Guidelines Breast
Version 2024.1D

FORSCHEN
LEHREN
HEILEN

Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Adjuvante endokrin-basierte Therapie bei prä- und postmenopausalen Patientinnen

Guidelines Breast
Version 2024.1D

Adjuvante endokrine Therapie bei prä- und postmenopausalen Patientinnen

- **Versionen 2002–2023:**
  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 2024:**
  Lux / Wöckel

Bestimmung des Steroid-Hormonrezeptorstatus

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

„Endokrines Ansprechen“ (früher rezeptorpositiv): Immunhistologie (ER und / oder PR)

0 %	**pos. Zellen:**	**endokrin nicht sensitiv**
1–10 %	**pos. Zellen:**	**endokrin fraglich sensitiv**
> 10 %	**pos. Zellen:**	**endokrin sensitiv**
Hormonrezeptor-Status unbekannt:		**endokrin sensitiv**

Bei ER negativ / PR positiv (> 10 % Zellen): immunhistochemische Reevaluation erforderlich.
Bei ER low (1-10%) Nennung der Relevanz im histopathologischen Bericht empfohlen.

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.
5. Panagiotis Malainou C, Stachika N, Damianou A et al. Estrogen-Receptor-Low-Positive Breast Cancer: Pathological and Clinical Perspectives. Curr Oncol. 2023 Nov 4;30(11):9734-9745. doi: 10.3390/curroncol30110706.

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, Knblauch 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.

Adjuvante endokrine Therapie
Bestimmung des Menopausenstatus

	Oxford		
	LoE	GR	AGO
Bestimmung des Menopausenstatus:			
▪ **Menstruationsanamnese**			++
▪ **FSH, E2**			++

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.

Adjuvante endokrine Therapie

	Oxford		
	LoE	GR	AGO
▪ **Endokrin sensitiv**	1a	A	++
▪ **Fraglich endokrin sensitiv**	3b	D	+
▪ **Endokrine Therapie sequentiell: nach einer adjuvanten Chemotherapie**	2a	B	+
▪ **Endokrine Therapie simultan mit Anti-HER2-Therapie ohne Chemotherapie**	2b	B	+
▪ **Nicht endokrin sensitiv**	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 219; 80(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.
13. Panagiotis Malainou C, Stachika N, Damianou A et al. Estrogen-Receptor-Low-Positive Breast Cancer: Pathological and Clinical Perspectives. Curr Oncol. 2023 Nov 4;30(11):9734-9745. doi: 10.3390/curroncol30110706.

Generelle Prinzipien der adjuvanten endokrinen Therapie AGO ++

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- **Die adjuvante endokrine Therapie wird in die initiale Therapie (Jahre 1–5) und die erweiterte adjuvante Therapie (EAT, Jahre 6–10+) eingeteilt. Die initiale adjuvante Therapie umfasst auch die endokrin-basierte Therapie (Jahre 1-2).**
- **Standard Therapiedauer der adjuvanten Therapie: 5 Jahre**
- **Erweiterte Therapiedauer und initial endokrin-basierte Therapie nach individueller Nutzen-Risiko-Abwägung.**
- **Dauer, Wahl & Sequenz von AI oder Tam oder die Kombination mit GnRHa hängen v. a. vom Menopausenstatus, der Verträglichkeit und dem Rückfall-Risiko ab.**
- **Der Wechsel auf eine andere endokrine Therapie (Tam oder AI) oder Tamoxifen low dose ist besser, als die Therapie zu stoppen.**
- **Beginn mit AI bei lobulären Karzinomen und / oder erhöhtem Rückfall-Risiko.**
- **Es existiert kein ausreichend validierter Biomarker für einen frühen versus einen späten Rückfall.**

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 art 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.
16. 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.
17. 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
18. Hortobagyi G, Stroyakovsky D, Yardley D, et al. Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2− early breast cancer: final invasive disease–free survival (iDFS) analysis from the NATALEE trial. SABCS, 2023, GS03-03
19. Importance of endocrine treatment adherence and persistence in breast cancer survivorship: a systematic review. Eliassen FM, Blåfjelldal V, Helland T, et al. BMC Cancer. 2023 Jul 4;23(1):625.
20. De Censi A. et al., 10 Year Results of Phase 3 Trial of low-dose Tamoxifen in noninvasive Breast Cancer, SABCS, 2022, GS408

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, Ambroisine 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 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.
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. 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.
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.

9. Adjuvant Endocrine Therapy in Premenopausal Breast Cancer: 12-Year Results From SOFT. Francis PA, Fleming GF, Láng I, et al.; SOFT Investigators and the International Breast Cancer Study Group (a division of ETOP IBCSG Partners Foundation). J Clin Oncol. 2023 Mar 1;41(7):1370-1375. doi: 10.1200/JCO.22.01065.

