Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

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Adjuvant Endocrine-based Therapy in pre- and postmenopausal Patients

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Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

- **Versions 2002–2023:**
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- **Version 2024:**
  Lux / Wöckel

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
If ER low (1-10%): Implications for therapy should be recommended in the pathology report

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.

Adjuvant Endocrine Therapy
Assessment of Menopausal Status

	Oxford		
	LoE	GR	AGO
Assessment of menopausal status:			
▪ **Menstruation history**			++
▪ **FSH, E2**			++

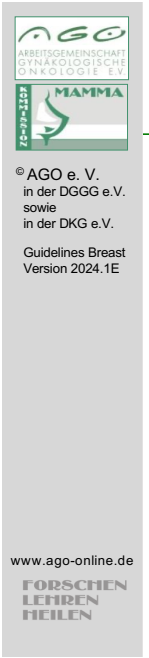
1. Partridge AH, Ruddy KJ, Gelber S et al. Ovarian reserve in women who remain premenopausal after chemotherapy for early stage breast cancer. Fertil Steril 2010;94(2):638-44.
2. Su HI, Chung K, Sammel MD et al. Antral follicle count provides additive information to hormone measures for determining ovarian 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.

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 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.

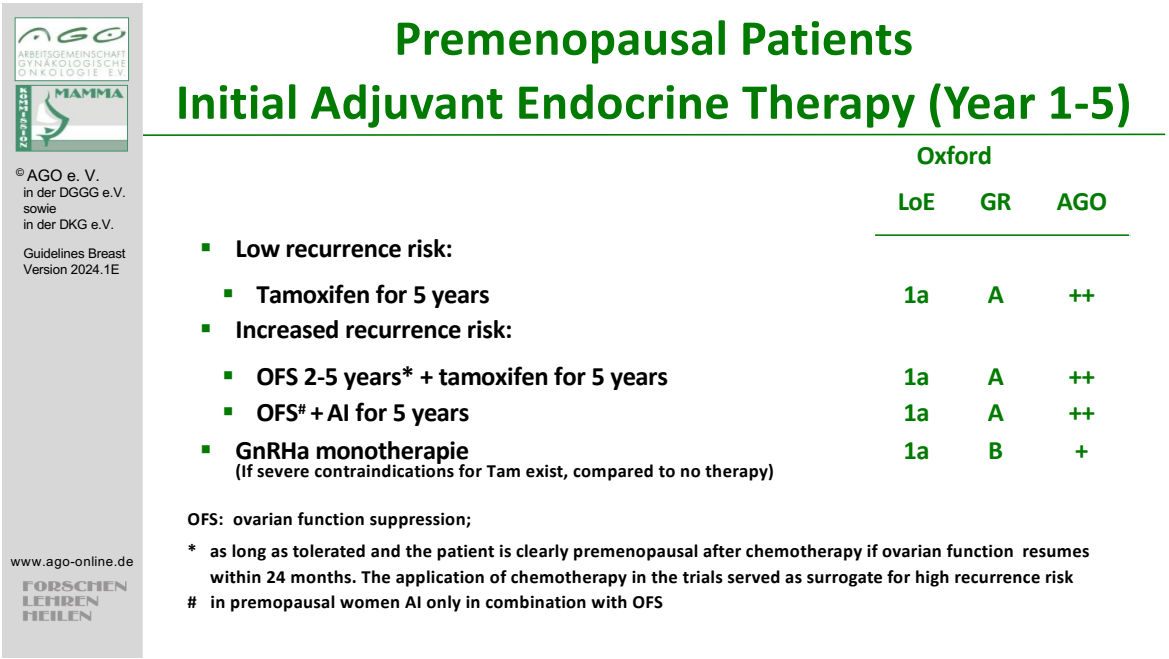


General Principles in Adjuvant Endocrine Therapy AGO ++

- **Adjuvant endocrine therapy is divided into initial therapy (years 1-5), extended adjuvant therapy (EAT, years 6-10+) and adjuvant endocrine-based treatment (years 1-2).**
- **Standard treatment duration is 5 years.**
- **Extended therapy and initial adjuvant endocrine-based therapy should be considered based on individual risks and benefits.**
- **Duration, choice & sequence of AI or Tam or the combination with GnRHa mainly depend on menopausal status, tolerability, and risk of recurrence.**
- **Switch to another better tolerated endocrine treatment (Tam or AI) or Tam low dose 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 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



Premenopausal Patients
Initial Adjuvant Endocrine Therapy (Year 1-5)

