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Guidelines Breast
Version 2023.1E

FORSCHEN
LEHREN
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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Adjuvant Endocrine-based Therapy in pre- and postmenopausal Patients



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Guidelines Breast
Version 2023.1E

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Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

■ Versions 2002–2022:

Bauerfeind / Dall / Diel / Fasching / Fersis / Fehm / Friedrich / Friedrichs /
Gerber / Göring / Hanf / Harbeck / Huober / Jackisch / Lisboa / Loibl / Lück
/ Lux / Maass / von Minckwitz / Möbus / Müller / Nitz / Oberhoff /
Schaller / Scharl / Schneeweiss / Schütz / Solomeyer / Stickeler /
Thomssen / Untch

■ Version 2023:

Gerber / Jackisch

Assessment of Steroid Hormone Receptor Status

Oxford LoE: 1

GR: A

AGO: ++

**Endocrine responsive – hormone receptor positive
Immunhistology (ER and/or PgR)**

0%	pos. cells:	endocrine resistant
1–10%	pos. cells:	possibly endocrine sensitive
> 10%	pos. cells:	endocrine sensitive
Unknown hormone receptor status:		endocrine sensitive

If ER negative / PR positive (> 10% positive cells): reassess IHC status

Endocrine responsiveness:

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(9472):1687–717.
2. 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.
3. 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.
4. Allison KH, Hammond MEH, Dowsett M, et al: Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. J Clin Oncol. 2020 Apr 20;38(12):1346-1366.

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.
5. Allison, K. H., et al. (2020). "Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update." *J Clin Oncol* 38(12): 1346-1366.

Adjuvant Endocrine Therapy Assessment of Menopausal Status

Assessment of menopausal status:

- Menstruation history
- FSH, E2

Oxford		
LoE	GR	AGO

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1. 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.
2. 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.
3. Furlanetto J , Marme F , Seiler S. Chemotherapy-induced ovarian failure in young women with early breast cancer: Prospective analysis of four randomised neoadjuvant/adjuvant breast cancer trials. *European Journal of Cancer* 152 (2021) 193e203.

Adjuvant Endocrine Therapy

	Oxford		
	LoE	GR	AGO
▪ Endocrine responsive	1a	A	++
▪ Endocrine doubtful responsiveness	3b	D	+
▪ Endocrine therapy sequentially after CT	2a	B	+
▪ Endocrine therapy simultaneous to anti-HER2 therapy (w/o chemotherapy)	2b	B	+
▪ Not sensitiv to 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. 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.
7. Chan, A., et al. "Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial." Lancet Oncol 2016;17(3): 367-377.

8. von Minckwitz, G., et al: "Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer." N Engl J Med 2019; 380(7): 617-628.
9. von Minckwitz, G., et al.: "Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer." N Engl J Med 2017; 377(2): 122-131
10. Early Breast Cancer Trialists' Collaborative, G.: "Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials." Lancet 2015; 386: 1341-1352.
11. Loibl S, H Chiun-Sheng, Mano MS, Adjuvant trastuzumab emtansine (T-DM1) vs trastuzumab (T) in patients with residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer: subgroup analysis from KATHERINE. ESMO Breast 2020
12. Burstein HJ, Curigliano G, Thürlimann B et al: Panelists of the St Gallen Consensus Conference. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. Ann Oncol. 2021 Oct;32(10):1216-1235.

General Principles in Adjuvant Endocrine Therapy AGO ++

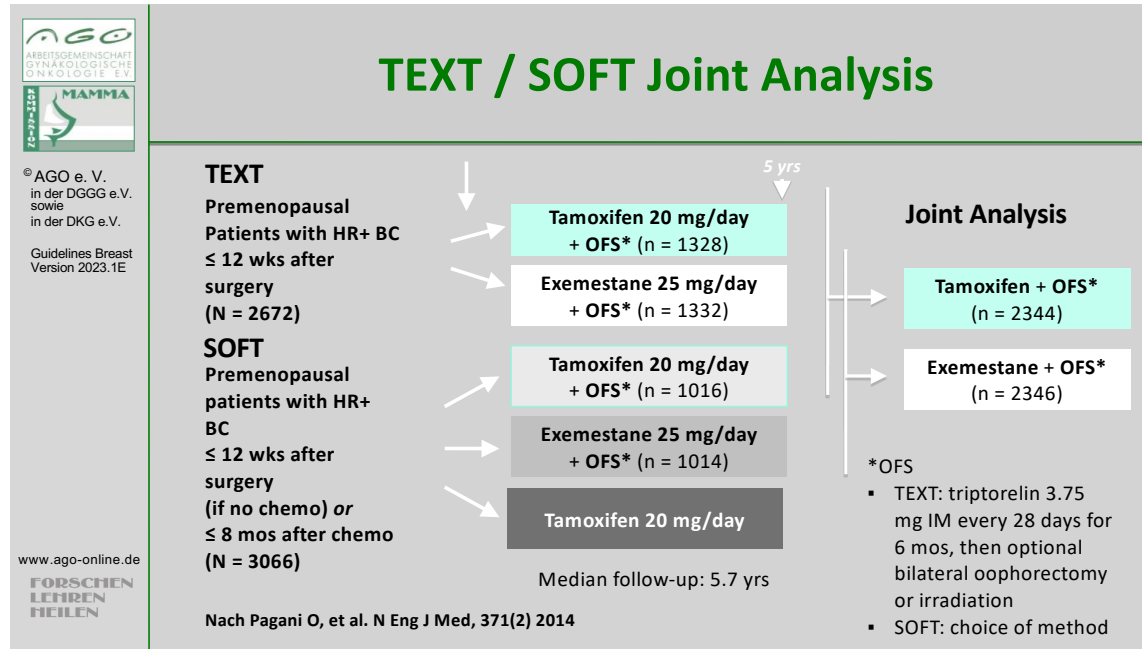
- Adjuvant endocrine therapy is divided into initial therapy (years 1-5) and extended adjuvant therapy (EAT, years 6-10+).
- Standard treatment duration is 5 years.
- Extended therapy should be considered based on individual risks and benefits.
- Duration, choice & sequence of AI or Tam mainly depend on menopausal status, tolerability, and risk of recurrence.
- Switch to another better tolerated endocrine treatment (Tam or AI) is better than stopping endocrine therapy altogether.
- AI should be used as first treatment in patients, in case of lobular cancers and / or high risk of recurrence.
- To date, there is no sufficiently validated biomarker for identification of patients at risk 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 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;26:106-140.
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.