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

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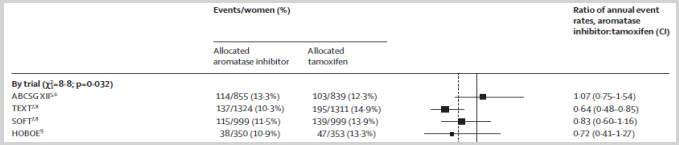

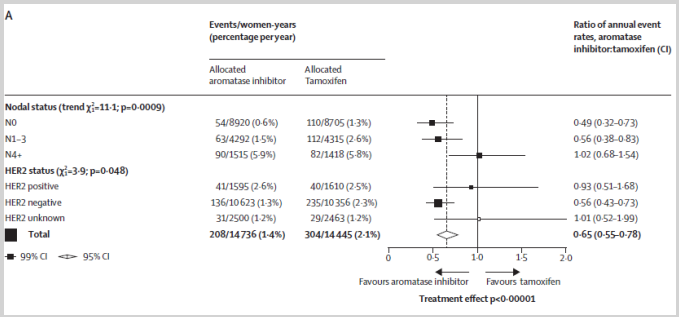

EBCTCG: Lancet Oncol. 2022;23:382-392

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. 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.

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

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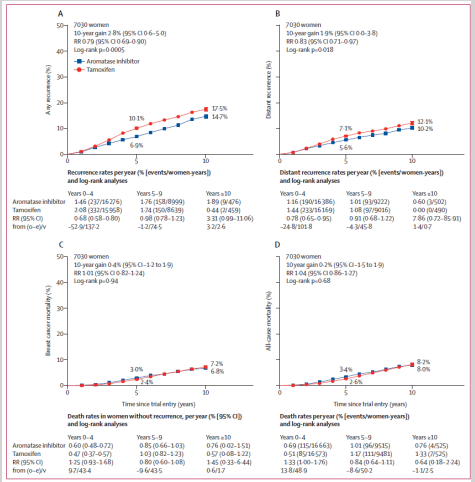
Any recurrence

Distant recurrence



Breast cancer mortality

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

Adjuvante endokrine Therapie bei postmenopausalen Patientinnen (Jahre 1-5)

	Oxford		
	LoE	GR	AGO
▪ **Aromatasehemmer für die ersten 5 Jahre**	1a	A	++
▪ Nicht-steroidaler AI bei lobulärem Karzinom	2b	B	+
▪ Hohes Rezidivrisiko	2b	B	+
▪ **Sequentielle Therapie für die ersten 5 Jahre***	1a	A	++
▪ 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	++
▪ **Tamoxifen 20 mg/d für die ersten 5 Jahre****	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 im Einzelfall in Abhängigkeit vom Alter, Rückfallrisiko und Kontraindikationslage eingesetzt werden.**

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 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. 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 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.

Patient care/ adherence and side effects

1. Inwa ld 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

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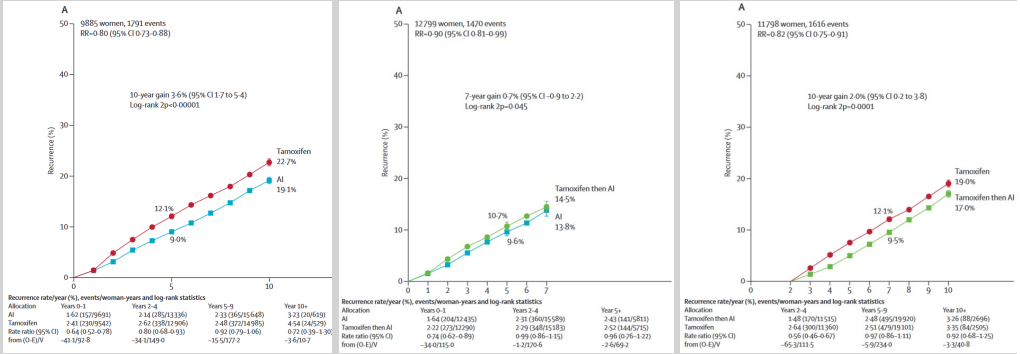

Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet. 2015 Oct 3;386(10001):1341-52.

