


Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

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Assessment of Steroid Hormone Receptor Status

Oxford LoE: 1	GR: A	AGO: ++
Endocrine responsiveness: formerly known as receptor negative Immunohistochemistry (ER and / or PgR)		
0% pos. cells:		endocrine non responsive
1–9% pos. cells:		endocrine doubtfully responsive
≥ 10% pos. cells:		endocrine responsive
Hormon Receptor Status unknown:		endocrine responsive
In case of ER negative / PR positive (> = 10% cells): consider immunohistochemical re-evaluation		

Endocrine responsiveness:


1. Hammond ME , Hayes DF, DowsettM et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol. 2010 Jun 1;28(16):2784-95. Review. Erratum in: J Clin Oncol. 2010 Jul 20;28(21):3543.
2. 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. 2005;365(9472):1687–717.
3. Traub L, Thill M, Nitschmann S: 20-Jahres-Ergebnisse einer 5-jährigen Hormontherapie bei Mammakarzinom : Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Internist (Berl). Springer Medizin 2018;59(4):410–2.
4. Pan H, Gray R, Braybrooke J et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. N Engl J Med. 2017;377(19):1836–46.

In case of ER negative / PR positive (>10% cells): consider immunohistochemical re-evaluation :

1. Viale G, Regan MM, Maiorano E et al. Prognostic and predictive value of centrally reviewed expression of estrogen and progesterone receptors in a randomized trial comparing letrozole and tamoxifen adjuvant therapy for postmenopausal early

breast cancer: BIG 1-98. J Clin Oncol 2007;25:3846-52.

2. Cserni G, Fracz M, Kalman E et al. Estrogen receptor negative and progesterone receptor positive breast carcinomas-how frequent are they? Pathol Oncol Res 2011;17:663-8.
3. Hefti MM, Hu R, Kniblauch NW et al. Estrogen receptor negative/progesterone receptor positive breast cancer is not a reproducible subtype. Breast Cancer Res 2013;15:R68.
4. Yi M, Huo L, Koenig KB et al. Which threshold for ER positivity? a retrospective study based on 9639 patients. Ann Oncol 2014;25:1004-11.



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Adjuvant Endocrine Therapy

Assessment of Menopausal Status

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LoE	GR	AGO
		+
		++

Assessment of menopausal status:

- **Menstruation history**
- **FSH, E2**


1. Ortmann O, Cufer T, Dixon JM et al. Adjuvant endocrine therapy for perimenopausal women with early breast cancer. Breast 2009;18(1):2-7.
2. Clemons M, Simmons C: Identifying menopause in breast cancer patients: considerations and implications. Breast Cancer Res Treat 2007;104(2):115-20.
3. Su HI, Sammel MD, Green J et al. Antimüllerian hormone and inhibin B are hormone measures of ovarian function in late reproductive-aged breast cancer survivors. Cancer 2010;116(3):592-9.
4. Partridge AH, Ruddy KJ, Gelber S et al. Ovarian reserve in women who remain premenopausal after chemotherapy for early stage breast cancer. Fertil Steril 2010;94(2):638-44.
5. Anders C, Marcom PK, Peterson B et al. A pilot study of predictive markers of chemotherapy-related amenorrhea among premenopausal women with early stage breast cancer. Cancer Invest 2008;26(3):286-95
6. Anderson RA, Cameron DA: Pretreatment serum anti-müllerian hormone predicts long-term ovarian function and bone mass after chemotherapy for early breast cancer. J Clin Endocrinol Metab 2011 96(5):1336-43.
7. Su HI, Chung K, Sammel MD et al. Antral follicle count provides additive information to hormone measures for determining ovarian function in breast cancer survivors. Fertil Steril 2011;95(5):1857-9.

