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Guidelines Breast
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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Adjuvant Endocrine-based Therapy in pre- and postmenopausal Patients



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Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

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Assessment of Steroid Hormone Receptor Status

Oxford LoE: 1 GR: A AGO: ++

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

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

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

Endocrine responsiveness:


1. Hammond ME , Hayes DF, Dowsett M et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol. 2010 Jun 1;28(16):2784-95. Review. Erratum in: J Clin Oncol. 2010 Jul 20;28(21):3543.
2. Early Breast Cancer Trialists Collaborative Group EBCTCG. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687–717.
3. Traub L, Thill M, Nitschmann S: 20-Jahres-Ergebnisse einer 5-jährigen Hormontherapie bei Mammakarzinom : Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Internist (Berl). Springer Medizin 2018;59(4):410–2.
4. Pan H, Gray R, Braybrooke J et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. N Engl J Med. 2017;377(19):1836–46.

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

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

98. J Clin Oncol 2007;25:3846-52.

2. Cserni G, Fracz M, Kalman E et al. Estrogen receptor negative and progesterone receptor positive breast carcinomas-how frequent are they? Pathol Oncol Res 2011;17:663-8.
3. Hefti MM, Hu R, 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: American Society of Clinical Oncology/College of American Pathologists Guideline Update." Arch Pathol Lab Med 144(5): 545-563.
6. 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			
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	LoE	GR	AGO
	Assessment of menopausal status:		
▪ Menstruation history			++
▪ FSH, E2			++


1. Ortmann O, Cufer T, Dixon JM et al. Adjuvant endocrine therapy for perimenopausal women with early breast cancer. Breast 2009;18(1):2-7.
2. Clemons M, Simmons C: Identifying menopause in breast cancer patients: considerations and implications. Breast Cancer Res Treat 2007;104(2):115-20.
3. Su HI, Sammel MD, Green J et al. Antimüllerian hormone and inhibin B are hormone measures of ovarian function in late reproductive-aged breast cancer survivors. Cancer 2010;116(3):592-9.
4. Partridge AH, Ruddy KJ, Gelber S et al. Ovarian reserve in women who remain premenopausal after chemotherapy for early stage breast cancer. Fertil Steril 2010;94(2):638-44.
5. Anders C, Marcom PK, Peterson B et al. A pilot study of predictive markers of chemotherapy-related amenorrhea among premenopausal women with early stage breast cancer. Cancer Invest 2008;26(3):286-95
6. Anderson RA, Cameron DA: Pretreatment serum anti-müllerian hormone predicts long-term ovarian function and bone mass after chemotherapy for early breast cancer. J Clin Endocrinol Metab 2011 96(5):1336-43.
7. Su HI, Chung K, Sammel MD et al. Antral follicle count provides additive information to hormone measures for determining ovarian function in breast cancer survivors. Fertil Steril 2011;95(5):1857-9.
8. 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 therapy:			
▪ Endocrine responsive	1a	A	++
▪ endocrine doubtful responsiveness	3b	D	+
▪ Endocrine therapy sequentially after CT	2a	B	+
▪ Endocrine therapy simultaneous to T-DM1 / anti-HER2 therapy (w/o chemotherapy)	2b	B	+
▪ Non-responsive: No endocrine therapy	1a	A	++

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

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

9. Villegas S, Lederer B: Similarities between low hormone receptor positive and hormone receptor negative breast cancer: an analysis of 4366 patients from multicenter clinical trials, SABCS 2018 P2-08-10
10. Chan, A., et al. (2016). "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* 17(3): 367-377.
11. von Minckwitz, G., et al. (2019). "Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer." *N Engl J Med* 380(7): 617-628.
12. von Minckwitz, G., et al. (2017). "Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer." *N Engl J Med* 377(2): 122-131
13. Early Breast Cancer Trialists' Collaborative, G. (2015). "Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials." *Lancet* 386(10001): 1341-1352.
14. 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



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General Principles in Adjuvant Endocrine Therapy AGO ++

- **Adjuvant endocrine therapy is divided into initial therapy (years 1-5) and extended adjuvant therapy (EAT, years 6-10+).**
- **Standard treatment duration is 5 years.**
- **Extended therapy should be considered based on individual risks and benefits.**
- **Duration, choice & sequence of AI or Tam mainly depend on menopausal status, tolerability, and risk of recurrence.**
- **Switch to another better tolerated endocrine treatment (Tam or AI) is better than stopping endocrine therapy altogether.**
- **AI should be used as first treatment in patients, especially 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 at 5 years. N Engl J Med 2017;1836-49.
8. Burstein HJ, Lacchetti C, Anderson H et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update. J Clin Oncol 2018 Nov 19;JCO1801160. doi: 10.1200/JCO.18.01160