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

Adjuvante endokrin-basierte Therapie mit CDK4/6 Inhibitoren und PARP Inhibitoren

	Oxford		
	LoE	GR	AGO
Bei erhöhtem Rückfallrisiko, entsprechenden Patientinnencharakteristika und Dosierung analog zu den Studien			
▪ **Abemaciclib für 2 Jahre***	1b	B	+
▪ **Olaparib für 1 Jahr bei *gBRCA1/2* Mutation****	1b	B	++

* entsprechend der MonarchE-Studie
** entsprechend der OlympiA-Studie

1. 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
2. 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
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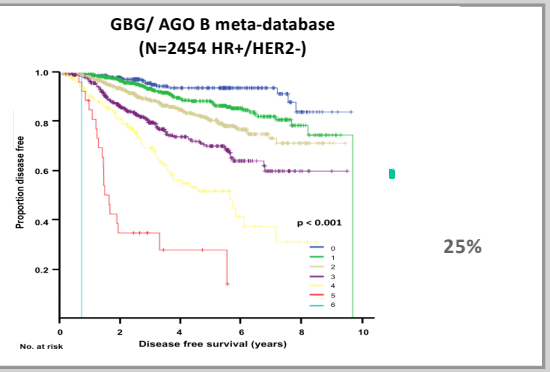
How to calculate CPS+EG Score?

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/isN0
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	



25%

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Adjuvant / Post-Neoadjuvant Treatment with CDK4/6i

Guidelines Breast
Version 2024.1D

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

	monarchE	PALLAS	PENELOPE[B]	NATALEE
N	5,637	5,600	1,250	5,101
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib	Ribociclib
% of pts. with NACT	37%	n.r.	100%	n.a.
Duration of CDK4/6i treatment	24 months	24 months	12 months	36 months
Follow-up	42.0 months	24 months	43 months	33.3 months
Discontinuation rate	30.6%	42%	20%	35.5%
Discontinuation rate due to AE_{CDKi}	18.5%	27%	5%	19.5%
IDFS-HR (95%-CI)	0.664 (0.578-0.762) p < 0.0001	0.96 (0.81-1.14) p = 0.65	0.93 (0.74-1.16) p = 0.525	0.749(0,628-0.892) P=0.0006
2-yrs IDFS	92.7% vs. 89.9%	n.r.	88% vs. 78%	93.5% vs. 92.0%
3-yrs IDFS	89.2% vs. 84.4%	88% vs. 89%	81% vs. 78%	90.7% vs. 87.6%
4-yrs IDFS	85.8% vs. 79.4%	84.2% vs. 84.5%	73% vs. 72%	

IDFS: invasive disease-free survival

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6. Hortobagyi GN, Stroyakovskiy D, Yardley DA et al. (GS03-03) Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2− early breast cancer: final invasive disease–free survival (iDFS) analysis from the NATALEE trial SABCS 2023 (GS03-03)

Erweiterte adjuvante endokrine Therapie (EAT) bei prämenopausalen Patientinnen (Jahre 6–10)

	Oxford		
	LoE	GR	AGO
Bei erhöhtem Rückfallrisiko			
▪ **5 Jahre Tamoxifen nach 5 Jahren Tamoxifen**	1a	A	++
▪ **2,5–5 Jahre AI nach 5 Jahren Tamoxifen prämenopausal, bei im Verlauf eindeutig nachgewiesener postmenopausaler Situation**	1b	B	+
▪ **5 Jahre Tamoxifen nach 5 Jahre endokriner Therapie + 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.
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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.

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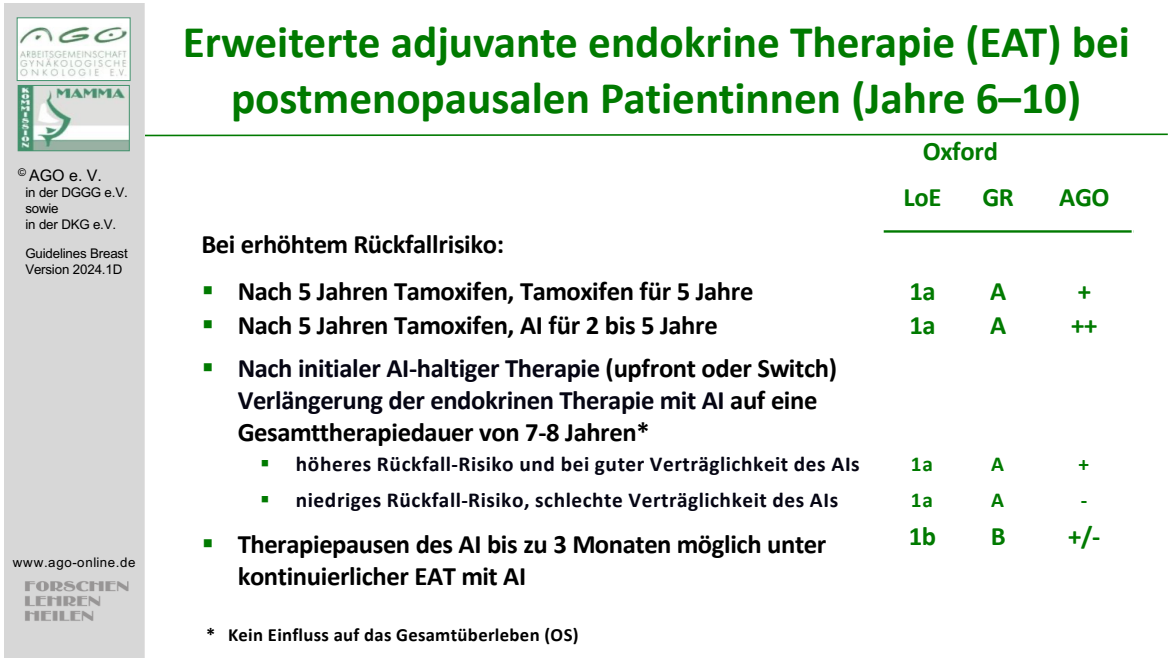

