

# Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

## Adjuvante endokrine Therapie bei prä- und postmenopausalen Patientinnen



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## Adjuvante endokrine Therapie bei prä- und postmenopausalen Patientinnen

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- **Version 2018:**

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## Bestimmung des Steroid-Hormonrezeptorstatus

**Oxford LoE: 1      GR: A      AGO: ++**

**„Endokrines Ansprechen“ (früher rezeptorpositiv):**


**Immunhistologie (ER und / oder PgR)**

<b>0% pos. Zellen:</b>	<b>endokrin nicht sensitiv</b>
<b>1-9% pos. Zellen:</b>	<b>endokrin fraglich sensitiv</b>
<b>≥ 10% pos. Zellen:</b>	<b>endokrin sensitiv</b>

**Hormonrezeptor Status**

**unbekannt:                      endokrin sensitiv**

1. Hammond ME 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.



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## Adjuvante endokrine Therapie

### Bestimmung des Menopausenstatus

	Oxford		
	LoE	GR	AGO
<b>Bestimmung des Menopausenstatus:</b>			
▪ Menstruationsanamnese			+
▪ FSH, E2			++


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

# Adjuvante endokrine Therapie

## Standardtherapie für endokrin sensitive / fraglich sensitive Tumoren:

	Oxford		
	LoE	GR	AGO
▪ Endokrine Therapie	1a	A	++
▪ Chemo-endokrine Therapie (abhängig vom individuellen Rückfall-Risiko und der Tumorbilogie)	1a	A	++

1. 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 Aug 27;378(9793):771-84. doi: 10.1016/S0140-6736(11)60993-8. Epub 2011 Jul 28
2. Goldhirsch A et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013 Ann Oncol 2013;24:206-2223
3. Hackshaw A 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 May 1;29(13):1657-63
4. Pagani O1,et al.Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med. 2014 Jul 10;371(2):107-18.
5. Albain KS 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 Dec 19;374(9707):2055-63.
6. Bedognetti D et al. Concurrent vs sequential adjuvant chemotherapy and hormone therapy in breast cancer: a multicenter randomized phase III trial. J Natl Cancer Inst. 2011 Oct 19;103(20):1529-39.
7. O'Neill SC et al. Endocrine therapy initiation, discontinuation and adherence and breast cancer imaging among 21-gene recurrence score assay-eligible women under age of 35. Breast Cancer Res Treat Research 2017;19:1-13



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# Adjuvante endokrine Therapie

- **Endokrin sensitiv & fraglich sensitiv:**  
endokrine Therapie
- **Endokrine Therapie sequentiell:**  
nach einer adjuvanten Chemotherapie
- **Nicht endokrin sensitiv:**  
keine endokrine Therapie

Oxford		
LoE	GR	AGO
1a	A	++
2b	C	++
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 Aug 27;378(9793):771-84.
3. Hackshaw A 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 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 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 et al. Revisiting the definition of estrogen receptor positivity in Her2-negative primary breast cancer. Ann Oncol 2017;28:2420-2428
7. Curigliano G. 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


## Generelle Prinzipien der adjuvanten endokrinen Therapie AGO ++

- Die adjuvante endokrine Therapie wird in die initiale Therapie (Jahre 0-5) und die erweiterte adjuvante Therapie (EAT, Jahre 6-15) eingeteilt.
- Standard Therapiedauer der adjuvanten Therapie: 5 Jahre
- Erweiterte Therapiedauer nach individueller Nutzen-Risiko-Abwägung.
- Dauer, Wahl & Sequenz von AI oder Tam hängen v.a. von Menopausenstatus, Verträglichkeit und dem Rückfall-Risiko ab.
- Der Wechsel auf eine andere endokrine Therapie (Tam oder AI) ist besser als die Therapie zu stoppen.
- Beginn mit AI bei postmenopausalen Patientinnen insbesondere bei lobulären Karzinomen und erhöhtem Rückfall-Risiko.
- Es existiert kein validierter Biomarker für einen frühen versus einen späten Rückfall.

