-98 trial. J Clin Oncol 26:1972-1979, 2008

15. Cuzick J: Hot flushes and the risk of recurrence retrospective, exploratory results from the ATAC trial. Presented at the 30th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 13-16, 2007 (abstr 2069)

16. Cuzick J, Sestak I, Cella D, et al: Treatment-emergent endocrine symptoms and the risk of breast cancer recurrence: A retrospective analysis of the ATAC trial. Lancet Oncol 9:1143-1148, 2008

17. Eastell R, Adams JE, Coleman RE, et al: Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. J Clin Oncol 26:1051-1057, 2008

18. Fallowfield LJ, Langridge CI, Kilburn LS, et al: Quality of life in the Intergroup Exemestane Study (IES) 5 years post-randomisation. Presented at the 30th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 13-16, 2007 (abstr 1091)

19. Forbes JF, Cuzick J, Buzdar A, et al: ATAC: 100 month median follow-up (FU) shows continued superior efficacy and no excess fracture risk for anastrozole (A) compared with tamoxifen (T) after treatment completion. Presented at the 30th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 13-16, 2007 (abstr 40)

20. Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group, Forbes JF, Cuzick J, et al: Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol 9:45-53, 2008

21. Gnant M, Mlineritsch B, Luschin-Ebengreuth G, et al: Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. Lancet Oncol 9:840-849, 2008

22. Gnant M, Mlineritsch B, Schippinger W, et al: Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 360:679-691, 2009

23. Goetz M, Ames M, Gnant M, et al: Pharmacogenetic (CYP2D6) and gene expression profiles (HOXB13/IL17BR and molecular grade index) for prediction of adjuvant endocrine therapy benefit in the ABCSG 8 trial. Presented at the 31st Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 10-14, 2008 (abstr 57)

24. Goss PE: Letrozole in the extended adjuvant setting: MA.17. Breast Cancer Res Treat 105:45-53, 2007 (suppl 1)

25. Goss PE, Ingle JN, Martino S, et al: Efficacy of letrozole extended adjuvant therapy according to estrogen receptor and progesterone receptor status of the primary tumor: National Cancer Institute of Canada Clinical Trials Group MA.17. J Clin Oncol 25:2006-2011, 2007

26. Hadji P, Ziller M, Kieback D, et al: Bone effects of exemestane vs. tamoxifen within the TEAM trial: Results of a prospective randomized bone sub study. Presented at the 31st Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 10-14, 2008 (abstr 1143)

27. Hozumi Y, Aihara T, Takatsuka Y, et al: Chronological changes of side effect profile of anastrozole compared with tamoxifen in Japanese women: Findings from N-SAS BC03 trial every 3 months after one year of randomization. Presented at the 30th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 13-16, 2007 (abstr 3059)

28. Ingle JN, Tu D, Pater JL, et al: Intent-to-treat analysis of the placebo-controlled trial of letrozole for extended adjuvant therapy in early breast cancer: NCIC CTG MA.17. Ann Oncol 19:877-882, 2008

29. Jakesz R, Gnant M, Griel R, et al: Tamoxifen and anastrozole as a sequencing strategy in postmenopausal women with hormone-responsive early breast cancer: Updated data from the Austrian breast and colorectal cancer study group trial 8. Presented at the 31st Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 10-14, 2008 (abstr 14)

30. Jakesz R, Greil R, Gnant M, et al: Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: Results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. J Natl Cancer Inst 99:1845-1853, 2007

31. Jones SE, Cantrell J, Vukelja S, et al: Comparison of menopausal symptoms during the first year of adjuvant therapy with either exemestane or tamoxifen in early breast cancer: Report of a Tamoxifen Exemestane Adjuvant Multicenter trial substudy. J Clin Oncol 25:4765-4771, 2007

32. Jones SE, Seynaeve C, Hasenburg A, et al: Results of the first planned analysis of TEAM (tamoxifen exemestane adjuvant multinational) prospective randomized phase III trial in hormone

sensitive postmenopausal early breast cancer. Presented at the 31st Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 10-14, 2008 (abstr 15)