Erweiterte adjuvante endokrine Therapie (EAT) bei postmenopausalen Patientinnen (Jahre 6–10)

	Oxford LoE	Oxford GR	Oxford AGO
Bei erhöhtem Rückfallrisiko:			
▪ **Nach 5 Jahren Tamoxifen, Tamoxifen für 5 Jahre**	1a	A	+
▪ **Nach 5 Jahren Tamoxifen, AI für 2 bis 5 Jahre**	1a	A	++
▪ **Nach initialer AI-haltiger Therapie (upfront oder Switch) Verlängerung der endokrinen Therapie mit AI auf eine Gesamttherapiedauer von 7-8 Jahren***			
▪ **höheres Rückfall-Risiko und bei guter Verträglichkeit des AIs**	1a	A	+
▪ **niedriges Rückfall-Risiko, schlechte Verträglichkeit des AIs**	1a	A	-
▪ **Therapiepausen des AI bis zu 3 Monaten möglich unter kontinuierlicher EAT mit AI**	1b	B	+/-

* **Kein Einfluss auf das Gesamtüberleben (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.
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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.
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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.
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12. Tjan-Heijnen VCG, Lammers SWM, Geurts SME et al. Extended adjuvant aromatase inhibition after sequential endocrine therapy in postmenopausal women with breast cancer: follow-up analysis of the randomised phase 3 DATA trial. ClinicalMedicine. 2023 Mar 20;58:101901. doi: 10.1016/j.eclinm.2023.101901. eCollection 2023 Apr.