1. Davies C. 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
2. Hackshaw A, 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.
3. Cuzick J et al. ATAC/LATTE investigators. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol. 2010;11(12):1135-41.
4. Higgins MJ1, Liedke PE, Goss PE. 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 Apr;86(1):23-32.
5. Regan MM 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 Nov;12(12):1101-8.
6. Ingle JN. Overview of adjuvant trials of aromatase inhibitors in early breast cancer. Steroids. 2011 Jul;76(8):765-7.
7. van de Velde CJ et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. Lancet. 2011 Jan 22;377(9762):321-31
8. 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.

9. Rydén L 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 Apr;26:106-140
10. Gnant M. The bumpy road to extending adjuvant therapy Discussant General Session 1, Dec. 7<sup>th</sup>, SABCs 2016, <https://watch.ondemand.org/OnlinePlayer/228>
11. Pan H et al. 20-year risks of breast recurrence after stopping endocrine therapy at 5 years. *N Engl J Med* 2017;1836-49





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## Adjuvante endokrine Therapie bei prämenopausalen Patientinnen (Jahr 0-5)

	Oxford		
	LoE	GR	AGO
▪ <b>Tamoxifen* 5-10 Jahre</b>	1a	A	++
▪ <b>GnRHa Monotherapie</b> (Bei relevanten Kontraindikationen für Tam, gegenüber keiner Therapie)	1a	B	+
▪ <b>Ohne Indikation zu neo-/adjuvanter Chemotherapie mit erhaltener Ovarialfunktion:</b>			
▪ Tamoxifen	1b	B	++
▪ Tamoxifen + OFS**	1b	B	+/-
▪ AI + OFS**	1b	B	+/-
▪ <b>Nach neo-/adjuvanter Chemotherapie mit erhaltener Ovarialfunktion (≤ 8 Monate EOC):</b>			
▪ Tamoxifen + OFS 5 Jahre** → Bei Patientinnen < 35 Jahre	1b	B	+
▪ AI + OFS 5 Jahre** → Bei Patientinnen < 35 Jahre	1b	B	++
	1b	B	+/-
	1b	B	+

OFS: Ovarialfunktions-Suppression; EOC: Ende der Chemotherapie  
OFS\*: Vermehrte Nebenwirkungen (AI+ OFS) gegenüber (Tam + OFS) vs. (Tam) können die Compliance beeinträchtigen.  
\* Behandlung nur solange sie tolerabel ist und die Pat. eindeutig prämenopausal ist  
\*\* Bisher liegen nur Daten für das krankheitsfreie Überleben (DFS) vor

### 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 365 (9472): 1687-717, 2005.
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 Aug 27;378(9793):771-84.
3. Davies C 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 et al. 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. Mathew A et al. Adjuvant endocrine therapy for premenopausal women with hormone-responsive breast cancer. Breast. 2015 Nov;24 Suppl 2:S120-5. doi: 10.1016/j.breast.2015.07.027.
6. Lei L, et al. . Association of CYP2D6\*10 (c.100C>T) polymorphisms with clinical outcome of breast cancer after tamoxifen adjuvant endocrine therapy in Chinese population. Am J Transl Res. 2016 Aug 15;8(8):3585-92
7. 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 (9472): 1687-


717, 2005.


8. Goel S et al: LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD004562.
9. Cuzick J 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 (ovarian function suppression) 5 years + Tam 5 years - OFS 5 years + AI 5 years  
■ in patients < 35 y.

1. Pagani O. 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 Nov;142(2):455-9
2. Ganz PA, 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 Mar 20;29(9):1110-6
3. Goel S et al: LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD004562.
4. Francis PA et al. The SOFT Investigators and the International Breast Cancer Study Group. Adjuvant Ovarian Suppression in Premenopausal Breast Cancer. N Engl J Med. 2015 Jan 29;372(5):436-46.
5. Pagani O 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 Jul 10;371(2):107-18
6. Gnant M et al: Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med. 2009 Feb 12;360(7):679-91.
7. Munholz RR, et al: Gonadotropin-Releasing hormone agonists for ovarian function preservation in premenopausal women undergoing chemotherapy for early stage breast cancer- A systematic Review and Meta Analysis. JAMA Oncol 2016;2:65-73
8. Shiba E 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 May;23(3):499-509.
9. Del Mastro L et al. New insights on the role of luteinizing hormone releasing hormone agonists in premenopausal early breast cancer patients. Cancer Treat Rev. 2016 Jan;42:18-23.10
10. Kim HA 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 May 19;16:319.
11. Poornima S et al., 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
12. Saha Poornima et al., 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