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

NEU:

- CTS-5
- BCI (H/I)

Premenopausal Patients Initial Adjuvant Endocrine Therapy (Year 1-5)			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Low recurrence risk: <ul style="list-style-type: none"> Tamoxifen for 5 years 	1a	A	++
<ul style="list-style-type: none"> Increased recurrence risk: <ul style="list-style-type: none"> OFS 2-5 years* + tamoxifen for 5 years OFS# + AI for 5 years 	1a 1a	A A	++ ++
<ul style="list-style-type: none"> GnRHa monotherapie (Bei relevanten Kontraindikationen für Tam, gegenüber keiner Therapie) 	1a	B	+

OFS: ovarian function suppression;
 * as long as tolerated and the patient is clearly premenopausal after chemotherapy if ovarian function resumes within 24 months
 The application of chemotherapy in the trials served as surrogate for high recurrence risk
 # in premenopausal women AI only in combination with OFS

Tamoxifen 5-10 yrs:

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-717.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011;378:771-84.
3. Davies C, Pan H, Godwin J et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381:805-806.
4. Tormey DC, Gray R, Falkson HC: Postchemotherapy adjuvant tamoxifen therapy beyond five years in patients with lymph node-positive breast cancer. Eastern Cooperative Oncology Group. J Natl Cancer Inst 1996;88:1828-33.
5. Goel S, Sharma R, Hamilton A et al: LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. Cochrane Database Syst Rev. 20097;(4):CD004562.
6. Ruhstaller T, Giobbie-Hurder A: 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 JCO 37:105-114

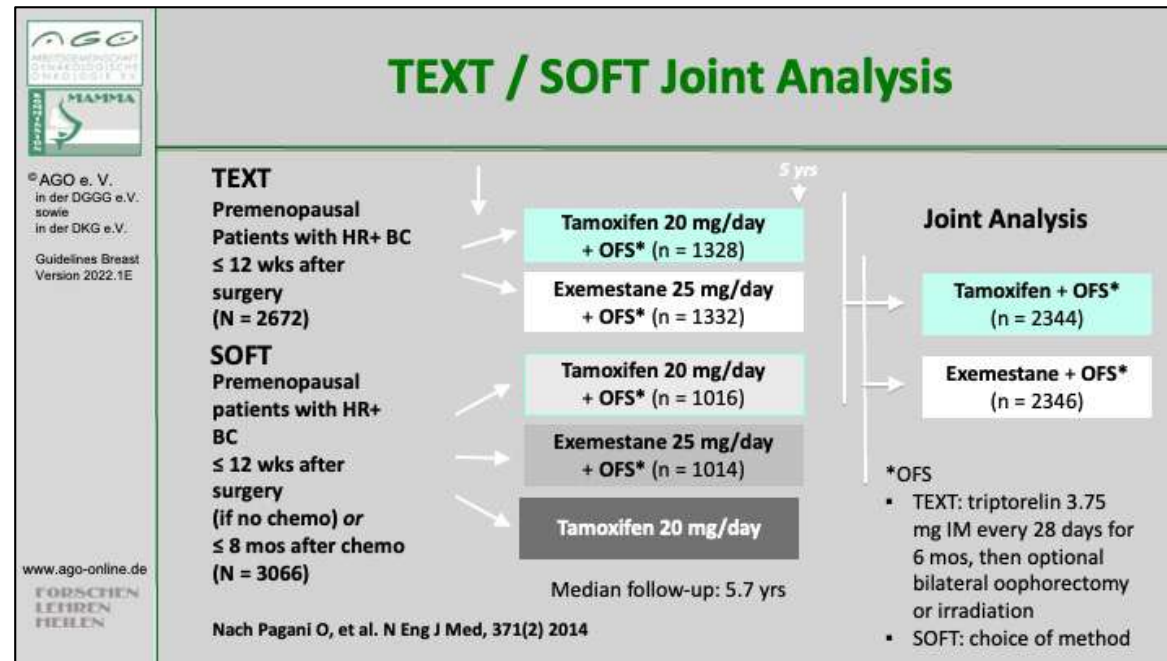
GnRH as monotherapy:

1. Cuzick J, Ambrosine L, Davidson N et al: Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. Lancet 2007; 369:1711-23.