<u>low risk, poor tolerabilty of the AI</u>

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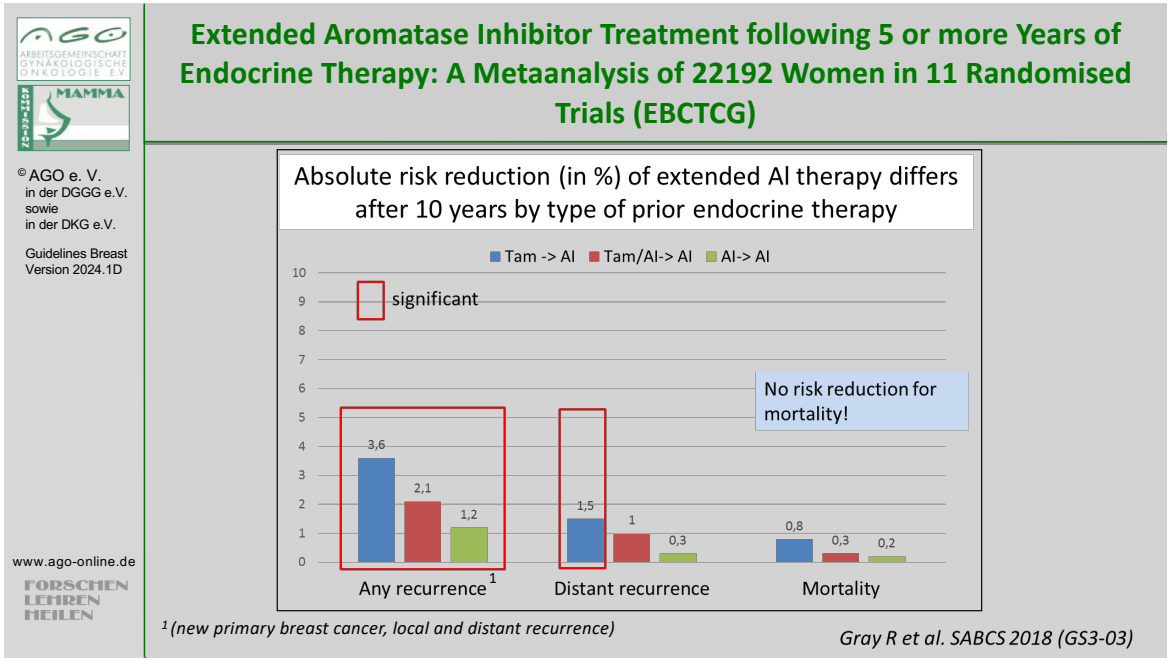
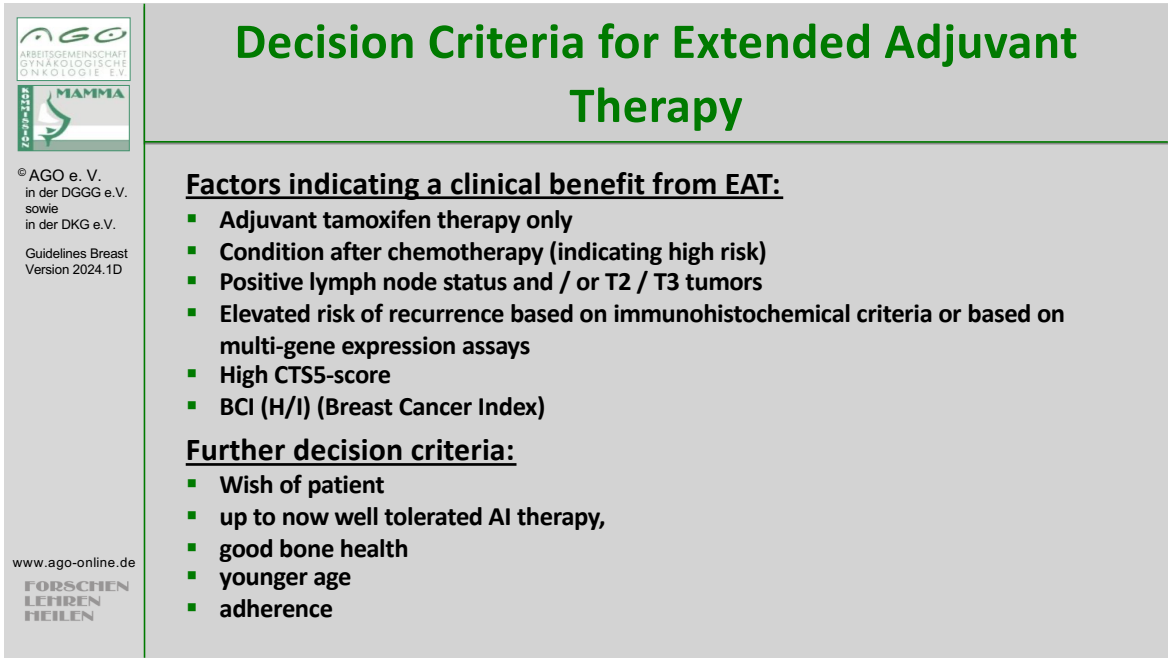


1. Gray R (EBCTCG) et al. Extended aromatase inhibitor treatment following 5 or more years of endocrine therapy: a metaanalysis of 22192 women in 11 randomised trials. SABCS 2018;GS3-03



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.
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Ovarschutz mit GnRH und Fertilitätserhalt bei prämenopausalen Patientinnen mit (neo-)adjuvanter Chemotherapie (CT)

	Oxford		
	LoE	GR	AGO
▪ **CTx + GnRHa (zur Prophylaxe des ovariellen Funktionsausfalls) (GnRHa Applikation > 2 Wochen vor Chemotherapie, unabhängig vom Hormonrezeptorstatus)**	1a	A	+
▪ **CTx + GnRHa (zur Erhöhung der Schwangerschaftsrate)**	2a	B	+/-
▪ **Angebot zur Beratung über Fertilitätserhaltung inkl. assistierter Reproduktion (ART) (Information: *https://fertiprotekt.com; S2k-Leitlinie Fertilitätserhalt bei onkologischen Erkrankungen*)**			++

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.
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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)