NEU:

- CTS-5
- BCI (H/I)



1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. Lancet Oncol. 2022 Mar;23(3):382-392. doi: 10.1016/S1470-2045(21)00758-0.
2. Francis PA, Fleming GF, Láng I, et al.; SOFT Investigators and the International Breast Cancer Study Group (a division of ETOP IBCSG Partners Foundation). Adjuvant Endocrine Therapy in Premenopausal Breast Cancer: 12-Year Results From SOFT. J Clin Oncol. 2022 Dec 9;JCO2201065. doi: 10.1200/JCO.22.01065.
3. Pagani O, Walley BA, Fleming GF et al. SOFT and TEXT Investigators and the International Breast Cancer Study Group (a division of ETOP IBCSG Partners Foundation). Adjuvant Exemestane With Ovarian Suppression in Premenopausal Breast Cancer: Long-Term Follow-Up of the Combined TEXT and SOFT Trials. J Clin Oncol. 2022 Dec 15;JCO2201064. doi: 10.1200/JCO.22.01064.

Premenopausal Patients

Initial Adjuvant Endocrine Therapy (Year 1-5)

	Oxford		
	LoE	GR	AGO
▪ Low recurrence risk:			
▪ Tamoxifen for 5 years	1a	A	++
▪ Increased recurrence risk:			
▪ OFS 2-5 years* + tamoxifen for 5 years	1a	A	++
▪ OFS# + AI for 5 years	1a	A	++
▪ GnRHa monotherapie (If severe contraindications for Tam exist, compared to no therapy)	1a	B	+

OFS: ovarian function suppression;

* as long as tolerated and the patient is clearly premenopausal after chemotherapy if ovarian function resumes within 24 months. The application of chemotherapy in the trials served as surrogate for high recurrence risk

in premenopausal women AI only in combination with OFS

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. 2009 7;(4):CD004562.

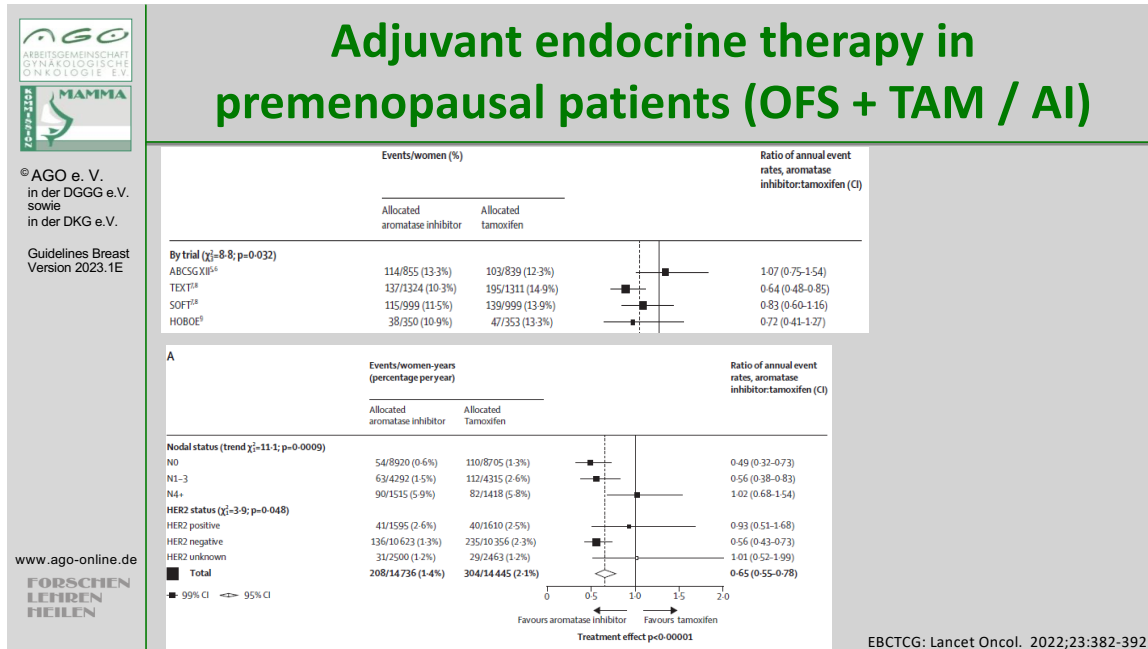
GnRH as monotherapy:

1. 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.

Ovarian function suppression (OFS) with Tam/AI and Tam with or without OFS:

1. 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.
2. Shiba E, Yamashita H, Kurebayashi J et al. A randomized controlled study evaluating safety and efficacy of leuporelin 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.
3. 6. Kim HA, Lee JW, Nam SJ et al. Adding Ovarian Suppression to Tamoxifen for Premenopausal Breast Cancer: A Randomized Phase III Trial. *J Clin Oncol*. 2019, <https://doi.org/10.1200/JCO.19.0012>
4. Regan MM, Walley BA, Fleming GF et al. Randomized comparisons of adjuvant exemestane + ovarian function suppression versus Tamoxifen + OFS versus tamoxifen in premenopausal women with HR + early breast : update of the TEXT and SOFT trials. *SABCS 2021*, GS2-05.
5. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. *Lancet Oncol*. 2022 Mar;23(3):382-392. doi: 10.1016/S1470-2045(21)00758-0.
6. Francis PA, Fleming GF, Láng I, et al.; SOFT Investigators and the International Breast Cancer Study Group (a division of ETOP IBCSG Partners Foundation). Adjuvant Endocrine Therapy in Premenopausal Breast Cancer: 12-Year Results From SOFT. *J Clin Oncol*. 2022 Dec 9;JCO2201065. doi: 10.1200/JCO.22.01065.
7. Paganí O, Walley BA, Fleming GF et al. SOFT and TEXT Investigators and the International Breast Cancer Study Group (a division of ETOP IBCSG Partners Foundation). Adjuvant Exemestane With Ovarian Suppression in Premenopausal Breast Cancer: Long-Term Follow-Up of the Combined TEXT and SOFT Trials. *J Clin Oncol*. 2022 Dec 15;JCO2201064. doi: 10.1200/JCO.22.01064.
8. Johansson A, Dar H, van't Veer et al. Twenty-years benefit from adjuvant goserelin and tamoxifen in premenopausal patients with breast cancer in a controlled clinical trial. *J Clin Oncol* 2022;40:4071-4082.



1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. Lancet Oncol. 2022 Mar;23(3):382-392
2. Francis PA, Fleming GF, Láng I, et al.; SOFT Investigators and the International Breast Cancer Study Group (a division of ETOP IBCSG Partners Foundation). Adjuvant Endocrine Therapy in Premenopausal Breast Cancer: 12-Year Results From SOFT. J Clin Oncol. 2022 Dec 9;JCO2201065. doi: 10.1200/JCO.22.01065.
3. Pagni O, Walley BA, Fleming GF et al. SOFT and TEXT Investigators and the International Breast Cancer Study Group (a division of ETOP IBCSG Partners Foundation). Adjuvant Exemestane With Ovarian Suppression in Premenopausal Breast Cancer: Long-Term Follow-Up of the Combined TEXT and SOFT Trials. J Clin Oncol. 2022 Dec 15;JCO2201064. doi: 10.1200/JCO.22.01064.

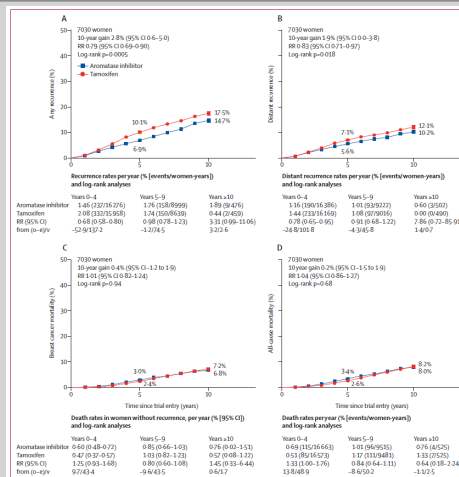
Adjuvant endocrine therapy in premenopausal patients (OFS + TAM / AI)

Any recurrence

Breast cancer mortality

Distant recurrence

All-case mortality



EBCTCG: Lancet Oncol. 2022;23:382-392

1. Bradley R, Braybrooke J, Gray R et al. Aromatase Inhibitors versus Tamoxifen in premenopausal women with ER + early stage breast cancer treated with ovarian suppression: A patient level meta-analysis of 7.030 women in four randomised trials. SABCS 2021, GS2-04.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. Lancet Oncol. 2022 Mar;23(3):382-392

Postmenopausal Patients

Initial Adjuvant Endocrine Therapy (Years 1-5)

■ Aromatase inhibitor (AI) for first 5 years

- Non steroidal-AI in lobular cancer
- High risk of recurrence

■ Sequential therapy for first 5 years *

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

■ Tamoxifen 20 mg/d for 5 years**

Oxford		
LoE	GR	AGO
1a	A	++
2b	B	+
2b	B	+
1a	A	++
1a	A	++
1b	C	++
1a	A	+

* in postmenopausal patients, AI should be integrated in the first five years

** Tamoxifen may be offered to individual patients with very low risk of recurrence or if contraindications for AI are present

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 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;26:106-14.
3. FACE Studie?

Especially in case of lobular cancer

1. 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:

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.

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.
5. De Placido S, Gallo C, De Laurentiis M, et al. GIM Investigators. Adjuvant anastrozole versus exemestane versus letrozole, upfront or after 2 years of tamoxifen, in endocrine-sensitive breast cancer (FATA-GIM3): a randomised, phase 3 trial. Lancet Oncol. 2018 Apr;19(4):474-485.

Tamoxifen 20 mg/d for first 5 yrs:

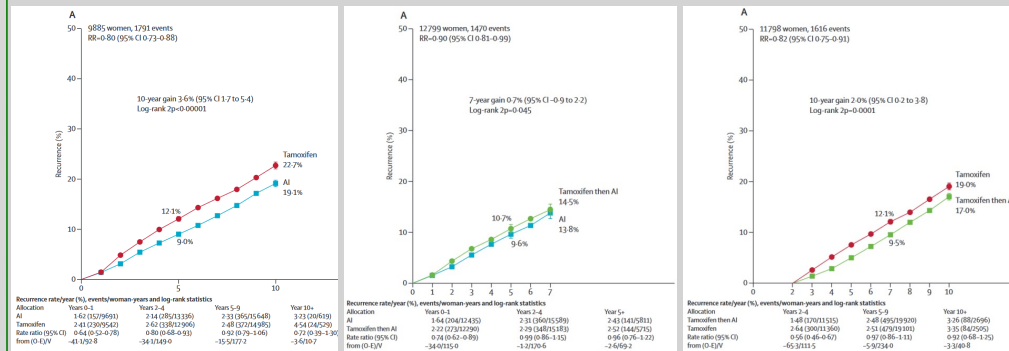
1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 378:771-84, 2011
2. Early Breast Cancer Trialists' Collaborative Group (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. Sequential Therapy - 5 years up-front Therapy



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.