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# Adjuvante endokrine Therapie bei postmenopausalen Patientinnen (Jahre 0-5)

	Oxford		
	LoE	GR	AGO
▪ <b>Aromatasehemmer für die ersten 5 Jahre</b>	1a	A	++
▪ Lobuläres Karzinom			
▪ Hohes Rezidivrisiko			
▪ <b>Sequentielle Therapie für die ersten 5 Jahre*</b>			++
▪ Tam (2-3 Jahre) gefolgt von AI bis zur Gesamtdauer von 5 Jahren	1a	A	
▪ AI (2-3 Jahre) gefolgt von Tamoxifen bis zur Gesamtdauer von 5 Jahren	1b	C	
▪ <b>Tamoxifen 20 mg/d für die ersten 5 Jahre**</b>	1a	A	+

\* Die endokrine adjuvante Therapie postmenopausaler Patientinnen sollte in den ersten 5 Jahren für 2-3 Jahre einen Aromatasehemmer enthalten

\*\* Eine Monotherapie mit Tamoxifen kann bei Patientinnen im Senium, bei niedrigem Risiko oder bei Kontraindikation für Aromatasehemmer eingesetzt werden

### AI for first 5 years

### Especially in case of lobular cancer

### High risk of recurrence

1. Cuzick J et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol. 2010 Dec;11(12):1135-41.
2. 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 Oct 3;386(10001):1341-52.
3. Rydén L 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 Apr;26:106-14
4. Mayer EL et al. Adjuvant endocrine therapy for postmenopausal women: Type and duration. Breast. 2015 Nov;24 Suppl 2:S126-8. doi: 10.1016/j.breast.2015.07.028. Epub 2015 Aug 14.

### 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 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 Apr;26:106-14

3. Mayer EL et al. Adjuvant endocrine therapy for postmenopausal women: Type and duration. *Breast*. 2015 Nov;24 Suppl 2:S126-8. doi: 10.1016/j.breast.2015.07.028. Epub 2015 Aug 14.
4. Derks MGM 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

#### 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 Oct 3;386(10001):1341-52.
3. Rydén L 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 Apr;26:106-14.
4. Mayer EL, Burstein HJ. Adjuvant endocrine therapy for postmenopausal women: Type and duration. *Breast*. 2015 Nov;24 Suppl 2:S126-8. doi: 10.1016/j.breast.2015.07.028. Epub 2015 Aug 14.

#### Patient care/ adherence and side effects

1. Inwa Id EC 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 Dec;141(12):2229-40.
2. Markopoulos C 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 Jun;27:27-34.
3. Kesmodel SB et al. Patient-reported Adherence to Adjuvant Aromatase Inhibitor Therapy Using the Morisky Medication Adherence Scale: An Evaluation of Predictors. *Am J Clin Oncol*. 2016 Jun

Erweiterte adjuvante endokrine Therapie (EAT) bei prä- und postmenopausalen Patientinnen (Jahre 6-10)			
	Oxford		
	LoE	GR	AGO
<b>Prämenopause:</b>			
▪ 2,5 - 5 Jahre AI nach 5 Jahren Tamoxifen prämenopausal, bei im Verlauf eindeutig nachgewiesener postmenopausaler Situation	1b	B	+
▪ 5 Jahre Tamoxifen nach 5 Jahren Tamoxifen (bei erhöhtem Rückfall-Risiko)	1a	A	++
<b>Postmenopause:</b>			
▪ Nach 2–5 Jahren Tamoxifen, AI für 2,5 bis 5 Jahre	1a	B	++
▪ Nach initialer AI-Therapie Verlängerung der endokrinen Therapie mit AI*			
▪ höheres Rückfall-Risiko und bei guter Verträglichkeit des AIs	1b	B	+
▪ niedriges Rückfall-Risiko, schlechte Verträglichkeit des AIs	1b	B	-
* Bislang ohne Einfluss auf das Gesamtüberleben (OS)			

2.5 - 5 years AI after 5 years Tamoxifen premenopausal in patients with validated postmenopausal status in the course of therapy

1. Goss PE 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 Sep 7;97(17):1262-71.

5 years Tamoxifen after 5 years Tamoxifen (in case of increased risk of relaps)

1. Davies C 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 Mar 9;381(9869):805-16. Erratum in: Lancet. 2013 Mar 9;381(9869):804.
2. Gray RG 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 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 Jul;140(2):233-40.