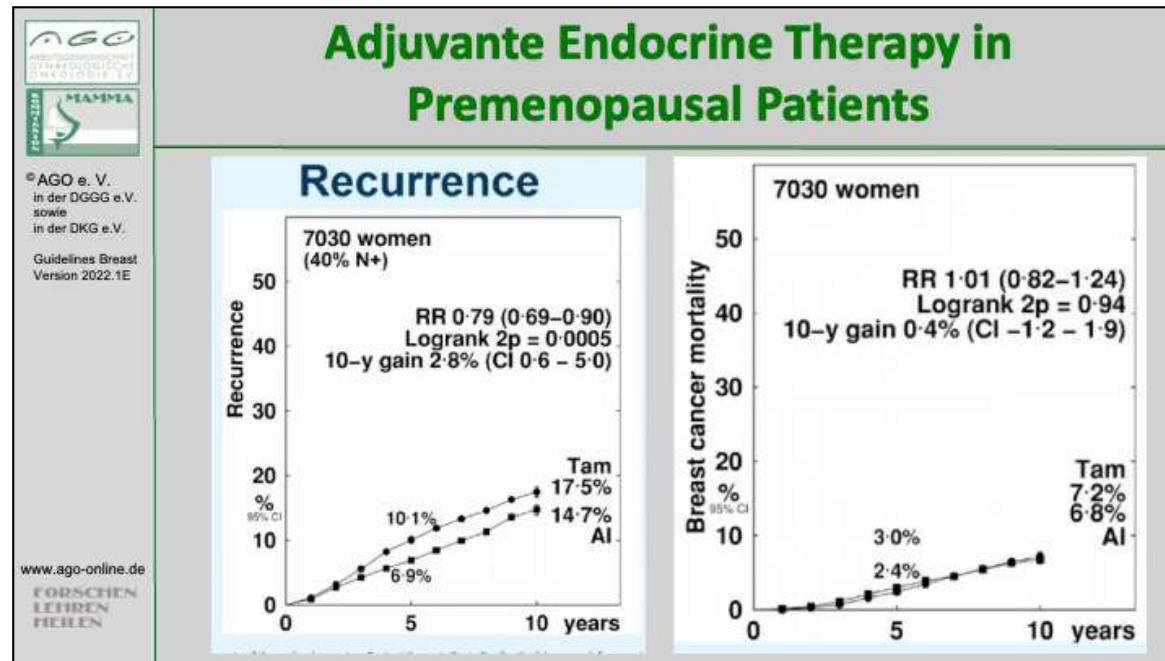
Ovarian function suppression (OFS) with Tam/AI and Tam with or without OFS:

1. 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;(4):CD004562.
2. Francis PA, Regan MM, Fleming GF et al. The SOFT Investigators and the International Breast Cancer Study Group. Adjuvant Ovarian Suppression in Premenopausal Breast Cancer. N Engl J Med 2015;372(5):436-46.
3. Pagani O, Regan MM, Walley BA et al. TEXT and SOFT Investigators; International Breast Cancer Study Group. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med 2014;371(2):107-18.
4. 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.
5. 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.
6. JSaha P, Regan MM, Pagani O: Treatment efficacy, adherence, and quality of life among younger than 35 years in the International Breast Cancer Study Group TEXT and SOFT adjuvant endocrine therapy trial. J Clin Oncol 2017;35:3113-3122.
7. Francis PA, Pagani O, Fleming GF et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. N Engl J Med 2018; 379: 122-137
8. 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>
9. 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.

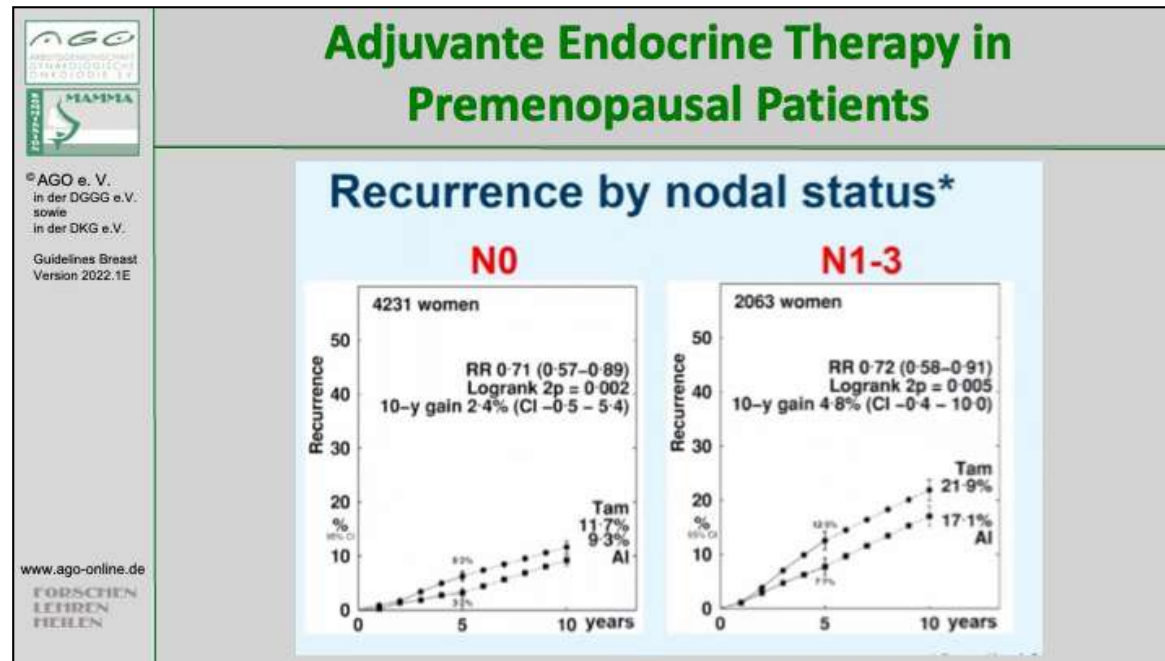
10. Regan MM, Walley BA, Fleming GF et al. Randomized comparisons of adjuvant exemestane + ovarian function suppression versus Tamoxifen + OFS versus tamoxifen in premenopausal women with HR + early breast : update of the TEXT and SOFT trials. SABCS 2021, GS2-05.