Adjuvante Endocrine-Based Therapy with CDK4/6 Inhibitors and PARP Inhibitors

In patients with increased risk of recurrence and characteristics corresponding to study criteria

- Abemaciclib for 2 years*
- Olaparib for 1 year in patients with *gBRCA1/2* mutations**

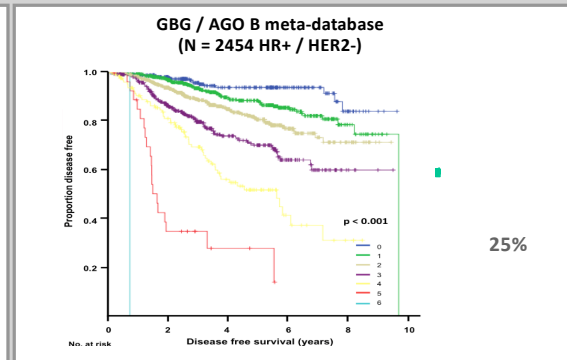
Oxford		
LoE	GR	AGO
1b	B	+
1b	B	++

* corresponding to MonarchE-Study
 ** corresponding to OlympiA-Study

- Loibl S, Marmé F, Martin M, et al. Palbociclib for Residual High-Risk Invasive HR-Positive and HER2-Negative Early Breast Cancer- The Penelope-B Trial. J Clin Oncol. 2021 May 10;39(14):1518-1530. doi: 10.1200/JCO.20.03639. Epub 2021 Apr 1. PMID: 33793299
- Harbeck N, Rastogi P, Martin M, et al. MonarchE Committee Members. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol. 2021 Dec;32(12):1571-1581. doi: 10.1016/j.annonc.2021.09.015. Epub 2021 Oct 14. PMID: 34656740
- Gnant M, Dueck AC, Frantal S, et al.; PALLAS groups and investigators. Adjuvant Palbociclib for Early Breast Cancer: The PALLAS Trial Results (ABCSG-42/AFT-05/BIG-14-03). J Clin Oncol. 2021 Dec 7;JCO2102554. doi: 10.1200/JCO.21.02554. Online ahead of print. PMID: 34874182
- Tutt ANJ, Garber JE, Kaufman B et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021 Jun 24;384(25):2394-2405. doi: 10.1056/NEJMoa2105215. Epub 2021 Jun 3. PMID: 34081848
- Johnston, SRD; Harbeck, N; Hegg, R et al-: Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol 2020; 38:3987-3998.
- Johnston SRD, Toi M, O'Shaughnessy J, Rastogi P et al_ Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. Lancet Oncol. 2023 Jan;24(1):77-90. doi: 10.1016/S1470-2045(22)00694-5. Epub 2022 Dec 6. PMID: 36493792

How to calculate CPS+EG Score?

Point assignment for CPS+EG score			
Clinical Stage			
I	0	T1N0; T0N1mi; T1N1mi	
IIA	0	T0N1; T1N1; T2N0	
IIB	1	T2N1; T3N0	
IIIA	1	T0-2N2	
IIIB	2	T4N0-2	
Pathologic Stage			
0	0	T0/sN0	
I	0	T1N0; T0N1mi; T1N1mi	
IIA	1	T0N1; T1N1; T2N0	
IIB	1	T2N1; T3N0	
IIIA	1	T0-2 N2	
IIIB	1	T4 N0-N2	
Tumor Biologic Factors			
ER negative	1		
Nuclear grade 3	1		



Mittendorf EA, J Clin Oncol 2011;29:1956-1962
Marmé F, et al. Eur J Cancer 2021;153:203-212

1. Mittendorf EA, Jeruss JS, TuckerSI et al. Validation of a Novel Staging System for Disease-Specific Survival in Patients With Breast Cancer Treated With Neoadjuvant Chemotherapy. J Clin Oncol 2011;29:1956-1962.
2. Marmé F, Solbach C, Michel L et al. Utility of the CPS + EG scoring system in triple-negative breast cancer treated with neoadjuvant chemotherapy. Eur J Cancer 2021;153:203-212.

Premenopausal Patients

Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)

	Oxford		
	LoE	GR	AGO
In case of high risk of recurrence			
▪ 5 years tamoxifen after 5 years tamoxifen	1a	A	++
▪ 2,5 – 5 years AI after 5 years tamoxifen in initially premenopausal patients who obtain validated postmenopausal status during course of therapy	1b	B	+
▪ 5 years tamoxifen after 5 years of endocrine therapy + OFS	5	D	+

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.

Postmenopausal Patients Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)

	Oxford		
	LoE	GR	AGO
In case of high risk of recurrence			
▪ 5 years tamoxifen after 5 years tamoxifen	1a	A	+
▪ 2–5 years AI after 5 years tamoxifen	1a	A	++
▪ After initial AI-containing therapy (upfront or switch), prolongation of endocrine therapy with AI in total for 7-8 years*			
▪ High-risk of recurrence and good tolerability of AI, good bone health	1a	A	+
▪ Low-risk, poor tolerability of AI	1a	A	-
▪ Interruption of endocrine treatment up to 3 months during EAT with AI	1b	B	+/-
* Up to date, no impact on OS			

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.