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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.
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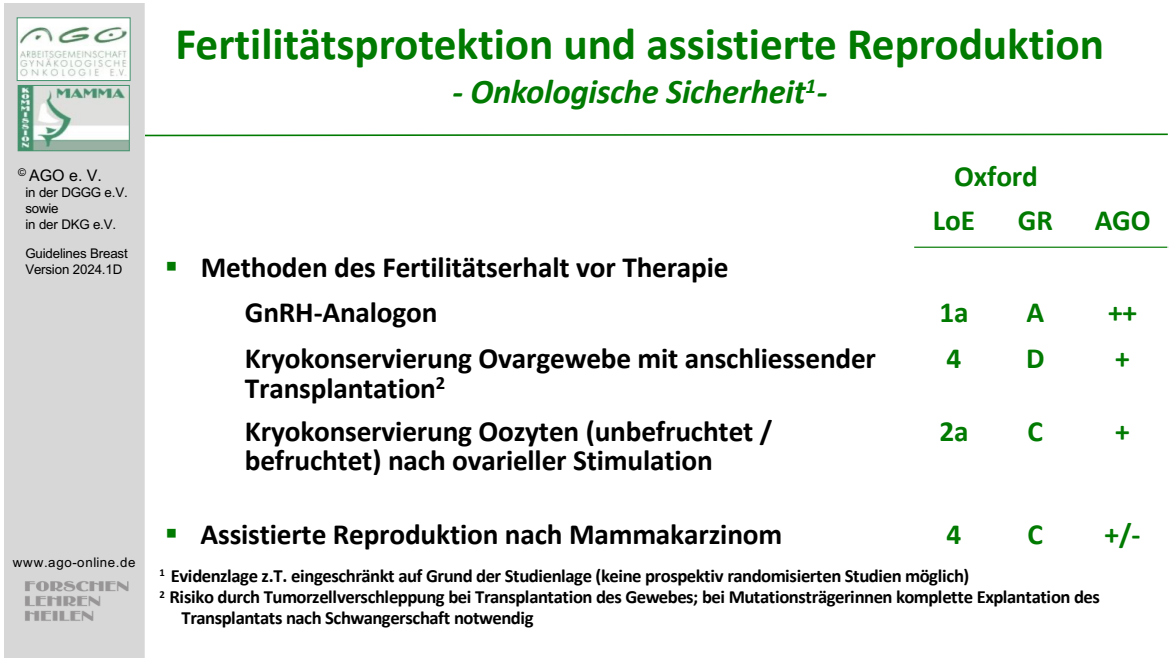
4. Lambertini M, Boni L, Michelotti A et al.; GIM study group. Long-Term Outcomes With Pharmacological Ovarian Suppression During Chemotherapy in Premenopausal Early Breast Cancer Patients. J Natl Cancer Inst. 2022;114(3):400-408.



Fertilitätsprotektion und assistierte Reproduktion

- Onkologische Sicherheit[1]-

	Oxford LoE	Oxford GR	AGO
▪ **Methoden des Fertilitätserhalt vor Therapie**			
GnRH-Analogon	1a	A	++
Kryokonservierung Ovargewebe mit anschliessender Transplantation[2]	4	D	+
Kryokonservierung Oozyten (unbefruchtet / befruchtet) nach ovarieller Stimulation	2a	C	+
▪ **Assistierte Reproduktion nach Mammakarzinom**	4	C	+/-

[1] Evidenzlage z.T. eingeschränkt auf Grund der Studienlage (keine prospektiv randomisierten Studien möglich)
[2] Risiko durch Tumorzellverschleppung bei Transplantation des Gewebes; bei Mutationsträgerinnen komplette Explantation des Transplantats nach Schwangerschaft notwendig

GnRH-Analogon:

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.

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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.
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1. Luke B, Brown MB, Missmer SA et al.: Assisted reproductive technology use and outcomes among women with a history of cancer. Hum Reprod. 2016 ;31(1):183-9.
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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.
2. Azim H, Niman S, Patridge A et al. Fertility preservation and assisted reproductive technologies in breast cancer pstien ts interrupting adjuvant endocrine therapy to attempt pregnancy.

   Results from the positive trial. SABCS 2023

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FORSCHEN
LEHREN
HEILEN

Adjuvante endokrine Therapie bei prämenopausalen Patn. mit Kinderwunsch

Eine Unterbrechung der endokrinen adjuvanten Therapie (ET)

(für max. 2 Jahre nach einer mindestens 18-monatigen Vortherapie)

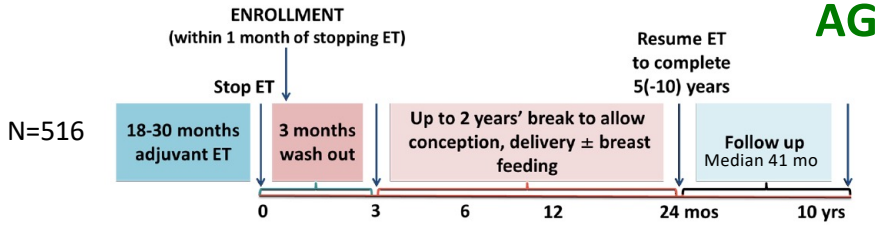
ist bei Kinderwunsch ohne kurzfristigen Überlebensnachteil