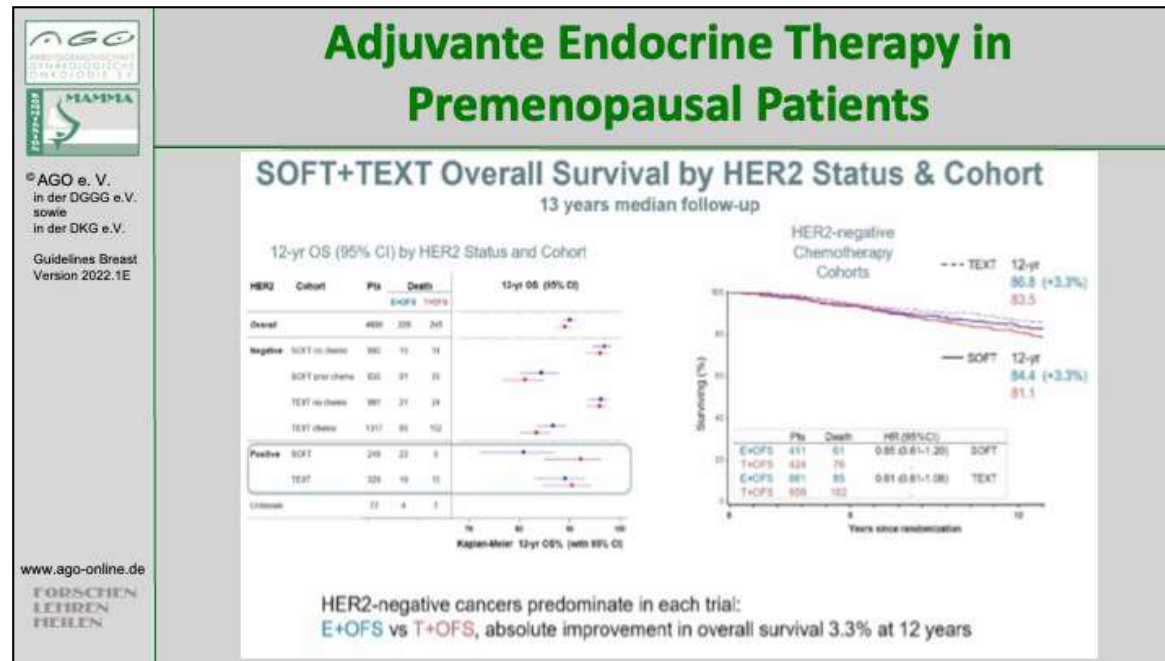
1. Pagani O, Gelber S, Colleoni M, et al. Impact of SERM adherence on treatment effect: International Breast Cancer Study Group Trials 13-93 and 14-93. Breast Cancer Res Treat 2013;142(2):455-9.
2. Francis PA, Regan MM, Fleming GF et al. The SOFT Investigators and the International Breast Cancer Study Group. Adjuvant Ovarian Suppression in Premenopausal Breast Cancer. N Engl J Med 2015;372(5):436-46.
3. 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.