After 2 - 5 years Tamoxifen AI for 2.5 - 5 years

1. Goss PE 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 Sep 7;97(17):1262-71.
2. Jakesz R 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 Dec 19;99(24):1845-53. Erratum in: J Natl Cancer Inst. 2008 Feb 6;100(3):226.


3. Mamounas EP 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. 2008 Apr 20;26(12):1965-71.

After initial therapy with AI further prolongation of endocrine therapy with AI\*  
high risk and good tolerability of the AI  
low risk, poor tolerability of the AI

1. Blok EJ et al. Optimal Duration of Extended Adjuvant Endocrine Therapy for early breast cancer; results of the IDEAL trial (BOOG 2006-05). J Natl Cancer Inst 2018;110(1): dx134
2. Bychkovsky BL et al. Identifying biomarkers to select patients with early breast cancer suitable for extended adjuvant endocrine therapy. Curr Opin Oncol. 2016 Nov;28(6):461-468.
3. Systemic Therapies for Nonmetastatic Breast Cancer: The Role of Neoadjuvant and Adjuvant Chemotherapy and the Use of Endocrine Therapy. Clin Obstet Gynecol. 2016 Dec;59(4):756-771.
4. Goss PE et al. Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years. N Engl J Med. 2016 Jul 21;375(3):209-19
5. Mamounas EP et al. NRG Oncology/NSABP. A randomized, double-blinded, placebo-controlled clinical trial of extended adjuvant endocrine therapy (tx) with letrozole (L) in postmenopausal women with hormone-receptor (+) breast cancer (BC) who have completed previous adjuvant tx with an aromatase inhibitor (AI): Results from NRG Oncology/NSABP B-42. 2016 San Antonio Breast Cancer Symposium, Publication Number: S1-05
6. O'Leary CG et al. Extended adjuvant endocrine therapy in hormone-receptor-positive early breast cancer. Curr Opin Oncol. 2016 Nov;28(6):455-460.
7. Sanft T et al. Prospective assessment of the decision-making impact of the Breast Cancer Index in recommending extended adjuvant endocrine therapy for patients with early-stage ER-positive breast cancer. Breast Cancer Res Treat. 2015 Dec;154(3):533-41.
8. Sestak I et al. Cross-Stratification and Differential Risk by Breast Cancer Index and Recurrence Score in Women with Hormone Receptor-Positive Lymph Node-Negative Early-Stage Breast Cancer. Clin Cancer Res. 2016 Oct 15;22(20):5043-5048
9. Tjan-Heijnen VC C et al. First results from the multicenter phase III DATA study comparing 3 versus 6 years of anastrozole after 2-3 years of tamoxifen in postmenopausal women with hormone receptor-positive early breast cancer. 2016 San Antonio Breast Cancer Symposium, Publication Number: S1-03
10. Zdenkowski N et al. Australia and New Zealand Breast Cancer Trials Group. Observation versus late reintroduction of letrozole as adjuvant endocrine therapy for hormone receptor-positive breast cancer (ANZ0501 LATER): an open-label

randomised, controlled trial. Ann Oncol. 2016 May;27(5):806-12.





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# Prophylaxe des ovariellen Funktionsausfalls und Fertilitätserhaltung bei prämenopausalen Patientinnen mit (neo-)adjuvanter Chemotherapie (CT)

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<ul style="list-style-type: none"> <li>■ CHT + GnRHa (zur Prophylaxe des ovariellen Funktionsausfalls) (GnRHa Applikation &gt; 2 Wochen vor Chemotherapie, unabhängig vom Hormonrezeptorstatus)</li> </ul>	1a	B	+
<ul style="list-style-type: none"> <li>■ CHT + GnRHa (zur Erhöhung der Schwangerschaftsrate)</li> </ul>	2a	B	+/-
<ul style="list-style-type: none"> <li>■ Angebot zur Beratung über Fertilitätserhaltung</li> </ul>	4	C	++
<ul style="list-style-type: none"> <li>■ Fertilitätserhalt mit assist. reprod. Therapie (Information: <a href="http://www.fertiprotect.de">www.fertiprotect.de</a>)</li> </ul>	4	C	+