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

Adjuvante endokrine Therapie bei prämenopausalen Patn. mit Kinderwunsch

AGO +



Untersucht wurden Frauen < 42 Jahre:

- Outcome: 64 % Lebendgeburten; 62 % der Mütter haben gestillt; 2 % Fehlbildungen
- Zeitlich begrenzte Unterbrechung der endokrinen Therapie zur Realisierung des Kinderwunsch ist ohne prognostische Nachteile (BCFI)
- ET Unterbrechung (max. 2 Jahre nach mind. 18 Monate Vortherapie) bei Kinderwunsch ohne kurzfristigen Überlebensnachteil

1. 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
2. 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.
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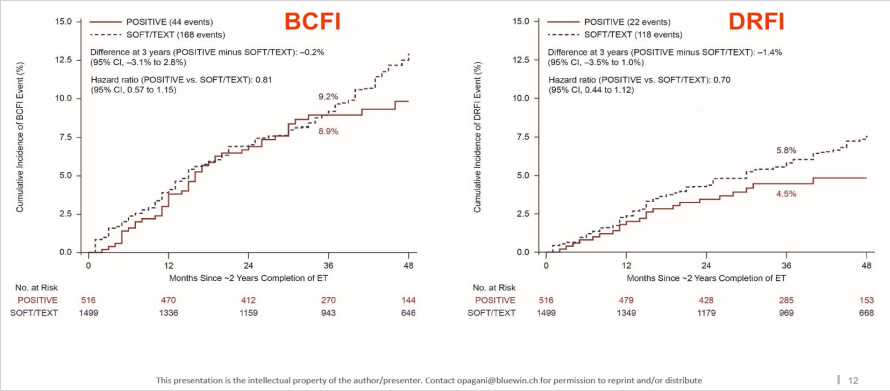
4. https://www.kup.at/kup/pdf/5326.pdf
5. Partridge, A. on behalf of the POSITIVE Consortium: Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsIVE breast cancer Initial Results from the POSITIVE Trial (IBCSG 48-14 / BIG 8-13 / Alliance A221405), SABCS 2022
6. Interrupting Endocrine Therapy to Attempt Pregnancy after Breast Cancer. Partridge AH, Niman SM, Ruggeri M, Peccatori FA, Azim HA Jr, Colleoni M, Saura C, Shimizu C, Sætersdal AB, Kroep JR, Mailliez A, Warner E, Borges VF, Amant F, Gombos A, Kataoka A, Rousset-Jablonski C, Borstnar S, Takei J, Lee JE, Walshe JM, Ruíz-Borrego M, Moore HCF, Saunders C, Bjelic-Radisic V, Susnjar S, Cardoso F, Smith KL, Ferreiro T, Ribi K, Ruddy K, Kammler R, El-Abed S, Viale G, Piccart M, Korde LA, Goldhirsch A, Gelber RD, Pagani O; International Breast Cancer Study Group; POSITIVE Trial Collaborators. N Engl J Med. 2023 May 4;388(18):1645-1656.

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



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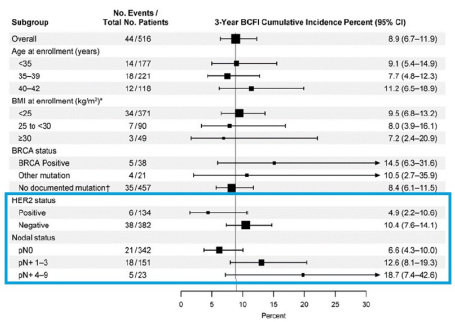
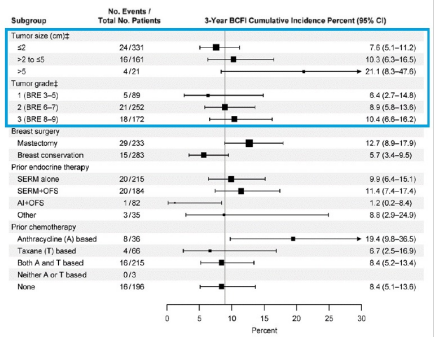
Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