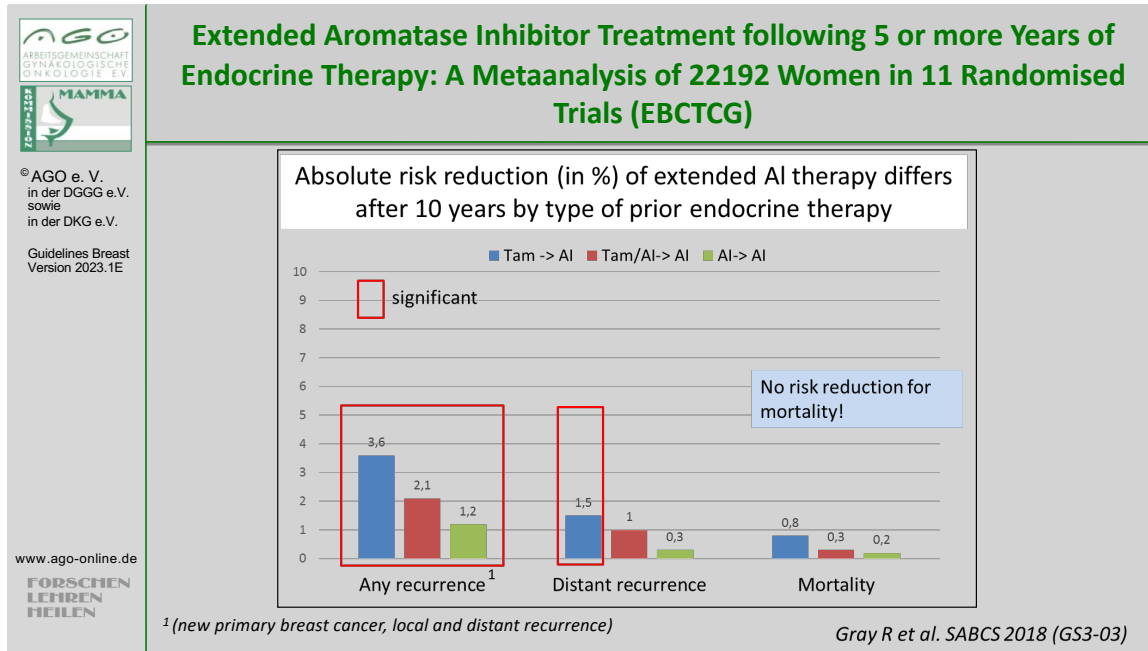
2. Jin H, Tu D, Zhao N et al. Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover. *J Clin Oncol* 2012;30(7):718-21.
3. Jakesz R, Greil R, Gnant M et al. Austrian Breast and Colorectal Cancer Study Group. 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.
4. 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* 2008;26(12):1965-71.
5. 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
6. Gnant M, G Steger, R Greil, et al. A prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years of Anastrozole after initial 5 years of adjuvant endocrine therapy - results from 3,484 postmenopausal women in the ABCSG-16 trial. *SABCS 2017*; GS3-01
7. Gray R (EBCTCG) et al. Extended aromatase inhibitor treatment following 5 or more years of endocrine therapy: a metaanalysis of 22192 women in 11 randomised trials. *SABCS 2018*;GS3-03
8. Zackariah C, 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(5):449-457.
9. Mamounas EP, Bandos H, Lembersky BC et al. Use of letrozole after aromatase inhibitor-based therapy in postmenopausal breast cancer (NRG Oncology/NSABP B-42): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019;20(1):88-99.
10. Del Mastro L, Masutti M, Bisagni G: Extended therapy with letrozole as adjuvant treatment of postmenopausal patients with early-stage breast cancer: a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2021; 22: 1458–67
11. Mamounas EP, Bandos H: Ten year results from NRG/NSABP – B42: a randomized , double blinded placebo controlle clinical trial of extended adjuvant endocrine therapy with letrozole in postmenopuasal women with hormone receptor + breast cancer who have completed prevoius adjuvant therapy with an aromatase inhibitor after initial AI containing therapy (upfront or switch) further prolongation of endocrine therapy with AI 2-5years. *SABCS 2019*, GS4-01

low risk, poor tolerability of the AI

1. Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E et al. Optimal Duration of Extended Adjuvant Endocrine Therapy for early breast cancer; results of the IDEAL trial (BOOG 2006-05). J Natl Cancer Inst 2018;110(1): dx134
2. Mamounas EP, Bandos H, Lembersky BC et al. Use of letrozole after aromatase inhibitor-based therapy in postmenopausal breast cancer (NRG Oncology/NSABP B-42): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20(1):88-99.
3. Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM et al. Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial. Lancet Oncol 2017;18(11):1502-1511.
4. Goss PE, Ingle JN, Pritchard KI et al. Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years. N Engl J Med. 2016;375(3):209-19.
5. Zdenkowski N, Forbes JF, Boyle FM 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;27(5):806-12.
6. Gray R (EBCTCG) et al. Extended aromatase inhibitor treatment following 5 or more years of endocrine therapy: a metaanalysis of 22192 women in 11 randomised trials. SABCS 2018;GS3-03
7. Zackariah C, 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(5):449-457.
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

Interruption of endocrine treatment up to 3 months during EAT:

1. Colleoni M, Luo W, Karlsson P et al. Extended adjuvant intermittent letrozole versus continuous letrozole in postmenopausal women with breast cancer (SOLE): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2018; 19: 127–38.



1. Gray R (EBCTCG) et al. Extended aromatase inhibitor treatment following 5 or more years of endocrine therapy: a metaanalysis of 22192 women in 11 randomised trials. SABCS 2018;GS3-03

Extended Adjuvant Treatment, Overview

Studie	Therapien															Die-Ratio- Vergleich e (Jahre)	HR für DFS	Ab- Trennung Jahre e (%)
Jahre nach Diagnose	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15			
Studien mit Tamoxifen nach 5 Jahren Tamoxifen																		
ATLAS																0 vs 10	0,75 - 0,91	0
ATTOM																0 vs 10	0,75 - 0,91	0
Studien mit AI nach 5 Jahren Tamoxifen																		
MA, T1																0 vs 10	0,57	0
NSABP B-33																0 vs 10	0,68	0
ABCSG 6a																0 vs 5	0,62	0
Studien mit anastrozol/ AI 7h. Nach 5 Jahren endokrin inst. AI																		
DATA																0 vs 5	0,79	100
NSABP B-42																0 vs 10	0,85	100
GBR 4																0 vs 7	0,78	100
MA, T1b																10 vs 15	0,65	100
Studien bzgl. optimaler Dauer für Jahre 5-10																		
BCOG 2006- B-05AL																7,5 vs 10	0,92	68
ABCSG 16																7 vs 10	1,007	49
SOL3																Cont vs unsteril	1,06	91

Braun: Tamoxifen


Grün: Tamoxifen
oder AI

Blau: AI

Gestreift: Zeit der
randomisierten
Intervention vs
keine
Therapie od.
Plazebo

***:** Rando-
misierungs-
zeitpunkt

§ : MA17R nach 5
Jahren AI mit
/ohne Tam zuvor



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in der DGGO e.V.
sowie
in der DKG e.V.