33. Kaufmann M, Jonat W, Hilfrich J, et al: Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after treatment with tamoxifen compared with continued tamoxifen: The ARNO 95 Study. J Clin Oncol 25:2664-2670, 2007

34. Kieback DG, Harbeck N, Bauer W, et al: Endometrial effects of exemestane compared to tamoxifen within the TEAM trial: Results of a prospective randomized study. J Clin Oncol 25:20s, 2007 (suppl; abstract 572)

35. Koeberle D, Thuerlimann B: Letrozole as upfront endocrine therapy for postmenopausal women with hormone-sensitive breast cancer: BIG 1-98. Breast Cancer Res Treat 105:55-66, 2007 (suppl 1)

36. Mamounas EP, Jeong JH, Wickerham DL, et al: Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: Intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial. J Clin Oncol 26:1965-1971, 2008

37. 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

38. Monnier AM: The Breast International Group 1-98 trial: Big results for women with hormone-sensitive early breast cancer. Expert Rev Anticancer Ther 7:627-634, 2007

39. BIG 1-98 Collaborative Group, Mouridsen H, Giobbie-Hurder A, et al: Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. N Engl J Med 361:766-776, 2009

40. Mouridsen H, Keshaviah A, Coates AS, et al: Cardiovascular adverse events during adjuvant endocrine therapy for early breast cancer using letrozole or tamoxifen: Safety analysis of BIG 1-98 trial. J Clin Oncol 25:5715-5722, 2007

41. Mouridsen HT, Giobbie-Hurder A, Mauriac L, et al: BIG 1-98: A randomized, double blind phase III study evaluating letrozole with tamoxifen given in sequence as adjuvant endocrine therapy for postmenopausal women with receptor (+) breast cancer. Presented at the 31st Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 10-14, 2008 (abstr 13)

42. Muss HB, Tu D, Ingle JN, et al: Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG intergroup trial MA.17. J Clin Oncol 26:1956-1964, 2008

43. Ohsumi S, Shimozuma K, Ohashi Y, et al: Health-related quality-of-life and psychological distress of postmenopausal breast cancer patients after surgery during the randomized trial, N-SAS BC 03, comparing further tamoxifen with switching to anastrozole after adjuvant tamoxifen for 1 to 4 years: The final results. Presented at the 31st Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 10-14, 2008 (abstr 1136)

44. Rasmussen BB, Regan MM, Lykkesfeldt AE, et al: Adjuvant letrozole versus tamoxifen according to centrally-assessed ERBB2 status for postmenopausal women with endocrine-responsive early breast cancer: Supplementary results from the BIG 1-98 randomised trial. Lancet Oncol 9:23-28, 2008

45. Schilder CM, Seynaeve C, Linn SC, et al: Effects of tamoxifen and exemestane on cognitive functioning of postmenopausal patients with early breast cancer: Results from the TEAM trial. Presented at the 31st Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 10-14, 2008 (abstr 1133)

46. Sestak I, Cuzick J, Sapunar F, et al: Risk factors for joint symptoms in patients enrolled in the ATAC trial: A retrospective, exploratory analysis. Lancet Oncol 9:866-872, 2008

47. Takehara M, Ohsumi S, Takei H, et al: Health-related quality of life and psychological distress in Japanese patients with breast cancer treated with tamoxifen, exemestane or anastrozole for adjuvant therapy: A phase III randomized study of National Surgical Adjuvant Study of Breast Cancer (N-SAS BC) 04. Presented at the 30th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 13-16, 2007 (abstr 2088)

48. van Nes JG, Voskuil DW, van Leeuwen FE, et al: Quality of life in relation to hormonal treatment of postmenopausal women in the Dutch Tamoxifen Exemestane Adjuvant Multicentre (TEAM) trial. Presented at the 31st Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 10-14, 2008 (abstr 21)

49. Viale G, Giobbie-Hurder A, Regan MM, et al: Prognostic and predictive value of centrally reviewed Ki-67 labeling index in postmenopausal women with endocrine-responsive breast cancer: Results from Breast International Group Trial 1-98 comparing adjuvant tamoxifen with letrozole. J Clin Oncol 26:5569-5575, 2008