	Oxford LoE	Oxford 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 premopausal 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, Ambroisine L, Davidson N et al: Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in

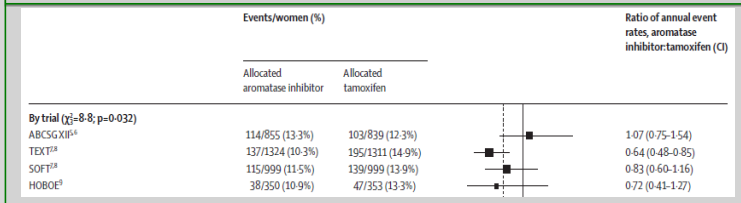
premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. Lancet 2007; 369:1711-23.

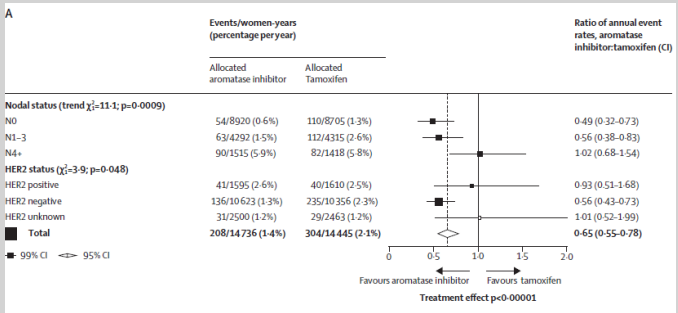
Ovarian function suppression (OFS) with Tam/AI and Tam with or without OFS:

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)





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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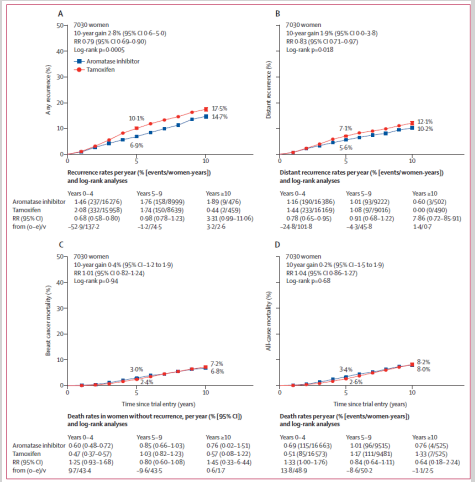
Any recurrence

Distant recurrence

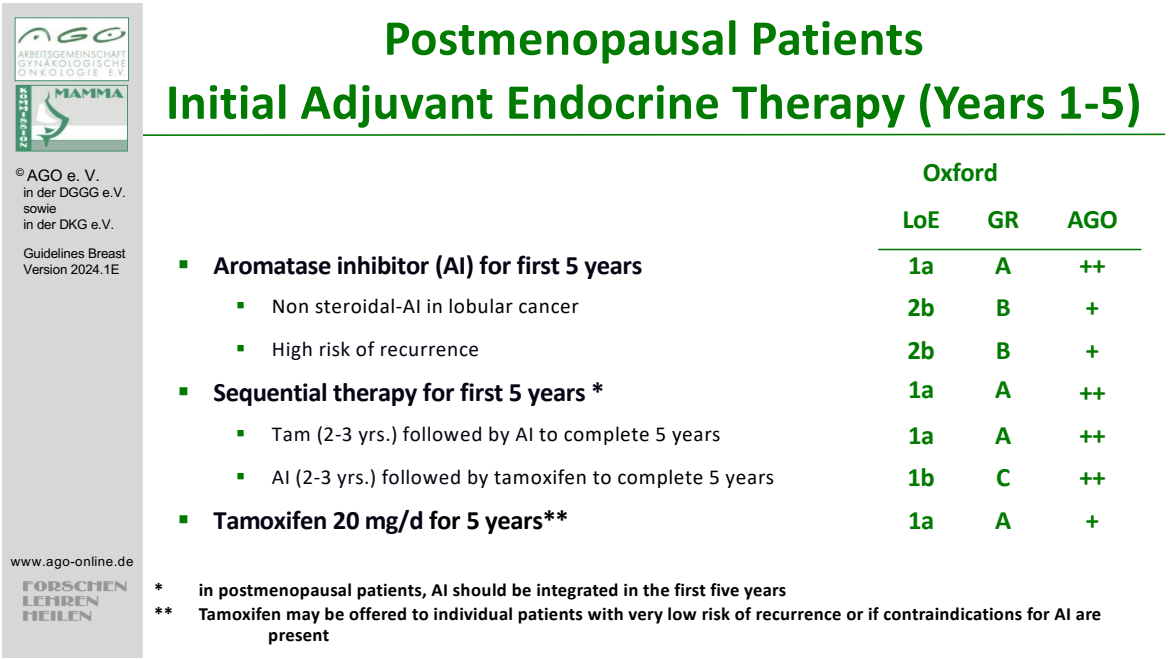


Breast cancer mortality

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



Postmenopausal Patients
Initial Adjuvant Endocrine Therapy (Years 1-5)