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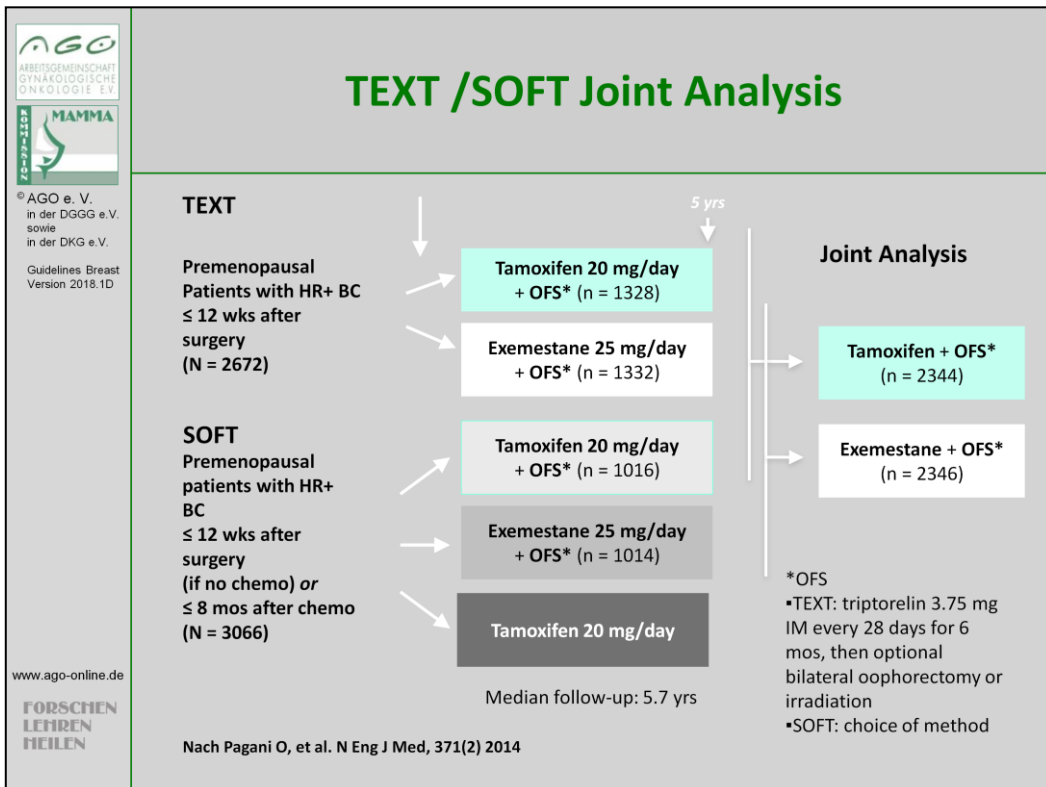
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Neu bearbeitet von M. Lux


Neu bearbeitet von M. Lux

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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**

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# Tamoxifen 5 yrs versus 10 yrs Breast Cancer Mortality in ER+ Rate Ratio per Period in aTTom and ATLAS

	10 yrs. vs. 5 yrs. Tam aTTom Trial (n=6934 ER+)	10 yrs. vs. 5 yrs. Tam Atlas Trial (n=10543 ER+)	10 yrs. vs. 5 yrs. Tam aTTom + Atlas combined (n=17477 ER+)
Years 5-9	1.08 (0.85-1.38)	0.92 (0.77-1.09)	0.97 (0.84-1.15)
Years 10+	0.75 (0.63-0.90) p = 0.07	0.75 (0.63-0.90) p = 0.002	0.75 (0.65-0.86) p = 0.00004
All years	0.88 (0.74-1.03) p = 0.1	0.83 (0.73-0.86) p = 0.004	0.85 (0.77-0.94) P= 0.001

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1. Gray RG et al., 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 31, 2013 (suppl; abstract 5)
2. Davies C, 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: 805–16.