Adjuvant Endocrine Therapy

	Oxford		
	LoE	GR	AGO
■ Endocrine responsive & doubtful responsive			
Endocrine therapy	1a	A	++
■ Endocrine therapy			
Sequentially after CT	1a	A	++
■ Non-responsive:			
No endocrine therapy	1a	A	++

1. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of randomised trials. Lancet 2005;365:1687-717.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011;378(9793):771-84.
3. Hackshaw A, Roughton M, Forsyth S et al. Long-term benefits of 5 years of tamoxifen: 10-year follow-up of a large randomized trial in women at least 50 years of age with early breast cancer. J Clin Oncol 2011;29(13): 1657-63.
4. Albain KS, Barlow WE, Ravdin PM, et al. Breast Cancer Intergroup of North America. Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial. Lancet 2009;374(9707):2055-63.
5. Bedognetti D, Sertoli MR, Pronzato P, et al. Concurrent vs sequential adjuvant chemotherapy and hormone therapy in breast cancer: a multicenter randomized phase III trial. J Natl Cancer Inst 2011;103(20):1529-39.
6. Fujii T, Kogawa T, Dong W et al. Revisiting the definition of estrogen receptor positivity in Her2-negative primary breast cancer. Ann Oncol 2017;28:2420-2428
7. Curigliano G, Burstein HJ, P Winer E et al. De-Escalating and escalating treatment for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer. Ann Oncol 2017;28:1700-1712 .
8. Regan MM, Walley BA, Francis PA et al. Concurrent and sequential initiation of ovarian function suppression with chemotherapy

in premenopausal women with endocrine-responsive early breast cancer: an exploratory analysis of TEXT and SOFT. *Ann Oncol* 2017;28:2225-2232.



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General Principles in Adjuvant Endocrine Therapy AGO ++

- **Adjuvant endocrine therapy is divided into initial therapy (years 0-5) and extended adjuvant therapy (EAT, years 6-15).**
- **Standard treatment duration is 5 years.**
- **Extended treatment should be considered based on individual benefits and risks.**
- **Duration, choice & sequence of AI or Tam mainly depend on menopausal status, tolerability and risk of recurrence.**
- **Switch to another better tolerated endocrine treatment (Tam or AI) is better than to stop.**
- **AI should be used as first treatment in postmenopausal patients especially in cases of lobular cancers and high risk of recurrence.**
- **To date, there is no sufficiently validated biomarker that identifies patients for early versus late recurrence.**

1. Ingle JN: Overview of adjuvant trials of aromatase inhibitors in early breast cancer. *Steroids* 2011;76(8):765-7.
2. Higgins MJ, Liedke PE, Goss PE et al. Extended adjuvant endocrine therapy in hormone dependent breast cancer: the paradigm of the NCIC-CTG MA.17/BIG 1-97 trial. *Crit Rev Oncol Hematol* 2013;86(1):23-32.
3. Regan MM, Neven P, Giobbie-Hurder A et al. BIG 1-98 Collaborative Group; International Breast Cancer Study Group (IBCSG). Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8.1 years median follow-up. *Lancet Oncol* 2011;12(12):1101-8.
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet* 2015;386(10001):1341-52.
5. Rydén L, Heibert Arnlind M, Vitols S et al. Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials. *Breast* 2016;26:106-140.
6. Goss PE, Ingle JN, Pritchard KI et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. *N Engl J Med* 2016;375(3):209.
7. Pan H, Gray R, Braybrooke J et al. 20-year risks of breast recurrence after stopping endocrine therapy at 5 years. *N Engl J Med* 2017;1836-49.
8. Burstein HJ, Lacchetti C, Anderson H et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update. *J Clin Oncol* 2018 Nov 19;JCO1801160. doi: 10.1200/JCO.18.01160

9. Strasser-Weippl K, Sudan G, Ramjeesingh R et al. Outcomes in women with invasive ductal or invasive lobular early stage breast cancer treated with anastrozole or exemestane in CCTG (NCIC CTG) MA.27. *Eur J Cancer* 2018;90:19-25.
10. 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.* 2018;110(1)djx141.
11. van Hellemond I, Geurts SME, Tjan-Heijnen VCG: Current status of extended adjuvant endocrine therapy in early stage breast cancer. *Curr Treat Options in Oncol* 2018;19:26.
12. Regan MM, Walley BA, Francis PA et al. Concurrent and sequential initiation of ovarian function suppression with chemotherapy in premenopausal women with endocrine-responsive early breast cancer: an exploratory analysis of TEXT and SOFT. *Ann Oncol* 2017;28:2225-2232.
13. Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E et al. Treatment decisions and the impact of adverse events before and during extended endocrine therapy in postmenopausal early breast cancer. *Eur J Cancer* 2018;95:59-67.
14. Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E et al: Relevant factors for the optimal duration of extended endocrine therapy in early breast cancer. *Breast Cancer Res Treat* 2018;168:413-420.
15. Clement Z, Kollias J, Bingham J et al: Extended duration of adjuvant aromatase inhibitor in breast cancer: a meta-analysis of randomized controlled trials. *Gland Surg* 2018;7:449-457.