	Oxford LoE	Oxford GR	AGO
▪ **Aromatase inhibitor (AI) for first 5 years**	1a	A	++
▪ Non steroidal-AI in lobular cancer	2b	B	+
▪ High risk of recurrence	2b	B	+
▪ **Sequential therapy for first 5 years ***	1a	A	++
▪ Tam (2-3 yrs.) followed by AI to complete 5 years	1a	A	++
▪ AI (2-3 yrs.) followed by tamoxifen to complete 5 years	1b	C	++
▪ **Tamoxifen 20 mg/d for 5 years****	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**

<u>AI for first 5 years:</u>

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?

<u>Especially in case of lobular cancer</u>

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

<u>High risk of recurrence:</u>

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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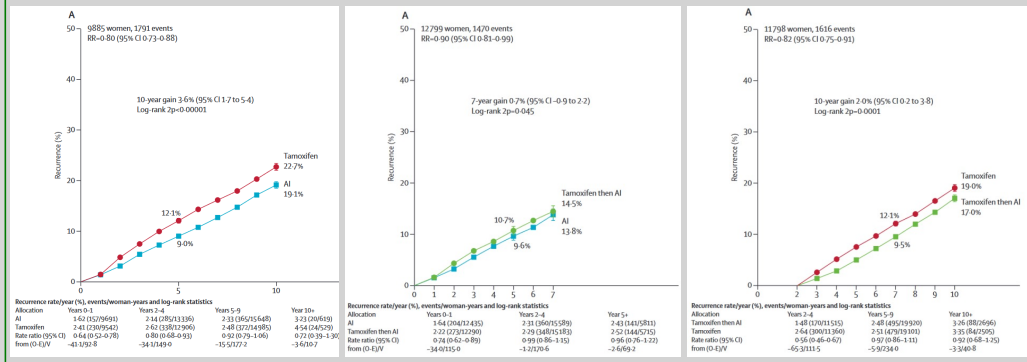

Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet. 2015 Oct 3;386(10001):1341-52.

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

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	Oxford		
	LoE	GR	AGO
In patients with increased risk of recurrence, characteristics and drug doses corresponding to study criteria			
▪ **Abemaciclib for 2 years***	1b	B	+
▪ **Olaparib for 1 year in patients with *gBRCA1/2* mutations****	1b	B	++

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

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
3. 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
4. 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
5. 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.
6. 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
7. Geyer CE, Garber JE, Gelber RD et al. Overall sirvival in the OlympiA phase III trial of adjuvant olaparib in patients with germ line