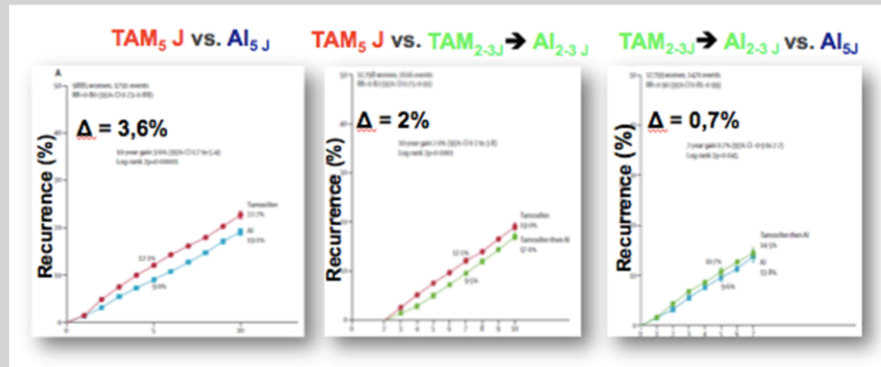
## Aromatase Inhibitors in Adjuvant Therapy Overview over Published Trials: Initial Therapy (years 1-5)

Trial	Source	AI	Indication	Pts	F/U mo	DFS/BCFS/TTR/ TTDR/CBC	OS	Side Effects	Remarks
ATAC	ATAC Trialists' Group 2010	A	upfront vs T	6241	120	HR + patients: DFS HR 0.86, p=0.003 TTR -0.79, p=0.0002 TTDR 0.85, p=0.02	HR 0.87 p=0.4	SAE T>A gyn AE T>A VE T>A SE A>T	only anastrozole vs tamoxifen, combination arm stopped after first analysis; ER+PR=ER+PR+ (Cuzick 2010) QoL→ (Cella 2006)
BIG 1-98	BIG 1-98 Collaborative Group 2011	L	upfront <sup>2</sup> vs T	4922	97	DFS = 0.86 P = 0.007	P = 0.048	SAE T=L gyn AE T>L TE T>L CE L>T SE L>T	L>T in particular in case of N+
NCIC CTG MA.27	Goss 2010	E	upfront vs A	7576	49	EFS HR 1.02 DDFS HR 0.95	ns	Osteoporosis A>E El. liver enzymes E>A Hyperlipidaemia A>E	Randomization for Celecoxib cancelled
Meta-analysis EBCTCG	EBCTCG 2015		5 y. AI vs. 2-3 y. tam → AI to y. 5 vs. 5 y. Tam	31920		10 y. gain recurrence rate 5 y. AI vs. 5 y. Tam 3.6%, p<0.00001	10 y. gain OS 5 y. AI vs. 5 y. Tam 2.1%, p<0.009		
						10 y. gain recurrence rate 5 y. AI vs. 2-3 y. Tam → AI to y. 5 0.7%, p<0.045	10 y. gain OS 5 y. AI vs. 2-3 y. Tam → AI to y. 5 1.1%, p<0.11		
						10 y. gain recurrence rate 2-3 y. Tam → AI to y. 5 vs. 5 y. Tam 2.0% p<0.0001	10 y. gain OS 2-3 y. Tam → AI to y. 5 vs. 5 y. Tam 1.5%, p<0.01		

A anastrozole; gyn AE, gynecological adverse event; BCFS, breast cancer-free survival; CBC, contralateral breast cancer; CE, cardiac events; CVE, cardiovascular events; Cx, chemotherapy; DFS, disease-free survival; RFS relapse-free survival; E, exemestane; ER, estrogen receptor; HR, hazard ratio; L, letrozole; OS, overall survival; P, placebo; PR, progesterone receptor; QoL, quality of life; Rx, radiotherapy; SAE, serious adverse event; SE, skeletal event; T, tamoxifen; TE, thromboembolism; TTR, time-to-recurrence; TTDR, time-to-distant-recurrence; VE, vascular event; (?) according to retrospective analysis. \* only HR positive population


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## Aromatase Inhibitor vs. Tamoxifen vs. Sequentieller Therapie - 5 Jahre Upfront Therapie