50. Aydiner A, Tas F: Meta-analysis of trials comparing anastrozole and tamoxifen for adjuvant treatment of postmenopausal women with early breast cancer. Trials 9:47, 2008

51. Cuppone F, Bria E, Verma S, et al: Do adjuvant aromatase inhibitors increase the cardiovascular risk in postmenopausal women with early breast cancer? Meta-analysis of randomized trials. Cancer 112:260-267, 2008

52. Ingle JN, Dowsett M, Cuzick J, et al: Aromatase inhibitors versus tamoxifen as adjuvant therapy for postmenopausal women with estrogen receptor positive breast cancer: Meta-analyses of randomized trials of monotherapy and switching strategies. Presented at the 31st Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 10-14, 2008 (abstr 12)

53. Kalder M, Hadji P: Bone health in postmenopausal women (PMW) with hormone-sensitive breast cancer (HSBC) receiving adjuvant aromatase inhibitor (AI) therapy. J Clin Oncol 26:611s, 2008 (suppl; abstr 11556)

54. Vakaet LA: Meta-analysis of side effects (SEs) of aromatase inhibitors (AI) and of tamoxifen (TAM) in large randomized clinical trials (RCT). J Clin Oncol 25:595s, 2007 (suppl; abstr 11015)

55. Bliss JM, Kilburn LS, Coleman RE, et al: Disease related outcome with long term follow-up: An updated analysis of the Intergroup Exemestane Study (IES). Presented at the 32nd Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 9-13, 2009

56. Rea D, Hasenburg A, Seynaeve C, et al: Five years of exemestane as initial therapy compared to 5 years of tamoxifen followed by exemestane: The TEAM Trial, a prospective, randomized, phase III trial in postmenopausal women with hormone-sensitive early breast cancer. Presented at the 32nd Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 9-13, 2009

57. Reference deleted

58. Breast International Group (BIG) 1-98 Collaborative Group, Thürlimann B, Keshaviah A, et al: A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 353:2747-2757, 2005

59. Jakesz R, Gnant M, Greil R, et al: The benefits of sequencing adjuvant tamoxifen and anastrozole in postmenopausal women with hormone-responsive early breast cancer: 5 year-analysis of ABCSG Trial 8. Presented at the 28th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 8-11, 2005 (abstr 13)

60. Dowsett M, Cuzick J, Ingle JN, et al: Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen J Clin Oncol 28:509-518, 2010

61. 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

62. Fisher B, Anderson S, Tan-Chiu E, et al: Tamoxifen and chemotherapy for axillary node-negative, estrogen receptor-negative breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-23. J Clin Oncol 19:931-942, 2001

63. Paik S, Shak S, Tang G, et al: A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 351: 2817-2826, 2004

64. Dowsett M, Cuzick J, Wale C, et al: Risk of distant recurrence using oncotype DX in postmenopausal primary breast cancer patients treated with anastrozole or tamoxifen: A Trans ATAC study. Presented at the 31st Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 10-14, 2008 (abstr 53)

65. Viale G, Regan MM, Dell'Orto P, et al: Central review of ER, PgR and HER2 in BIG 1-98 evaluating letrozole vs letrozole followed by tamoxifen vs tamoxifen followed by letrozole as adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive breast cancer. Cancer Res Treat 69:504s, 2009 (suppl; abstr 76)

66. Giordano SH, Perkins GH, Broglio K, et al: Adjuvant systemic therapy for male breast carcinoma. Cancer 104:2359-2364, 2005

67. Technology Evaluation Center (Blue Cross Blue Shield Association): CYP2D6 Pharmacogenomics of Tamoxifen Treatment, 2008. http://www.bcbs.com/blueresources/tec/vols/23/23_01.pdf

68. Albain K, Barlow WE, Shak S, et al: Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal, node-positive, ER-positive breast cancer (S8814,INT0100). Presented at the 30th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 13-16, 2007 (abstr 10)