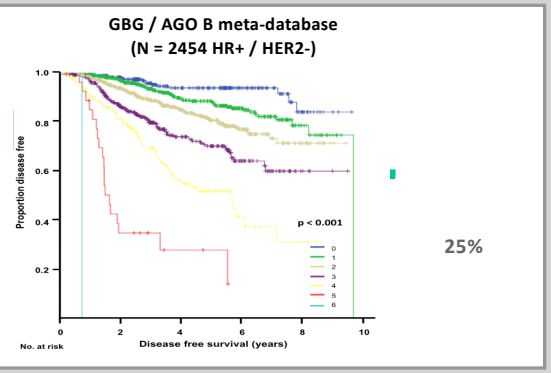
pathologic variants in BRCA1/2 and high-risk, early breast cancer. Ann Oncol 2023;33(12):1250-1268.
8. Hortobagyi G, Stroyakovsky D, Yardley D, et al. Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2− early breast cancer: final invasive disease–free survival (iDFS) analysis from the NATALEE trial. SABCS, 2023, GS03-03
9. Efficacy of adjuvant CDK4/6 inhibitors in hormone receptor-positive breast cancer: a systematic review and meta-analysis. Ergun Y, Dogan M, Ucar G, et al. Expert Opin Pharmacother. 2023 Sep-Dec;24(17):1901-1909. doi: 10.1080/14656566.2023.2258791. Epub 2023 Sep 13.
10. Rationale and trial design of NATALEE: a Phase III trial of adjuvant ribociclib + endocrine therapy versus endocrine therapy alone in patients with HR+/HER2- early breast cancer. Slamon DJ, Fasching PA, Hurvitz S, et al. Ther Adv Med Oncol. 2023 May 29;15:17588359231178125. doi: 10.1177/17588359231178125.
11. 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. Johnston SRD, Toi M, O'Shaughnessy J, et al; monarchE Committee Members. Lancet Oncol. 2023 Jan;24(1):77-90. doi: 10.1016/S1470-2045(22)00694-5.
12. Efficacy and safety results by menopausal status in monarchE: adjuvant abemaciclib combined with endocrine therapy in patients with HR+, HER2-, node-positive, high-risk early breast cancer. Paluch-Shimon S, Neven P, Huober J, et al. Ther Adv Med Oncol. 2023 Feb 3;15:17588359231151840. doi: 10.1177/17588359231151840.
13. Schäffler H, Mergel F, Pfister K et al. The Clinical Relevance of the NATALEE Study: Application of the NATALEE Criteria to a Real-World Cohort from Two Large German Breast Cancer Centers. Int J Mol Sci. 2023 Nov 15;24(22):16366. doi: 10.3390/ijms242216366.

How to calculate CPS+EG Score?

Guidelines Breast
Version 2024.1E

Point assignment for CPS+EG score

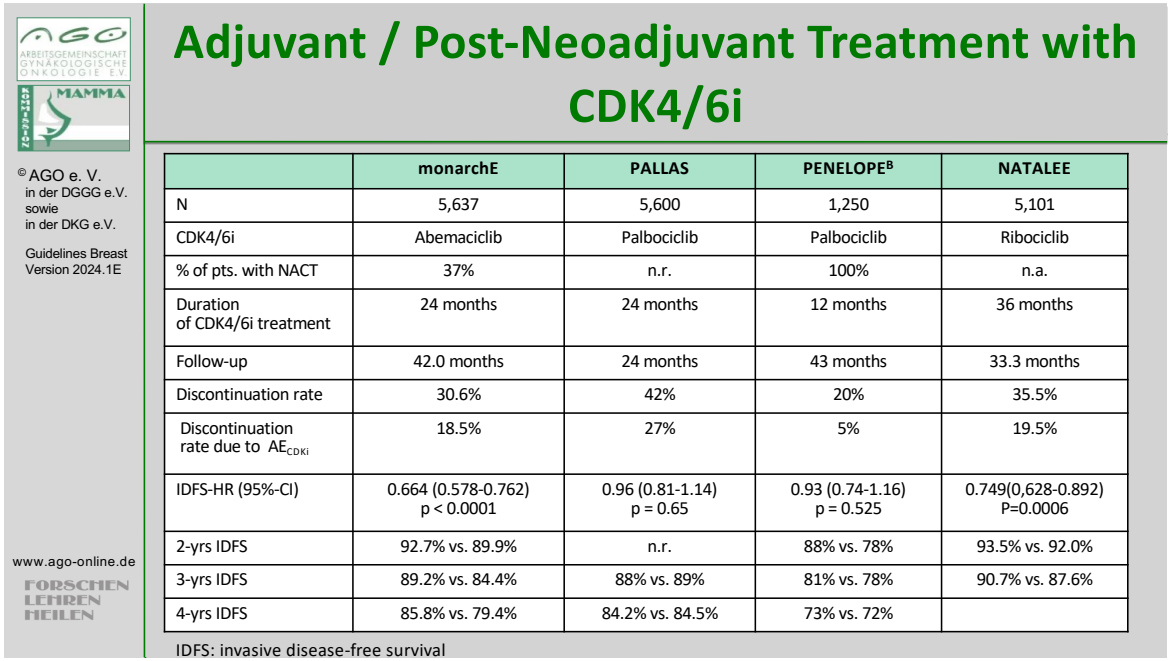
Clinical Stage		
I	0	T1N0; T0N1mi, T1N1mi
IIA	0	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2N2
IIIB	2	T4N0-2
Pathologic Stage		
0	0	T0/isN0
I	0	T1N0; T0N1mi, T1N1mi
IIA	1	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2 N2
IIIB	1	T4 N0-N2
Tumor Biologic Factors		
ER negative	1	
Nuclear grade 3	1	



25%

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.