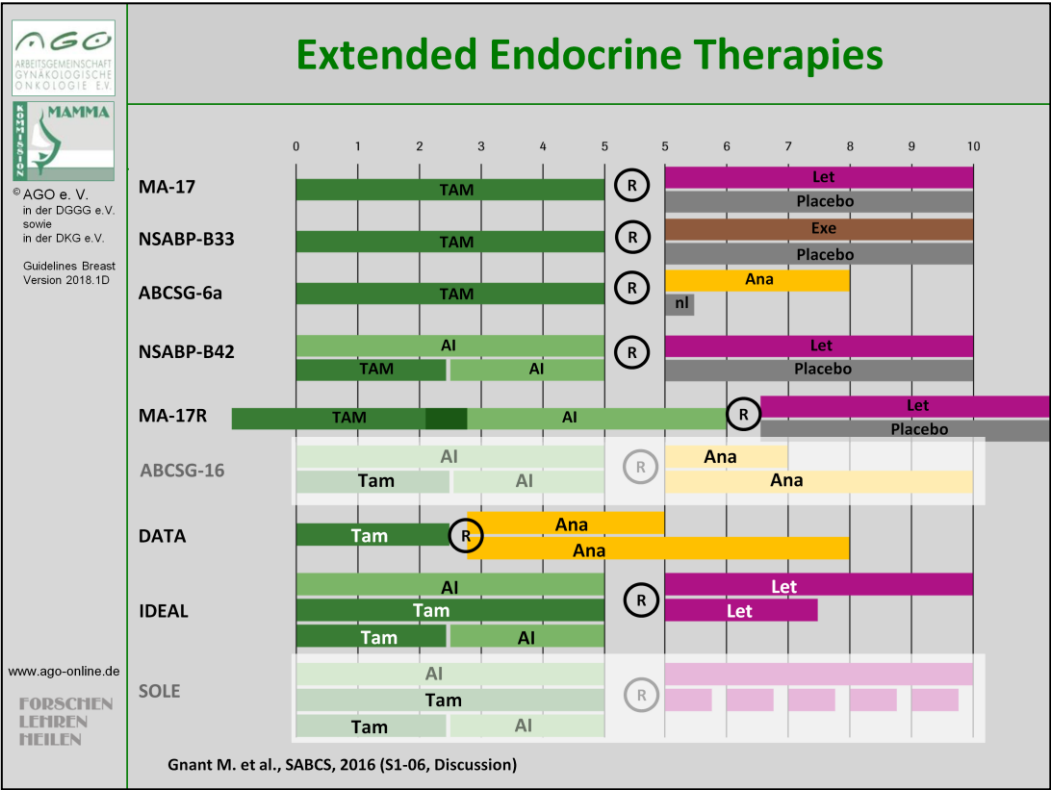


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1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015;386(10001):1341-52.

 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2018.1D</p> <p>www.ago-online.de</p> <p><b>FORSCHEN LEHREN HEILEN</b></p>	<h2 style="text-align: center; color: green;">Meta-analyses of DFS and OS</h2> <h3 style="text-align: center; color: green;">Upfront monotherapy vs. sequential therapy</h3> <p><b>Rydén L, Heibert Arnlind M, Vitols et al.</b></p> <p><b>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.</b></p> <p><b>Breast 2016; 26:106-114.</b></p>
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## Aromatase Inhibitors in Adjuvant Therapy Overview over Published Trials: Extended Therapy I

Trial	Source	Patient number	Population	Upfront therapy	Trial Arms	Reported outcomes
ECOG	Tormey 1996	193	Prem./postm.	Tamoxifen	Tamoxifen vs. no therapy	RFS: 85% vs. 73% (p=0.10) OS: 86% vs. 89% (p=0.52)
Scottish	Stewart 1996	342	Prem./postm.	Tamoxifen	Tamoxifen vs. no therapy	Events: 60 vs. 49 EFS HR: 1.27 (0.87-1.85)
NSABP B-14	Fisher 2001	1142	Prem./postm.	Tamoxifen	Tamoxifen vs. placebo	DFS: 78% vs. 82% (p=0.03) OS: 91% vs. 94% (p=0.07)
ATLAS	Davies 2013	6846	Prem./postm.	Tamoxifen	Tamoxifen vs. placebo	Recurrence: 617 vs. 711 (p=0.01) OM: 639 vs. 722 (p=0.01)
aTTOM	Gray 2013	6953	Prem./postm.	Tamoxifen	Tamoxifen vs. no therapy	Recurrence: 580 vs. 672 (p=0.003) OM: 849 vs. 910 (p=0.1)
MA.17	Goss 2005	5187	Postm.	Tamoxifen	Letrozole vs. placebo	DFS: HR 0.68 (0.55-0.83; p=0.001) OS: HR 0.98 (0.78-1.22; p=0.85)
NSABP B-33	Mamounas 2008	1598	Postm.	Tamoxifen	Exemestane vs. placebo	DFS: 91% vs. 89% (p=0.07) RFS: 96% vs. 94% (p=0.004)
ABCSG-6a	Jakesz 2007	856	Postm.	Tamoxifen	Anastrozole vs. placebo	Recurrence: 30 vs. 56, HR 0.64 (0.41-0.99; p=0.047)
Meta-analysis	Petrelli 2013	29138	Prem./postm.	Tamoxifen	Fixed duration (5 years) with an extended course of endocrine therapy vs. no therapy	RFS OR: 0.72 (0.56-0.92; p=0.01) BCSS OR: 0.78 (0.69-0.9; p=0.0003) OS OR: 0.89 (0.80-0.99; p=0.03)