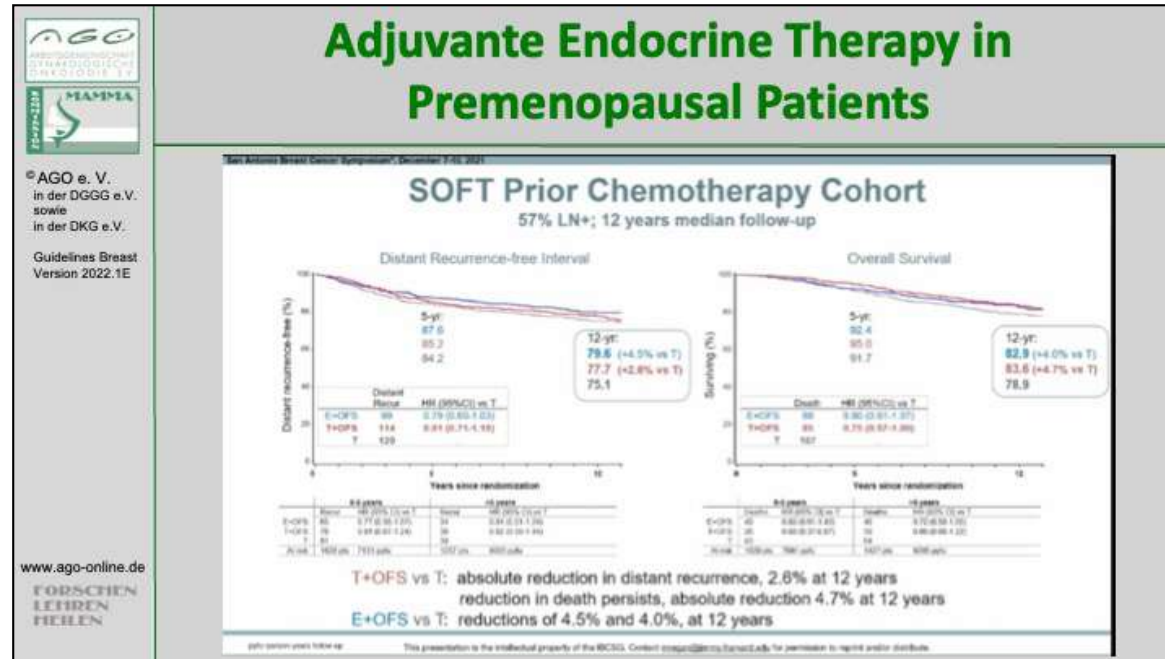
1. Bradley R, Braybrooke J, Gray R et al. Aromatase Inhibitors versus Tamoxifen in premenopausal women with ER + early stage breast cancer treated with ovarian suppression: A patient level meta-analysis of 7.030 women in four randomised trials. SABCS 2021, GS2-04.



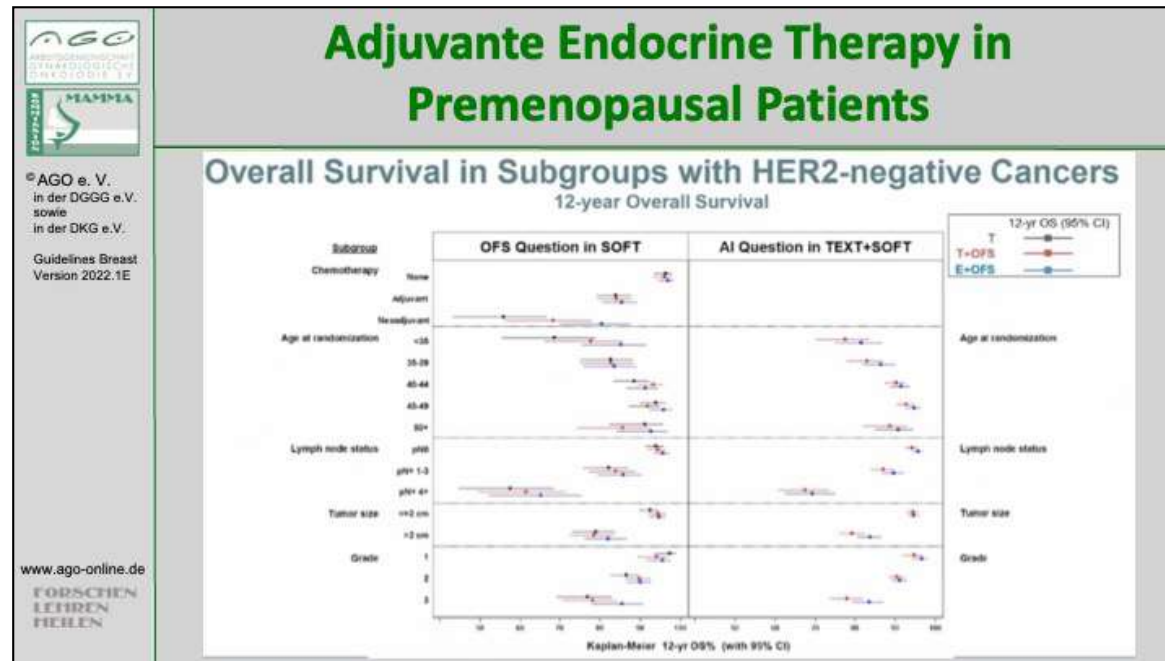
1. Bradley R, Braybrooke J, Gray R et al. Aromatase Inhibitors versus Tamoxifen in premenopausal women with ER + early stage breast cancer treated with ovarian suppression: A patient level meta-analysis of 7.030 women in four randomised trials. SABCS 2021, GS2-04.