1. Mayer EL, Gnant MI, DeMichele A et al. PALLAS: A randomized phase III trial of adjuvant palbociclib with endocrine therapy versus endocrine therapy alone for HR+/HER2- early breast cancer. Ann Oncol (2020) 31 (suppl_4): S1142-S1215. 10.1016/annonc/annonc325
2. 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
3. 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
4. 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
5. Johnston et al. SABCS 2022
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)

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**	**+**

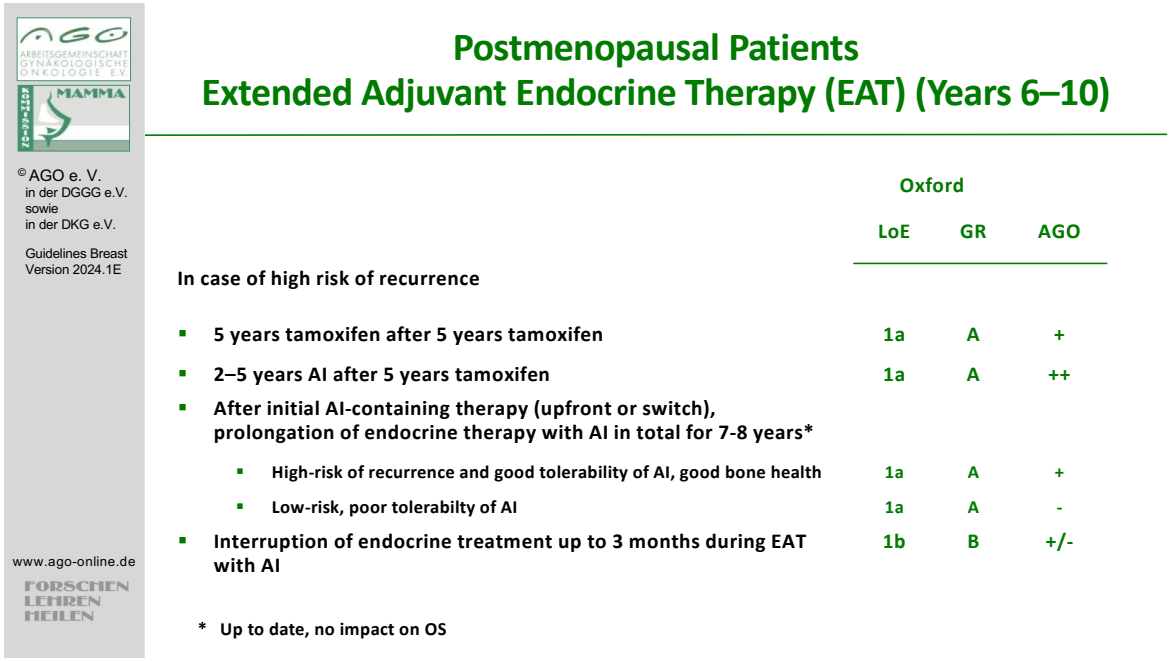
5 years Tamoxifen after 5 years Tamoxifen:

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)

In case of high risk of recurrence	Oxford LoE	Oxford GR	Oxford AGO
▪ 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 tolerabilty 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
5. 10 years or less of extended adjuvant endocrine therapy for postmenopausal breast cancer patients: A systematic review and network meta-analysis.Petrelli F, Cavallone M, Dottorini L.. Eur J Cancer. 2023 Nov;193:113322. doi: 10.1016/j.ejca.2023.113322.
6. Tailoring the optimal duration of the extended adjuvant endocrine therapy in patients with early-stage breast cancer. A systematic review and meta-analysis of randomized clinical trials. Pala L, De Pas T, Pagan E, et al. Breast. 2023 Jun;69:258-264. doi:

10.1016/j.breast.2023.02.012.