<div>  <div> Premenopausal Patients Initial Adjuvant Endocrine Therapy (Year 0-5) </div> </div>			
	Oxford		
	LoE	GR	AGO
■ Tamoxifen* 5–10 years	1a	A	++
■ GnRH alone (only, if relevant contraindication for Tam)	1a	B	+
■ Without indication for neo-/adjuvant chemotherapy and preserved ovarian function			
■ Tamoxifen	1b	B	++
■ Tamoxifen + OFS**	1b	B	+/-
■ AI + OFS**	1b	B	+/-
■ Following neo-/adjuvant chemotherapy and preserved ovarian function (≤ 8 months EOC)			
■ Tamoxifen + OFS 5 years** → in patients < 35 years	1b	B	+
	1b	B	++
■ AI + OFS** → in patients < 35 years	1b	B	+/-
	1b	B	+
<small>OFS: ovarian Function-Suppression; EOC: end of chemotherapy treatment as long as tolerable and the pat. is clearly premenopausal ** only limited data on OS available</small>			

Tamoxifen 5-10 yrs:

1. 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 2005;365:1687-717.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011;378:771-84.
3. Davies C, Pan H, Godwin J et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381:805-806.
4. Tormey DC, Gray R, Falkson HC: Postchemotherapy adjuvant tamoxifen therapy beyond five years in patients with lymph node-positive breast cancer. Eastern Cooperative Oncology Group. J Natl Cancer Inst 1996;88:1828-33.
5. Goel S, Sharma R, Hamilton A et al: LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. Cochrane Database Syst Rev. 20097;(4):CD004562.

GnRH as monotherapy:

Cuzick J, Ambrosine L, Davidson N et al: Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in

premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. Lancet 2007; 369:1711-23.

In patients with ovarian function (within 8 mon.) after adjuvant chemotherapy:

OFS 5 years + Tam 5 years

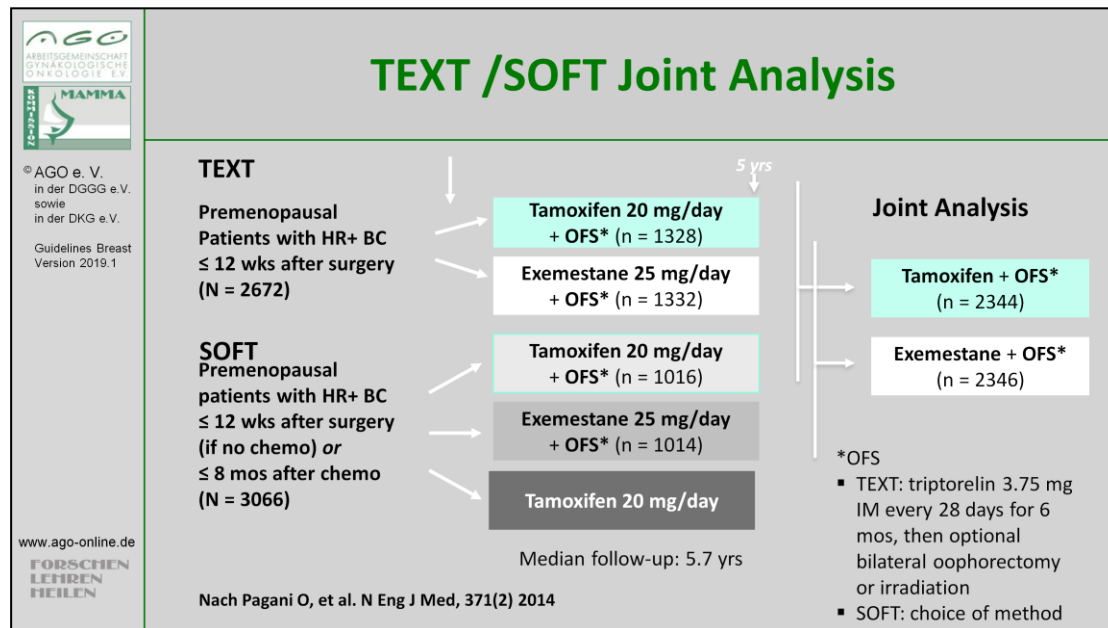
OFS 5 years + AI 5 years

in patients < 35 y.