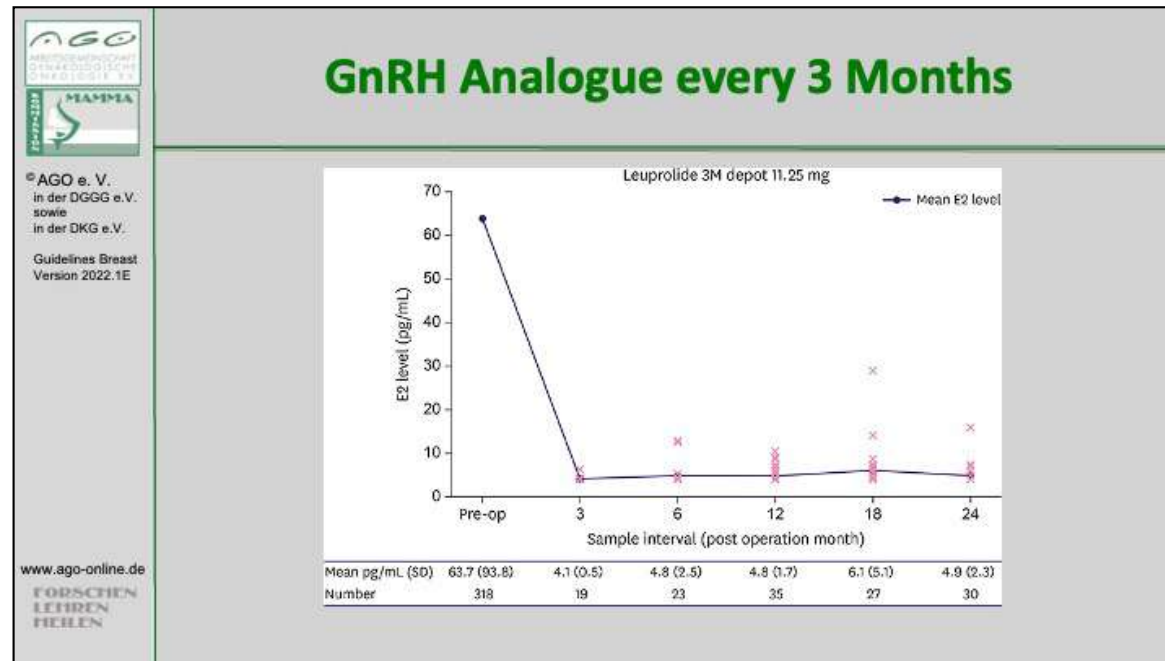
1. Bradley R, Braybrooke J, Gray R et al. Aromatase Inhibitors versus Tamoxifen in premenopausal women with ER + early stage breast cancer treated with ovarian suppression: A patient level meta-analysis of 7.030 women in four randomised trials. SABCS 2021, GS2-04.



1. 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.



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.



1. Schmid P, Untch M, Kossé V, et al. Leuporelin acetate every-3-months depot versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant treatment in premenopausal patients with node-positive breast cancer: the TABLE study. J Clin Oncol 2007;25:2509-15.
2. Masuda N, Iwata H, Rai Y, et al. Monthly versus 3-monthly goserelin acetate treatment in pre-menopausal patients with estrogen receptor-positive early breast cancer. Breast Cancer Res Treat 2011;126:443-51.
3. Bellet M, Gray KP, Francis PA, et al. Twelve-month estrogen levels in premenopausal women with hormone receptor-positive breast cancer receiving adjuvant triptorelin plus exemestane or tamoxifen in the Suppression of Ovarian Function Trial (SOFT): the SOFT-EST substudy. J Clin Oncol 2016;34:1584-93.
4. Young-Jin L et al. Change in estradiol levels among premenopausal patient with breast cancer treated using leuprolide acetate 11.25mg 3months depot and tamoxifen. J Breast Cancer. 2020 Oct;23(5):553-559. <https://doi.org/10.4048/jbc.2020.23.e57>

Postmenopausal Patients Initial Adjuvant Endocrine Therapy (Years 1-5)			
	Oxford		
	LoE	GR	AGO
▪ Aromatase inhibitor (AI) for first 5 years			
▪ Non steroidal-AI in lobular cancer	1a	A	++
▪ High risk of recurrence	2b	B	+
▪ Sequential therapy for first 5 years *			
▪ 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

AI for first 5 years:

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

Especially in case of lobular cancer

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

High risk of recurrence:

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Aromatase inhibitors versus tamoxifen in early breast cancer: patient-

level meta-analysis of the randomised trials. Lancet 2015;386(10001):1341-52.