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-

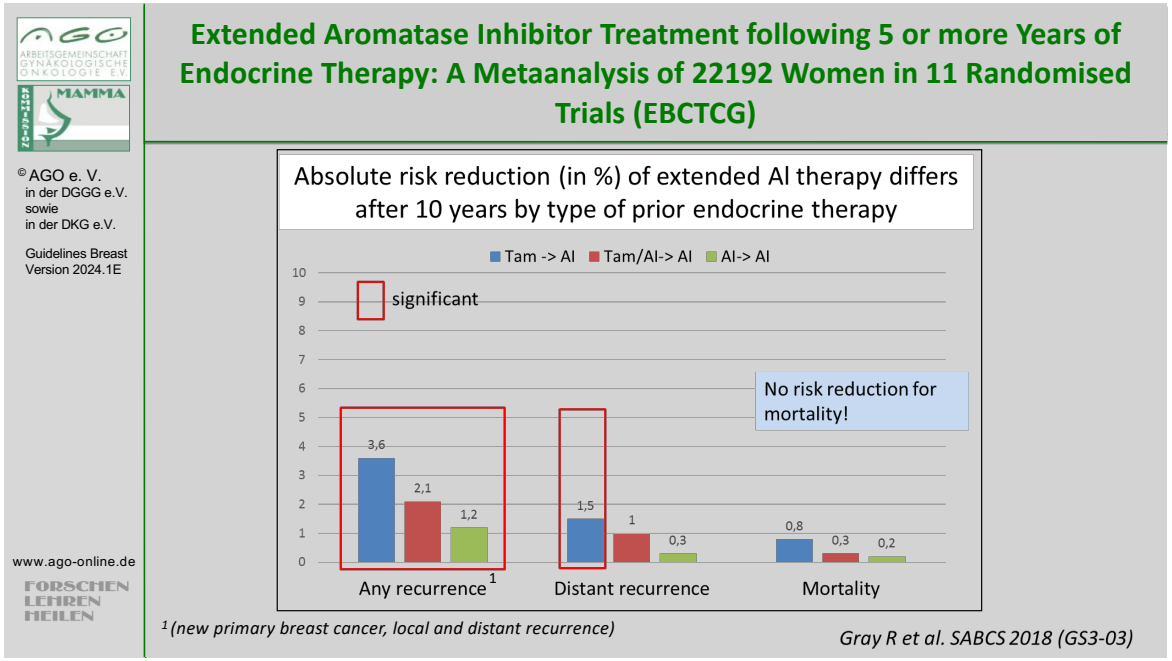
stage breast cancer: a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2021; 22: 1458–67
11. Mamounas EP, Bandos H: Ten year results from NRG/NSABP – B42: a randomized , double blinded placebo controlle clinical trial of extended adjuvant endocrine therapy with letrozole in postmenopuasal 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
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>

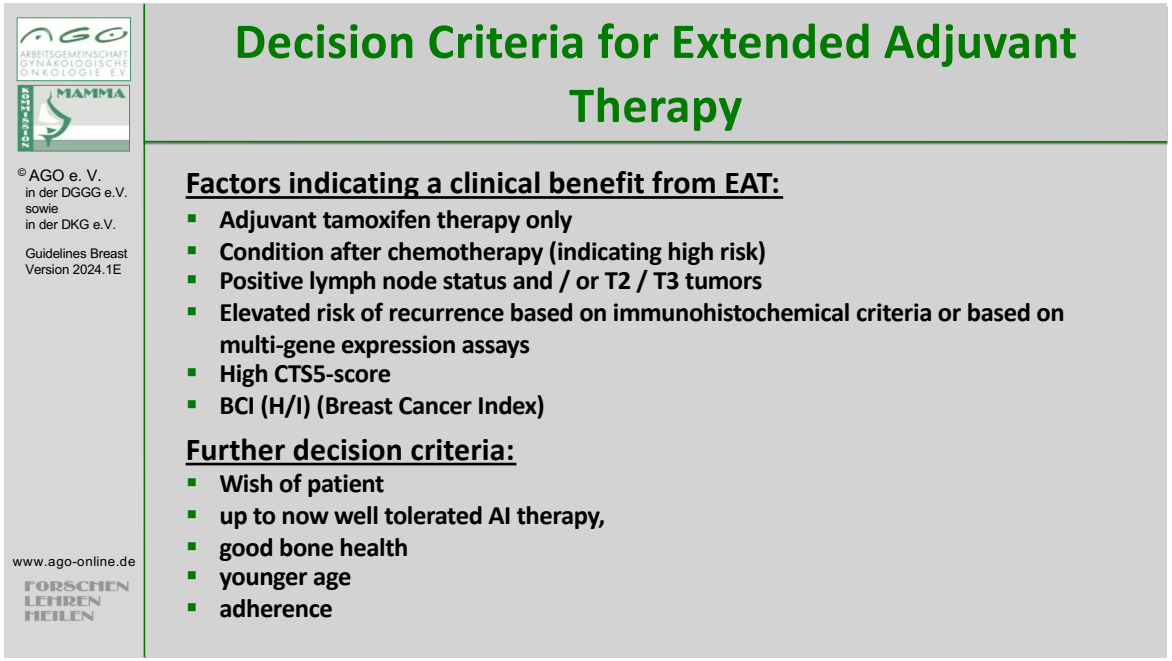
1. Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E et al. Optimal Duration of Extended Adjuvant Endocrine Therapy for early breast cancer; results of the IDEAL trial (BOOG 2006-05). J Natl Cancer Inst 2018;110(1): djx134
2. Mamounas EP, Bandos H, Lembersky BC et al. Use of letrozole after aromatase inhibitor-based 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



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 art 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.
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.