1. Pagani O, Gelber S, Colleoni M, et al. Impact of SERM adherence on treatment effect: International Breast Cancer Study Group Trials 13-93 and 14-93. Breast Cancer Res Treat 2013;142(2):455-9.
2. Ganz PA, Land SR, Geyer CE Jr et al. Menstrual history and quality-of-life outcomes in women with node-positive breast cancer treated with adjuvant therapy on the NSABP B-30 trial. J Clin Oncol 2011;29(9):1110-6.
3. Goel S, Sharma R, Hamilton A et al: LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. Cochrane Database Syst Rev 20097;(4):CD004562.
4. Francis PA, Regan MM, Fleming GF et al. The SOFT Investigators and the International Breast Cancer Study Group. Adjuvant Ovarian Suppression in Premenopausal Breast Cancer. N Engl J Med 2015;372(5):436-46.
5. Pagani O, Regan MM, Walley BA et al. TEXT and SOFT Investigators; International Breast Cancer Study Group. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med 2014;371(2):107-18.
6. Gnant M, Mlineritsch B, Schippinger W et al: Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 2009;360(7):679-91.
7. Shiba E, Yamashita H, Kurebayashi J et al. A randomized controlled study evaluating safety and efficacy of leuprorelin acetate every-3-months depot for 2 versus 3 or more years with tamoxifen for 5 years as adjuvant treatment in premenopausal patients with endocrine-responsive breast cancer. Breast Cancer 2016;23(3):499-509.
8. Kim HA, Ahn SH, Nam SJ et al. The role of the addition of ovarian suppression to tamoxifen in young women with hormone-sensitive breast cancer who remain premenopausal or regain menstruation after chemotherapy (ASTRRA): study protocol for a

randomized controlled trial and progress. BMC Cancer 2016;16:319.

9. Saha P, Regan MM, Pagani O: Treatment efficacy, adherence, and quality of life among younger than 35 years in the International Breast Cancer Study Group TEXT and SOFT adjuvant endocrine therapy trial. J Clin Oncol 2017;35:3113-3122.



1. Pagani O, Gelber S, Colleoni M, et al. Impact of SERM adherence on treatment effect: International Breast Cancer Study Group Trials 13-93 and 14-93. Breast Cancer Res Treat 2013;142(2):455-9.
2. Francis PA, Regan MM, Fleming GF et al. The SOFT Investigators and the International Breast Cancer Study Group. Adjuvant Ovarian Suppression in Premenopausal Breast Cancer. N Engl J Med 2015;372(5):436-46.



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Incomplete Ovarian Suppression within SOFT – Study (SOFT-EST-Substudy)

- **In Soft-EST: Exe + OFS: E2, E1, E1-Sulfate - levels were significantly lower than in pats. with Tam + OS**
- **66% of premenopausal pats. on Exe + OFS had profound persistent suppression of E2 etc. for 12 months.**
- **However, 34% had an E2 level greater than menopausal threshold at least once, 17% at all time-points:**
 - These patients were more likely younger than 35 y; chemo-naïve; had higher BMI
 - **Importantly:** Combining ABCSG-12, SOFT, and TEXT studies, **showed 65 fewer DFS events** (HR 0.89, 95% CI 0.57–1.39) **but 30 more deaths** for ovarian suppression plus aromatase inhibitor compared to ovarian suppression plus tamoxifen (HR 1.31, 95% CI 0.93–1.84, P = 0.12, s = 0.03, heterogeneity, P = 0.18).
- **Hence the question arises, whether incomplete ovarian suppression led to this discrepancy**

1. Chlebowski RT, Pan K, Col NF: Ovarian suppression in combination endocrine adjuvant therapy in premenopausal women with early breast cancer. Breast Cancer Res Treat 2017;161(2):185-190.