3-YEAR BCFI CUMULATIVE INCIDENCE – POSITIVE only

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



Subgroup	No. Events / Total No. Patients	3-Year BCFI Cumulative Incidence Percent (95% CI)
Overall	44/516	8.9 (6.7–11.9)
Age at enrollment (years)		
<35	14/177	9.1 (5.4–14.9)
35–39	18/221	7.7 (4.8–12.3)
40–42	12/118	11.2 (6.5–18.9)
BMI at enrollment (kg/m²)*		
<25	34/371	9.5 (6.8–13.2)
25 to <30	7/90	8.0 (3.9–16.1)
≥30	3/49	7.2 (2.4–20.9)
BRCA status		
BRCA Positive	5/38	14.5 (6.3–31.6)
Other mutation	4/21	10.5 (2.7–35.9)
No documented mutation†	35/457	8.4 (6.1–11.5)
HER2 status		
Positive	6/134	4.9 (2.2–10.6)
Negative	38/382	10.4 (7.6–14.1)
Nodal status		
pN0	21/342	6.5 (4.3–10.0)
pN+ 1–3	18/151	12.6 (8.1–19.3)
pN+ 4–9	5/23	18.7 (7.4–42.6)



Subgroup	No. Events / Total No. Patients	3-Year BCFI Cumulative Incidence Percent (95% CI)
Tumor size (cm)‡		
≤2	24/331	7.6 (5.1–11.2)
>2 to ≤5	16/161	10.3 (6.3–16.5)
>5	4/21	21.1 (8.3–47.6)
Tumor grade‡		
1 (BRE 3–5)	5/89	6.4 (2.7–14.8)
2 (BRE 6–7)	21/252	8.9 (5.8–13.6)
3 (BRE 8–9)	18/172	10.4 (6.6–16.2)
Breast surgery		
Mastectomy	29/233	12.7 (8.9–17.9)
Breast conservation	15/283	5.7 (3.4–9.5)
Prior endocrine therapy		
SERM alone	20/215	9.9 (6.4–15.1)
SERM+OFS	20/184	11.4 (7.4–17.4)
AI+OFS	1/62	1.2 (0.2–8.4)
Other	3/35	8.6 (2.9–24.9)
Prior chemotherapy		
Anthracycline (A) based	8/36	19.4 (9.8–36.5)
Taxane (T) based	4/66	6.7 (2.5–16.9)
Both A and T based	16/215	8.4 (5.2–13.4)
Neither A or T based	0/3	
None	16/196	8.4 (5.1–13.6)

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

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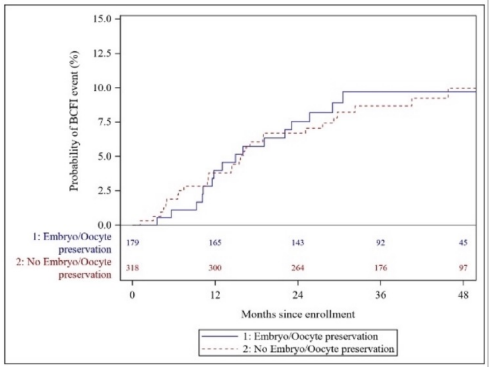
Ovarian stimulation and breast cancer outcome – results from the POSITIVE trial

1) As part of embryo/oocyte cryopreservation - after BC diagnosis

At 3-years, BCFI-events cumulative incidence

- **9.7%** (95% CI: 6.0% to 15.4%) for the 179 patients who underwent ovarian stimulation
- **8.7%** (95% CI: 6.0% to 12.5%) for the 318 patients who did not



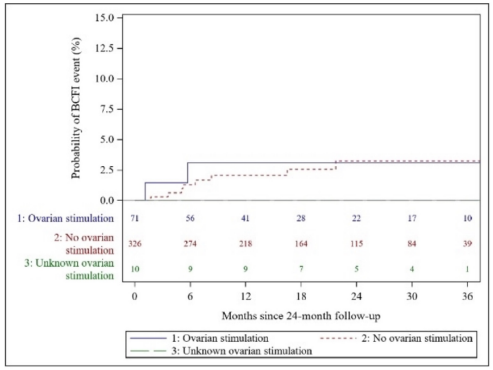
1. Azim H, Niman S, Patridge A, et al. Fertility preservation and assisted reproductive technologies (ART) in breast cancer (BC) patients (pts) interrupting endocrine therapy (ET) to attempt pregnancy. SABCS 2023, GS02-11

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

Ovarian stimulation and breast cancer outcome – results from the POSITIVE trial

2) As part of ART - after enrollment

- **397 patients alive and BC free at 24-months (landmark analysis)**
  - 2 BC events amongst 71 patients in the ovarian stimulation group
  - 8 BC events amongst 326 patients in the non-ovarian stimulation group



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