69. Borges S, Desta Z, Li L, et al: Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: Implication for optimization of breast cancer treatment. Clin Pharmacol Ther 80:61-74, 2006

70. Goetz MP, Knox SK, Suman VJ, et al: The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. Breast Cancer Res Treat 101:113-121, 2007

71. Goetz MP, Rae JM, Suman VJ, et al: Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. J Clin Oncol 23:9312-9318, 2005

72. Gonzalez-Santiago S, Zárate R, Haba-Rodríguez J, et al: CYP2D6*4 polymorphism as blood predictive biomarker of breast cancer relapse

in patients receiving adjuvant tamoxifen. J Clin Oncol 25:25s, 2007 (suppl; abstr 590)

73. Schroth W, Goetz MP, Hamann U, et al: Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. JAMA 302:1429-1436, 2009

74. Cella D, Fallowfield L, Barker P, et al: Quality of life of postmenopausal women in the ATAC ("Arimidex", tamoxifen, alone or in combination) trial after completion of 5 years' adjuvant treatment for early breast cancer. Breast Cancer Res Treat 100: 273-284, 2006

75. Fallowfield L, Cella D, Cuzick J, et al: Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. J Clin Oncol 22:4261-4271, 2004

76. Fallowfield LJ, Bliss JM, Porter LS, et al: Quality of life in the intergroup exemestane study: A randomized trial of exemestane versus continued tamoxifen after 2 to 3 years of tamoxifen in postmenopausal women with primary breast cancer. J Clin Oncol 24:910-917, 2006

77. Whelan TJ, Goss PE, Ingle JN, et al: Assessment of quality of life in MA.17: A randomized, placebo-controlled trial of letrozole after 5 years of tamoxifen in postmenopausal women. J Clin Oncol 23:6931-6940, 2005

78. Osborne CK: Tamoxifen in the treatment of breast cancer. N Engl J Med 339:1609-1618, 1998

79. Rabaglio M, Sun Z, Price KN, et al: Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial. Ann Oncol 20:1489-1498, 2009

80. Brufsky A, Harker WG, Beck JT, et al: Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. J Clin Oncol 25:829-836, 2007

81. Bundred NJ, Campbell ID, Davidson N, et al: Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results. Cancer 112:1001-1010, 2008

82. Hillner BE, Ingle JN, Chlebowski RT, et al: American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 21:4042-4057, 2003

83. Burstein HJ, Winer EP: Aromatase inhibitors and arthralgias: A new frontier in symptom management for breast cancer survivors. J Clin Oncol 25: 3797-3799, 2007

84. Crew KD, Greenlee H, Capodice J, et al: Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. J Clin Oncol 25:3877-3883, 2007

85. Henry NL, Giles JT, Ang D, et al: Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors. Breast Cancer Res Treat 111:365-372, 2008

86. Sestak I, Sapunar F, Cuzick J: Aromatase inhibitor-induced carpal tunnel syndrome: Results from the ATAC trial. J Clin Oncol 27:4961-4965, 2009

87. Goss PE, Ingle JN, Martino S, et al: Outcomes of women who were premenopausal at diagnosis of early stage breast cancer in the NCIC CTG MA.17 trial. Cancer Res Treat 69:487s, 2009 (suppl; abstr 13)

88. Burstein HJ, Mayer E, Patridge AH, et al: Inadvertent use of aromatase inhibitors in patients with breast cancer with residual ovarian function: Cases and lessons. Clin Breast Cancer 7:158-161, 2006

89. Smith IE, Dowsett M, Yap YS, et al: Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: Caution and suggested guidelines. J Clin Oncol 24:2444-2447, 2006

90. Harris L, Fritsche H, Mennel R, et al: American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol 25:5287-5312, 2007

91. Haynes RB, Ackloo E, Sahota N, et al: Interventions for enhancing medication adherence. Cochrane Database Syst Rev 2: CD000011, 2008