Guidelines Breast
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Decision Criteria for Extended Adjuvant 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
- BCI (H/I) (Breast Cancer Index)

Further decision criteria:

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

1. Gnant M, G Steger, R Greil, et al. A prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years of Anastrozole after initial 5 years of adjuvant endocrine therapy - results from 3,484 postmenopausal women in the ABCSG-16 trial. SABCS 2017; GS3-01
2. Li L, Chang B, Jiang X et al. Clinical outcomes comparison of 10 years versus 5 years of adjuvant endocrine therapy in patients with early breast cancer. Clinical outcomes comparison of 10 years versus 5 years of adjuvant endocrine therapy in patients with early breast cancer. BMC Cancer 2018;18:977
3. 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
4. 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.
5. 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.
6. Munzone E, Colleoni M: Optimal management of luminal breast cancer: how much endocrine therapy is long enough? Ther Adv Med Oncol 2018;10: 1–11.
7. Dowsett M, Sestak I, Regan MM et al. Integration of clinical variables for the prediction of late distant recurrence in patients with estrogen receptor–positive breast cancer treated with 5 years of endocrine therapy: CTS5. J Clin Oncol 2018 : 36(19): 1941–1948.

8. Sestak I, Buus R, Cuzick J et al. Comparison of the performance of 6 prognostic signatures for estrogen receptor–positive breast cancer: a secondary analysis of a randomized clinical trial. *JAMA Oncol* 2018; 4(4): 545–553.
9. 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
10. Bartlett J, Sgroi DTrans-aTTom: Breast Cancer Index predicts benefit of extended endocrine therapy in HR+ breast cancers treated in the adjuvant tamoxifen-to offer meore (aTTom) trial Abstract 505 ASCO 2019
11. Dennis C Sgroi, et al. Correlative studies of the breast cancer index (HOXB13/IL17BR) and ER, PR, AR, AR/ER ratio and Ki67 for prediction of extended endocrine benefit: A trans-aTTom study, SABCs 2020; GS4-09.

Ovarian Protection with GnRHa and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT)

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> CTx + GnRHa (preservation of ovarian function) (GnRHa application > 2 weeks prior to chemotherapy, independent of hormone receptor status) 	1a	A	+
<ul style="list-style-type: none"> CTx + GnRHa (preservation of fertility) 	2a	B	+/-
<ul style="list-style-type: none"> Fertility preservation counselling including referral of all potential patients to appropriate reproductive specialists (ART; further information https://fertifrotekt.com/english; S2k guideline Fertility protection in patients with malignancies) 			++

Fertility preservation counselling

1. Loren AW, Mangu PB, Beck LN et al. Fertility Preservation for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2013;31(19):2500–10.
2. Peccatori FA, Azim Jr HA, Orecchia R et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160–70.
3. Abe A, Kuwahara A, Iwasa T et al.: A survey on fertility management in young women of reproductive age treated with chemotherapy. Int J Clin Oncol. 2016 Dec;21(6):1183-1190.
4. Marklund A, et al. Reproductive Outcomes After Breast Cancer in Women With vs Without Fertility Preservation. JAMA Oncol. 2021 Jan 1;7(1):86-91.
5. https://register.awmf.org/assets/guidelines/015-082l_S2k_Fertilitaetserhaltung-bei-onkologischen-Therapien_2017-12-verlaengert.pdf

Fertility preservation with assisted reproduction therapy

1. Lambertini M, Fontana V, Massarotti C et al.: Prospective study to optimize care and improve knowledge on ovarian function and/or fertility preservation in young breast cancer patients: Results of the pilot phase of the PREgnancy and FERTility (PREFER) study. Breast 2018, 41:51-6.

2. Luke B, Brown MB, Missmer SA et al.: Assisted reproductive technology use and outcomes among women with a history of cancer. Hum Reprod. 2016 Jan;31(1):183-9.
3. Oktay K, Turan V, Bedoschi G et al.: Fertility Preservation Success Subsequent to Concurrent Aromatase Inhibitor Treatment and Ovarian Stimulation in Women With Breast Cancer. J Clin Oncol. 2015;33(22):2424–9.
4. Marklund A, et al. Efficacy and safety of controlled ovarian stimulation using GnRH antagonist protocols for emergency fertility preservation in young women with breast cancer-a prospective nationwide Swedish multicenter study. Hum Reprod. 2020 Apr 28;35(4):929-938.

Prognosis is not influenced by fertility preservation and ART:

Arecco L, Blondeaux E, Bruzzzone M, et al.. Safety of fertility preservation techniques before and after anticancer treatments in young women with breast cancer: a systematic review and meta-analysis. Hum Reprod. 2022; 37(5):954-968. doi: 10.1093/humrep/deac035. PMID: 35220429; PMCID: PMC9071231.