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

	Oxford		
	LoE	GR	AGO
▪ **CTx + GnRHa (preservation of ovarian function) (GnRHa application > 2 weeks prior to chemo-therapy, independent of hormone receptor status)**	1a	A	+
▪ **CTx + GnRHa (preservation of fertility)**	2a	B	+/-
▪ **Fertility preservation counselling including referral of all potential patients to appropriate reproductive specialists (ART; further information *https://fertiprotekt.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, 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.

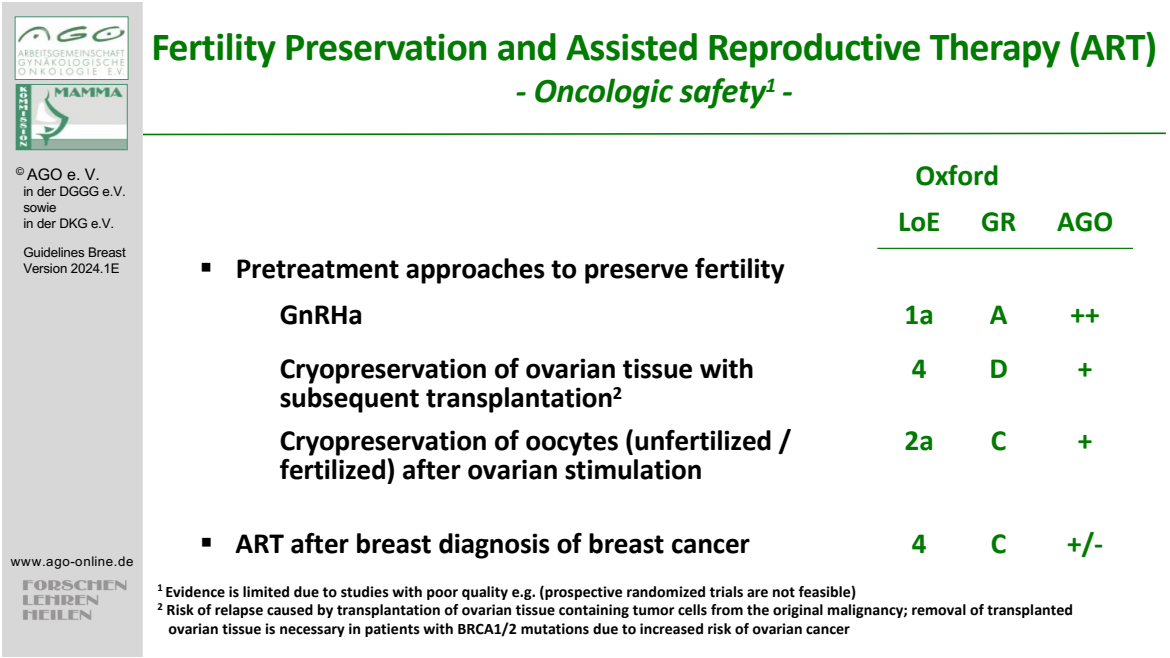
Ovarian function protection

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 safety[1] -

	Oxford LoE	Oxford GR	Oxford 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 breast diagnosis of breast cancer**	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-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.

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. 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.
2. 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.
3. 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.
4. 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;32(5):1033-1045. doi: 10.1093/humrep/dex027. PMID: 28333356.
5. Beebeejaun 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.
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
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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.