Sequential therapy for first 5 years:

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

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

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 2015;386(10001):1341-52.
2. Rydén L, Heibert Arnlin M, Vitols S et al. Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials. Breast 2016;26:106-14.
3. Derks MGM, Blok EJ, Seynaeve C et al. Adjuvant tamoxifen and exemestane in women with postmenopausal early breast cancer (TEAM): 10-year follow-up of a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2017;18:1211-1220.
4. Ruhstaller T, Giobbie-Hurder A, Colleoni M et al. Adjuvant letrozole and tamoxifen alone or sequentially for postmenopausal women with hormone receptor-positive breast cancer: long-term follow-up of the BIG 1-98 trial. J Clin Oncol 2019;37(2):105-114.
5. De Placido S, Gallo C, De Laurentiis M, et al. GIM Investigators. Adjuvant anastrozole versus exemestane versus letrozole, upfront or after 2 years of tamoxifen, in endocrine-sensitive breast cancer (FATA-GIM3): a randomised, phase 3 trial. Lancet Oncol. 2018 Apr;19(4):474-485.

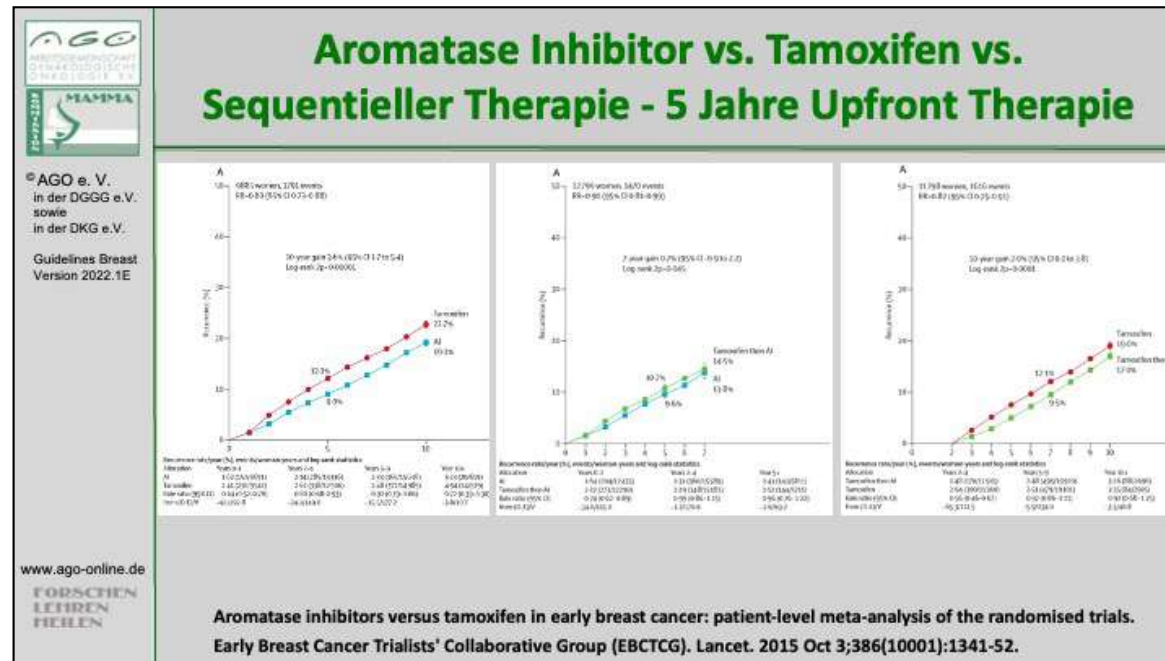
Tamoxifen 20 mg/d for first 5 yrs:

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

clinical trials. Breast. 2016;26:106-14.