Ovarian function protection

1. Del Mastro L, Ceppi M, Poggio F et al.: Gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in cancer women: systematic review and meta-analysis of randomized trials. Cancer Treat Rev. 2014 Jun;40(5):675-83.
2. Munholz RR, et al: Gonadotropin-Releaseing 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
3. Lambertini M, Boni L, Michelotti A et al.: Ovarian Suppression With Triptorelin During Adjuvant Breast Cancer Chemotherapy and Long-term Ovarian Function, Pregnancies, and Disease-Free Survival: A Randomized Clinical Trial. JAMA. 2015 Dec 22-29;314(24):2632-40. doi: 10.1001/jama.2015.17291.
4. Lambertini M, Moore HCF, Leonard RCF et al.: 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. J Clin Oncol 2018, 36:1981-90
5. Lambertini M, Boni L, Michelotti A et al.; GIM study group. Long-Term Outcomes With Pharmacological Ovarian Suppression During Chemotherapy in Premenopausal Early Breast Cancer Patients. J Natl Cancer Inst. 2022;114(3):400-408.

6. Zong X, Yu Y, Yang H, Chen W et al. Effects of Gonadotropin-Releasing Hormone Analogs on Ovarian Function Against Chemotherapy-Induced Gonadotoxic Effects in Premenopausal Women With Breast Cancer in China: A Randomized Clinical Trial. *JAMA Oncol.* 2022;8(2):252-258
7. Zong X, Yu Y, Chen W, Zong W, Yang H, Chen X. Ovarian reserve in premenopausal women with breast cancer. *Breast.* 2022;64:143-150
8. Li ZY, Dong YL, Cao XZ, Ren SS, Zhang Z. Gonadotropin-releasing hormone agonists for ovarian protection during breast cancer chemotherapy: a systematic review and meta-analysis. *Menopause.* 2022;29(9):1093-1100

Pregnancy rates

1. Lambertini M, Ceppi M, Poggio F et al.: Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. *Ann Oncol* 2015; 26(12):2408-19.
2. Moore HCF, Unger JM, Phillips K-A et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. *N Engl J Med.* 2015;372(10):923–32.
3. Lambertini M, Boni L, Michelotti A et al. Ovarian suppression with triptorelin during adjuvant breast cancer chemotherapy and long-term ovarian function, pregnancies, and disease-free survival. A randomized clinical trial. *JAMA.* 2015;314(24):2632-40.
4. Lambertini M, Boni L, Michelotti A et al.; GIM study group. Long-Term Outcomes With Pharmacological Ovarian Suppression During Chemotherapy in Premenopausal Early Breast Cancer Patients. *J Natl Cancer Inst.* 2022;114(3):400-408.

Fertility Preservation and Assisted Reproductive Therapy (ART) - Oncologic safety¹ -

	Oxford		
	LoE	GR	AGO
▪ Pretreatment approaches to preserve fertility			
GnRHa	1a	A	++
Cryopreservation of ovarian tissue with subsequent transplantation ²	4	D	+
Cryopreservation of oocytes (unfertilized / fertilized) after ovarian stimulation	2a	C	+
▪ ART after (neo-)adjuvant systemic treatment	4	C	+

¹ Evidence is limited due to studies with poor quality e.g. (prospective randomized trials are not feasible)

² Risk of relapse caused by transplantation of ovarian tissue containing tumor cells from the original malignancy; removal of transplanted ovarian tissue is necessary in patients with BRCA1/2 mutations due to increased risk of ovarian cancer

GnRH-Analagon:

1. Lambertini M, Moore HCF, Leonard RCF, et al. 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. J Clin Oncol. 2018;36(19):1981-1990.
2. Lambertini M, Boni L, Michelotti A, et al. ; GIM study group. Long-Term Outcomes With Pharmacological Ovarian Suppression During Chemotherapy in Premenopausal Early Breast Cancer Patients. J Natl Cancer Inst. 2022;114(3):400-408. doi: 10.1093/jnci/djab213. PMID: 34850043; PMCID: PMC8902441.

Cryopreservation of ovarian tissue:

1. Bastings L, Beerendonk CC, Westphal JR, et al. Autotransplantation of cryopreserved ovarian tissue in cancer survivors and the risk of reintroducing malignancy: a systematic review. Hum Reprod Update. 2013;19(5):483-506. doi: 10.1093/humupd/dmt020. Epub 2013 Jun 30. PMID: 23817363.
2. Rosendahl M, Greve T, Andersen CY. The safety of transplanting cryopreserved ovarian tissue in cancer patients: a review of the literature. J Assist Reprod Genet. 2013;30(1):11-24. doi: 10.1007/s10815-012-9912-x. Epub 2012 Dec 22. PMID: 23263841;

PMCID: PMC3553351.

Cryoconservation of oocytes after ovarian stimulation:

1. Arecco L, Blondeaux E, Bruzzone M, et al.. Safety of fertility preservation techniques before and after anticancer treatments in young women with breast cancer: a systematic review and meta-analysis. Hum Reprod. 2022; 37(5):954-968. doi: 10.1093/humrep/deac035. PMID: 35220429; PMCID: PMC9071231.
2. Rodgers RJ, Reid GD, Koch J, Deans R, et al. The safety and efficacy of controlled ovarian hyperstimulation for fertility preservation in women with early breast cancer: a systematic review. Hum Reprod. 2017 May 1;32(5):1033-1045. doi: 10.1093/humrep/dex027. PMID: 28333356.
3. Beebejaun Y, Athithan A, Copeland TP, et al. Risk of breast cancer in women treated with ovarian stimulation drugs for infertility: a systematic review and meta-analysis. Fertil Steril. 2021; 116(1):198-207. doi: 10.1016/j.fertnstert.2021.01.044. PMID: 34148584.

ART after treatment:

1. Arecco L, Blondeaux E, Bruzzone M, et al.. Safety of fertility preservation techniques before and after anticancer treatments in young women with breast cancer: a systematic review and meta-analysis. Hum Reprod. 2022; 37(5):954-968. doi: 10.1093/humrep/deac035. PMID: 35220429; PMCID: PMC9071231.

Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

Temporary interruption of adjuvant endocrine treatment (ET) after 18-30 month of ET, allowing a wash out period of 3 months, the attempt to get pregnant in a period of up to 2 years for those women with the desire to get pregnant does not impact short-term breast cancer outcome.