AI = aromatase inhibitor; BCSS = breast cancer specific survival; DFS = disease-free survival;  
EFS = event free survival; HR = hazard ratio; OM = overall mortality; OS = overall survival;  
prem. = premenopausal; postm. = postmenopausal; RFS = relapse-free survival

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## Aromatase Inhibitors in Adjuvant Therapy

### Overview over Published Trials:

### Extended Therapy II

Trial	Source	Patient number	Population	Upfront therapy	Trial Arms	Reported outcomes
LATER	Zdenkowski 2016	360	Postm.	≥ 4 years of endocrine therapy (11.7% AI, 50.3% Tam, 38.0% other)	5 y. letrozole vs. observation	Breast cancer recurrence difference: 8.4% (3.8%-13.0%), p=0.0004
MA17R	Goss 2016	1918	Postm.	5 years of any other AI with or without prior tamoxifen	Letrozole vs. placebo	DFS: 95% vs. 91% (HR for disease recurrence or occurrence of contralateral breast cancer: 0.66; p=0.01) OS: 93% vs. 94% (HR: 0.97; p=0.83)
IDEAL	Blok 2016	1824	Postm.	5 years of tamoxifen, AI or tamoxifen → AI	Letrozole 2.5 vs. 5 years	DFS HR: 0.88 (0.64-1.21; p=0.43) 5-year DFS: 88.4 vs. 87.9% OS HR: 1.09 (0.70-1.70)
DATA	Tjan-Heijnen 2016	1912	Postm.	Tamoxifen 2-3 years	Anastrozole 6 vs. 3 years	DFS HR: 0.79 (0.62-1.02; p=0.07) 5-year DFS: 83.1 vs. 79.4 OS HR: 0.91 (0.65-1.29)
NSABP B-42	Mamounas 2016	3923	Postm.	AI or tamoxifen → AI 5 years	Letrozole vs. placebo	DFS HR: 0.85 (0.73-0.99; p=0.048*) * did not reach statistical significance level of 0.0418

AI = aromatase inhibitor; BCSS = breast cancer specific survival; DFS = disease-free survival;  
EFS = event free survival; HR = hazard ratio; OM = overall mortality; OS = overall survival;  
prem. = premenopausal; postm. = postmenopausal; RFS = relapse-free survival



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## Vorschlag für eine mögliche Entscheidungsfindung für die erweiterte Adjuvanz

- Nach 2 bis 5 Jahren Tamoxifen → Hinzunahme von Aromatasehemmer für 2,5 bis 5 Jahren
  
- Nach initialer Aromatasehemmertherapie sorgfältige Überlegung und Abwägung:
  - weitere Therapie mit AI:
    - bisherige gute Verträglichkeit der AI-Therapie,
    - gute Knochengesundheit,
    - jüngeres Alter,
    - hohes Rückfall-Risiko nach immunhistochemischen Kriterien oder Multi-Gen Assays
    - positiver Nodalstatus

nach Gnant M. et al., SABCS, 2016 (S1-06, Discussion)

1. Gnant M. et al., SABCS, 2016 (S1-06, Discussion)

# Adjuvante endokrine Therapie Prä- und Postmenopause im Überblick