Postmenopausal Patients Initial Adjuvant Endocrine Therapy (Years 0-5)			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Aromatase Inhibitor (AI) for first 5 years <ul style="list-style-type: none"> Non steroidal-AI in lobular cancer High risk of recurrence 	1a	A	++
	2b	B	+
<ul style="list-style-type: none"> Sequential therapy for first 5 years * <ul style="list-style-type: none"> Tam (2-3 yrs.) followed by AI to complete 5 years AI (2-3 yrs.) followed by Tamoxifen to complete 5 years 	1a	A	++
	1b	C	
<ul style="list-style-type: none"> Tamoxifen 20 mg/d for 5 years** 	1a	A	+

* in postmenopausal patients AI should be integrated in the first five years at some point
 ** Tamoxifen might be offered to very old patients or in patients with very low risk of recurrence or if contraindications for AI are present

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AI for first 5 years:

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 2015;386(10001):1341-52.
2. Rydén L, Heibert Arnlin M, Vitols S et al. Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials. Breast 2016;26:106-14.

-Especially in case of lobular cancer

3. Strasser-Weippl K et al. Outcomes in women with invasive ductal or invasive lobular early stage breast cancer treated with anastrozole or exemestane in CCTG (NCIC CTG) MA.27. Eur J Cancer 2018;90:19-25. doi: 10.1016/j.ejca.2017.11.014

-High risk of recurrence:

4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 2015;386(10001):1341-52.

Sequential therapy for first 5 years:

Tam (2-3 yrs.) followed by AI to complete 5 years

AI (2-3 yrs.) followed by Tam to complete 5 years

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 2015;386(10001):1341-52.
2. Rydén L, Heibert Arnlin M, Vitols S et al. Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials. Breast 2016;26:106-14.
3. Derks MGM, Blok EJ, Seynaeve C et al. Adjuvant tamoxifen and exemestane in women with postmenopausal early breast cancer (TEAM): 10-year follow-up of a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2017;18:1211-1220.
4. Ruhstaller T, Giobbie-Hurder A, Colleoni M et al. Adjuvant letrozole and tamoxifen alone or sequentially for postmenopausal women with hormone receptor-positive breast cancer: long-term follow-up of the BIG 1-98 trial. J Clin Oncol 2019;37(2):105-114.

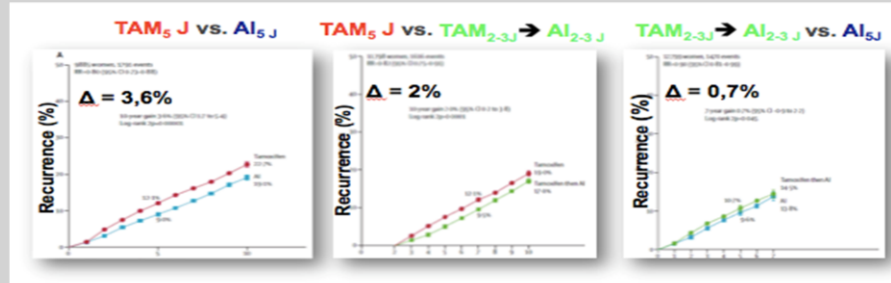
Tamoxifen 20 mg/d for first 5 yrs:

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 378:771-84, 2011
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 2015;386:1341-52.
3. Rydén L, Heibert Arnlin M, Vitols S et al. Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials. Breast. 2016;26:106-14.

Patient care/ adherence and side effects


1. Inwa Id EC, Koller M, Klinkhammer-Schalke M et al. Adjuvant endocrine therapy in pre- versus postmenopausal patients with steroid hormone receptor-positive breast cancer: results from a large population-based cohort of a cancer registry. *J Cancer Res Clin Oncol* 2015;141(12):2229-40.
2. Markopoulos C, Koukouras D, Venizelos V et al. Impact of chemotherapy followed by aromatase inhibitors on bone health of women with ER-positive early breast cancer in real world clinical settings in Greece: Results of the POCHARBI trial conducted by the Hellenic Society of Breast Surgeons. *Breast* 2016 ;27:27-34.
3. Kesmodel SB, Goloubeva OG, Rosenblatt PY et al. Patient-reported adherence to adjuvant aromatase inhibitor therapy using the Morisky Medication Adherence Scale: An evaluation of predictors. *Am J Clin Oncol* 2018;41(5):508-512.