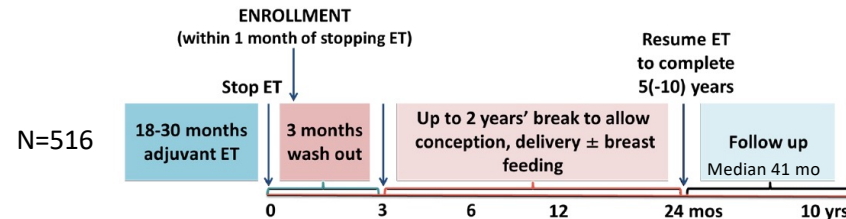
AGO +

1. Partridge, A. on behalf of the POSITIVE Consortium: Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsive breast cancer Initial Results from the POSITIVE Trial (IBCSG 48-14 / BIG 8-13 / Alliance A221405), SABCS 2022
2. Barbara Buonomo, B; Brunello, A; Noli, A: Tamoxifen Exposure during Pregnancy: A Systematic Review and Three More Cases. Breast Care 2020;15:148–156
3. Schuurman, TN; 1 , P O Witteveen, PO; van der Wall, E: Tamoxifen and pregnancy: an absolute contraindication? Breast Cancer Res Treat 2019 May;175(1):17-25.
4. Braems G, Denys H, De Wever O, Cocquyt V, Van den Broecke R: Use of tamoxifen before and during pregnancy. Oncologist. 2011;16(11):1547-51
5. <https://www.kup.at/kup/pdf/5326.pdf>

Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

Study design

AGO +



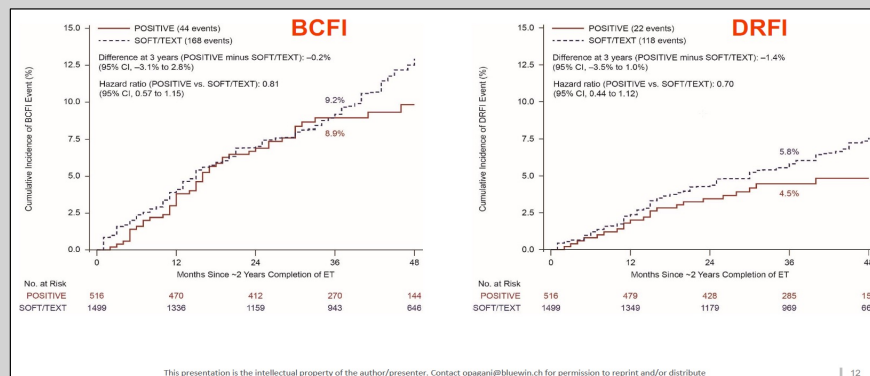
- Premenopausal women (≤ 42 years at study entry) wishing to get pregnant
- At least 18 months and no more than 30 months of prior adjuvant ET for stage I-III HR+ BC
- Up to 2 years to attempt pregnancy, conceive, deliver, and breastfeed, including
- 3-months washout period
- If no pregnancy by 1 y., fertility assessment recommended
- ET resumption strongly recommended after pregnancy to complete planned 5-10 yrs.

1. Partridge, A. on behalf of the POSITIVE Consortium: Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsive breast cancer Initial Results from the POSITIVE Trial (IBCSG 48-14 / BIG 8-13 / Alliance A221405), SABCS 2022
2. Barbara Buonomo, B; Brunello, A; Noli, A: Tamoxifen Exposure during Pregnancy: A Systematic Review and Three More Cases. Breast Care 2020;15:148–156
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4. Braems G, Denys H, De Wever O, Cocquyt V, Van den Broecke R: Use of tamoxifen before and during pregnancy. Oncologist. 2011;16(11):1547-51
5. <https://www.kup.at/kup/pdf/5326.pdf>

Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

Pregnancies outcome: 317 (64% of all women) had at least one live birth, 62% reported breast feeding, 2% showed birth defects

BREAST CANCER OUTCOMES – POSITIVE & SOFT/TEXT

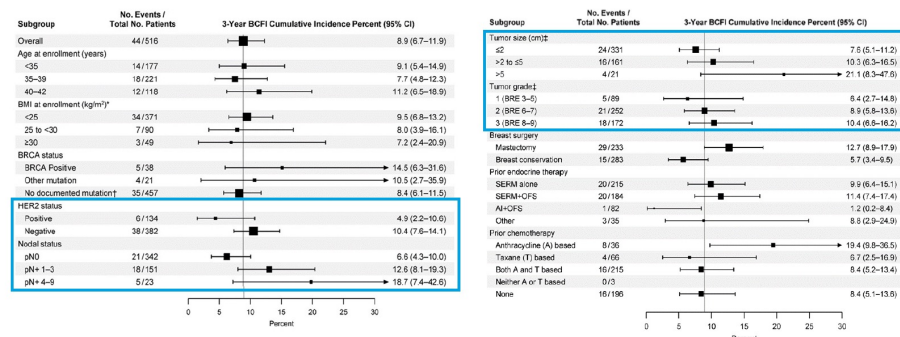


1. Ann Partridge on behalf of the POSITIVE Consortium: **Pregnancy Outcome and Safety of Interrupting Therapy** for women with endocrine responsive breast cancer Initial Results from the **POSITIVE Trial** (IBCSG 48-14 / BIG 8-13 / Alliance A221405), SABCS 2022

Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

3- YEAR BCFI CUMULATIVE INCIDENCE – POSITIVE only

- 3-year BCFI varied according to clinical-pathological characteristics



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- Ann Partridge on behalf of the POSITIVE Consortium: **Pregnancy Outcome and Safety of Interrupting Therapy** for women with endocrine responsive breast cancer Initial Results from the **POSITIVE Trial** (IBCSG 48-14 / BIG 8-13 / Alliance A221405), SABCS 2022