92. Adjuvant! Online. http://www.adjuvantonline.com

93. Ravdin PM: A computer program to assist in making breast cancer adjuvant therapy decisions. Semin Oncol 23:43-50, 1996 (suppl 1)

94. Barron TI, Connolly R, Bennett K, et al: Early discontinuation of tamoxifen: A lesson for oncologists. Cancer 109:832-839, 2007

95. Partridge AH, Wang PS, Winer EP, et al: Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. J Clin Oncol 21:602-606, 2003

96. Owusu C, Buist DS, Field TS, et al: Predictors of tamoxifen discontinuation among older women with estrogen receptor-positive breast cancer. J Clin Oncol 26:549-555, 2008

97. Chlebowski RT, Geller ML: Adherence to endocrine therapy for breast cancer. Oncology 71: 1-9, 2006

98. Partridge AH, LaFountain A, Mayer E, et al: Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. J Clin Oncol 26:556-562, 2008

99. Horne R, Weinman J: Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res 47:555-567, 1999

100. Demissie S, Silliman RA, Lash TL: Adjuvant tamoxifen: Predictors of use, side effects, and discontinuation in older women. J Clin Oncol 19:322-328, 2001

101. Kahn KL, Schneider EC, Malin JL, et al: Patient centered experiences in breast cancer: Predicting long-term adherence to tamoxifen use. Med Care 45:431-439, 2007

102. Schrag D, Hanger M: Medical oncologists' views on communicating with patients about chemotherapy costs: A pilot survey. J Clin Oncol 25:233-237, 2007

103. Meropol NJ, Schrag D, Smith TJ, et al: American Society of Clinical Oncology guidance statement: The cost of cancer care. J Clin Oncol 27:3868-3874, 2009

104. U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999-2002, Incidence and Mortality Web-based Report. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute Atlanta, 2005. http://apps.nccd.cdc.gov/uscs/

105. American Cancer Society. Cancer Facts and Figures for African Americans 2005-2006. Atlanta, 2005. http://www.cancer.org/downloads/STT/CAFF2005AACorrPWSecured.pdf

106. Mead H, Cartwright-Smith L, Jones K, et al: Racial and Ethnic Disparities in U.S. Health Care: A Chartbook. New York, NY, The Commonwealth Fund, 2008

107. Ries LA, Eisner MP, Kossary CL, et al: SEER Cancer Statistics Review, 1973-1997. National Cancer Institute. Bethesda, MD, 2000. http://seer.cancer.gov/csr/1973_1997/

108. Smedley BD, Stith AY, Nelson AR: Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Washington, DC, National Academies Press, 2003

109. Bickell NA, Wang JJ, Oluwole S, et al: Missed opportunities: Racial disparities in adjuvant breast cancer treatment. J Clin Oncol 24:1357-1362, 2006

110. Kimmick G, Anderson R, Camacho F, et al: Adjuvant hormonal therapy use among insured, low-income women with breast cancer. J Clin Oncol 27:3445-3451, 2009

111. Baum M, Budzar AU, Cuzick J, et al: Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial. Lancet 359:2131-2139, 2002

112. Boccardo F, Rubagotti A, Amoroso D, et al: Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment. Breast Cancer Res Treat 82, 2003 (abstr 3)

113. Coombes RC, Hall E, Gibson LJ, et al: A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 350:1081-1092, 2004

114. Jakesz R, Jonat W, Gnant M, et al: Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 366:455-462, 2005

115. Goss PE, Ingle JN, Martino S, et al: A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 349:1793-1802, 2003

116. Jakesz R, Samonigg H, Greil R, et al: Extended adjuvant treatment with anastrozole: Results from the Austrian Breast and Colorectal Cancer Study Group Trial 6a (ABCSG-6a). J Clin Oncol 23:10s, 2005 (suppl; abstr 527)

117. Mamounas EP, Jeong JH, Wickerham L, et al: Benefit from exemestane (EXE) as extended adjuvant therapy after 5 years of tamoxifen (TAM): Intent-to-treat analysis of NSABP B-33. Breast Cancer Res Treat 100:A49, 2006 (suppl 1)