Aromatase Inhibitor vs. Tamoxifen vs. Sequentiell Therapy – 5 Years Upfront Therapie



Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials.
Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet. 2015 Oct 3;386(10001):1341-52.

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015;386(10001):1341-52.


	<h2>Premenopausal Patients Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)</h2>		
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<p>▪ 5 years Tamoxifen after 5 years Tamoxifen)</p>	<p>1a</p>	<p>A</p>	<p>++</p>
<p>▪ 2–5 years AI after 5 years Tamoxifen in initially premenopausal patients with validated postmenopausal status in the course of therapy</p>	<p>1b</p>	<p>B</p>	<p>+</p>
<p>▪ 5 years Tamoxifen after 5 years of endocrine therapy + OFS</p>	<p>5</p>	<p>D</p>	<p>+</p>
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5 years Tamoxifen after 5 years Tamoxifen:

1. Davies C, Pan H, Godwin J et al. Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381(9869):805-16. Erratum in: Lancet. 2013;381(9869):804.
2. Gray RG, Rea D, Handley K et al. ATTom: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6953 women with early breast cancer. J Clin Oncol 2013; 31 (18 suppl):5.
3. Petrelli F, Coinu A, Cabiddu M et al. Five or more years of adjuvant endocrine therapy in breast cancer: a meta-analysis of published randomised trials. Breast Cancer Res Treat 2013;140(2):233-40.
4. 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 2014;32(21):2255-69.

2–5 years AI after 5 years Tamoxifen in initially premenopausal patients with validated postmenopausal status in the course of therapy:

1. Goss PE, Ingle JN, Martino S et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst 2005;97(17):1262-71.
2. Jin H, Tu D, Zhao N et al. Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover. J Clin Oncol 2012;30(7):718-21
3. 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. 2014;32(21):2255-69.

	<h2>Postmenopausal Patients Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)</h2>		
<p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1</p>	<p>In case of high risk of recurrence</p>		
<p>■ 5 years Tamoxifen after 5 years Tamoxifen</p>	1a	A	+
<p>■ 2–5 years AI after 5 years Tamoxifen</p>	1a	A	++
<p>■ After initial AI containing therapy (upfront or switch) prolongation of endocrine therapy with AI for 2–5 years*</p>			
<p>■ high risk and good tolerability of the AI</p>	1a	A	+
<p>■ low risk, poor tolerability of the AI</p>	1a	A	-
<p>■ Interruption of endocrine treatment up to 3 months during EAT</p>	1b	B	+/-
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<p>* Up to date, no impact on OS</p>			

5 years Tamoxifen after 5 years Tamoxifen:

1. Davies C, Pan H, Godwin J et al. Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381(9869):805-16. Erratum in: Lancet. 2013;381(9869):804.
2. Gray RG, Rea D, Handley K et al. ATTom: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6953 women with early breast cancer. J Clin Oncol 2013; 31 (18 suppl):5.
3. Petrelli F, Coinu A, Cabiddu M et al. Five or more years of adjuvant endocrine therapy in breast cancer: a meta-analysis of published randomised trials. Breast Cancer Res Treat 2013;140(2):233-40.
4. Burstein HJ, Lacchetti C, Anderson H et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update. J Clin Oncol. 2018 Nov 19;JCO1801160. doi: 10.1200/JCO.18.01160

2–5 years AI after 5 years Tamoxifen

1. Goss PE, Ingle JN, Martino S et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst 2005;97(17):1262-71.

2. Jin H, Tu D, Zhao N et al. Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover. J Clin Oncol 2012;30(7):718-21.
3. Jakesz R, Greil R, Gnant M et al. Austrian Breast and Colorectal Cancer Study Group. 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. 2007;99(24):1845-53. Erratum in: J Natl Cancer Inst 2008;100(3):226.
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After initial AI containing therapy (upfront or switch) further prolongation of endocrine therapy with AI 2-5years*:

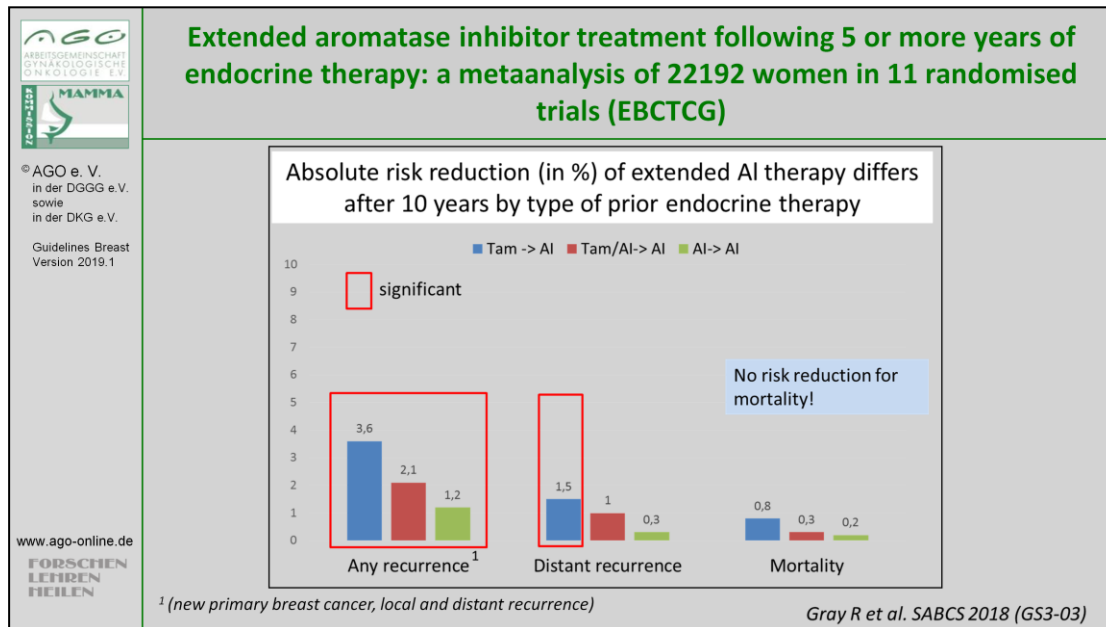
high risk and good tolerability of the AI

low risk, poor tolerability of the AI


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Interruption of endocrine treatment up to 3 months during EAT:

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Decision criteria for extended therapy

Factors indicating a clinical benefit from EAT:

- Adjuvant tamoxifen therapy only
- Condition after chemotherapy (indicating high risk)
- Positive lymph node status and /or T2/T3 tumors
- Elevated risk of recurrence based on immunohistochemical criteria or based on multi-gene expression assays
- High CTS5-score

Further decision criteria:

- Wish of patient
- up to now well tolerated AI therapy,
- good bone health
- younger age
- adherence

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Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT)			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> CT + GnRHa (preserve ovarian function) (GnRHa application > 2 weeks prior to chemotherapy, independently of hormone receptor status) 	1a	A	+
<ul style="list-style-type: none"> CHT + GnRHa (preserve fertility) 	1b	A	+/-
<ul style="list-style-type: none"> Fertility preservation counselling including referral of all potential patients to appropriate reproductive specialists (further information www.fertiprotect.de) 			++




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Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients With Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient–Level Data

N= 837 patients from 5 trial, median follow-up time 5.0 years (IQR, 3.0-6.3 years)

	Control	GnRH	HR (95%-CI)	P-value
POI ^{1,2}	30.9%	14.1%	0.38; 0.26 to 0.57	< 0.001
Pregnancy ³	5.5%	10.3%	1.83; 1.06 to 3.15;	0.03

¹premature ovarian insufficiency, ² different definitions and time points were used

³ i n most trials POI and not pregnancy was defined as the primary endpoint

No significant differences in disease-free survival and overall survival were observed between groups.

Lambertini M et al. J Clin Oncol 2018

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Adjuvant Endocrine Therapy in Pre- und Postmenopausal Patients