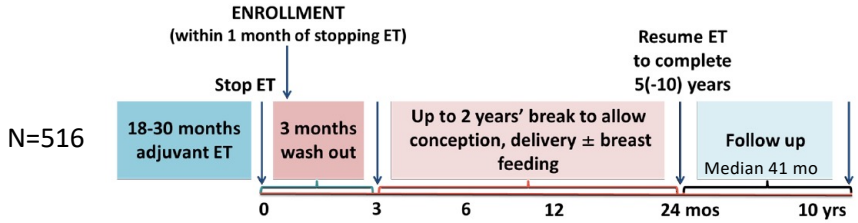
AGO +

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. 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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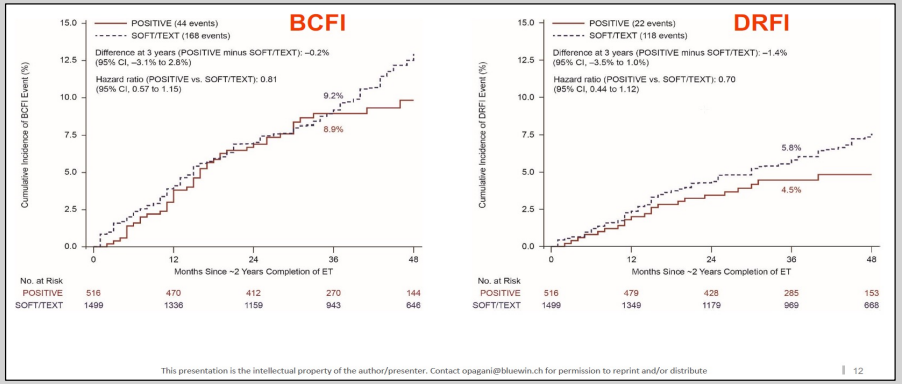
5. Partridge, A. on behalf of the POSITIVE Consortium: Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsIVE breast cancer Initial Results from the POSITIVE Trial (IBCSG 48-14 / BIG 8-13 / Alliance A221405), SABCS 2022
6. Interrupting Endocrine Therapy to Attempt Pregnancy 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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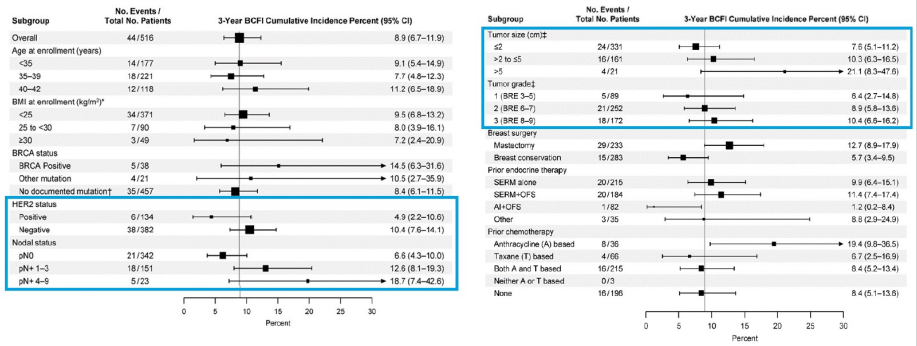
Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

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	6.6 (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)
Tumor size (cm)‡		
≤2	24/331	7.5 (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	1/82	1.2 (0.2–8.4)
Other	3/35	8.8 (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)

1. Ann Partridge on behalf of the POSITIVE Consortium: **P**regnancy **O**utcome and **S**afety of **I**nterrupting **T**herapy for women with endocrine respons**IVE** 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

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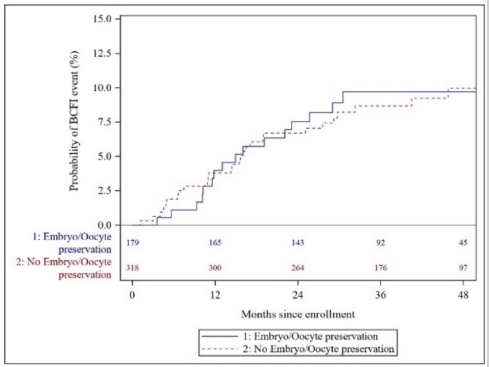
Ovarian stimulation and breast cancer outcome – results from the POSITIVE trial

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



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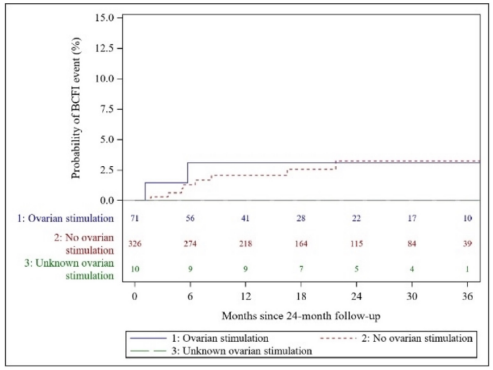
Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

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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