Patient care/ adherence and side effects

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



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

Adjuvante Endocrine-Based Therapy with CDK4/6 Inhibitors and PARP Inhibitors			
	Oxford		
	LoE	GR	AGO
In patients with increased risk of recurrence and characteristics corresponding to study criteria			
■ Abemaciclib for 2 years*	1b	B	+
■ Olaparib for 1 year in patients with <i>gBRCA1/2</i> mutations**	1b	B	+
■ Palbociclib for 1-2 years	1b	B	-

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. 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

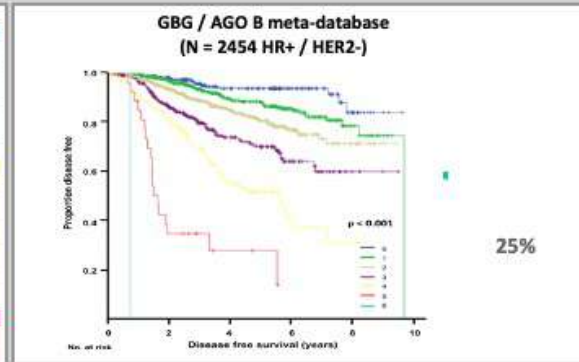


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How to calculate CPS+EG Score?

Point assignment for CPS+EG score			
Clinical Stage			
I	0	T1N0, T0N0m, T1N0m	
IIA	0	T0N1, T1N1, T1N0	
II	1	T2N1, T2N0	
IIIA	1	T0-2N2	
IIIB	2	T4N0-2	
IVC	2	Any T N3	
Pathologic Stage			
0	0	T1u/1N0	
I	0	T1N0, T0N1m, T1N1m	
IIA	1	T0N1, T1N1, T1N0	
II	1	T2N1, T2N0	
IIIA	1	T0-2 N2	
IIIB	2	T4 N0-2	
IVC	2	Any T N3	
Tumor Biologic Factors			
ER negative	1		
Nuclear grade 3	1		



Mittendorf EA, J Clin Oncol 2011;
Marmé F, et al. Eur J Cancer 2016



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CDK4/6 Inhibitors in Addition to Standard Endocrine Therapy in the Adjuvant / Post-Neoadjuvant Situation

	monarchE	PALLAS	PENELOPE ^B
N	5,637	5,600	1,250
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib
% of pts. with NACT	37%	n.r.	100%
Duration of CDK4/6i treatment	24 mths	24 mths	12 mths
Follow-up	27.1 mths	24 mths	43 mths
Discontinuation rate	28%	42%	20%
Discontinuation rate due to AE _{CDKi}	17%	27%	5%
IDFS-HR (95%-CI)	0.70 (0.58-0.82) p<0.0001	0.96 (0.81-1.14) p=0.65	0.93 (0.74-1.16) p=0.525
2-yrs IDFS	92.7% vs. 90.0%	n.r.	88% vs. 78%
3-yrs IDFS	88.8% vs. 83.4%	88% vs. 89%	81% vs. 78%
4-yrs IDFS	n.r.	84.2% vs. 84.5%	73% vs. 72%

IDFS: invasive disease-free survival

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

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 years AI after 5 years tamoxifen in initially premenopausal patients who obtain validated postmenopausal status during course of therapy	1b	B	+
▪ 5 years tamoxifen after 5 years of endocrine therapy + OFS	5	D	+

5 years Tamoxifen after 5 years Tamoxifen:

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

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

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

2. Jin H, Tu D, Zhao N et al. Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover. J Clin Oncol 2012;30(7):718-21
3. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update. J Clin Oncol. 2014;32(21):2255-69.

Postmenopausal Patients Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)			
	Oxford		
	LoE	GR	AGO
In case of high risk of recurrence			
▪ 5 years tamoxifen after 5 years tamoxifen	1a	A	+
▪ 2–5 years AI after 5 years tamoxifen	1a	A	++
▪ After initial AI-containing therapy (upfront or switch), prolongation of endocrine therapy with AI for 2–5 years*			
▪ High-risk and good tolerability of AI	1a	A	+
▪ Low-risk, poor tolerability of AI	1a	A	-
▪ Interruption of endocrine treatment up to 3 months during EAT with AI	1b	B	+/-
* Up to date, no impact on OS			

5 years Tamoxifen after 5 years Tamoxifen:

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

2–5 years AI after 5 years Tamoxifen

1. Goss PE, Ingle JN, Martino S et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005;97(17):1262-71.
2. Jin H, Tu D, Zhao N et al. Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover. *J Clin Oncol* 2012;30(7):718-21.
3. Jakesz R, Greil R, Gnant M et al. Austrian Breast and Colorectal Cancer Study Group. Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. *J Natl Cancer Inst*. 2007;99(24):1845-53. Erratum in: *J Natl Cancer Inst* 2008;100(3):226.
4. Mamounas EP, Jeong JH, Wickerham DL et al. Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial. *J Clin Oncol* 2008;26(12):1965-71.
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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.
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

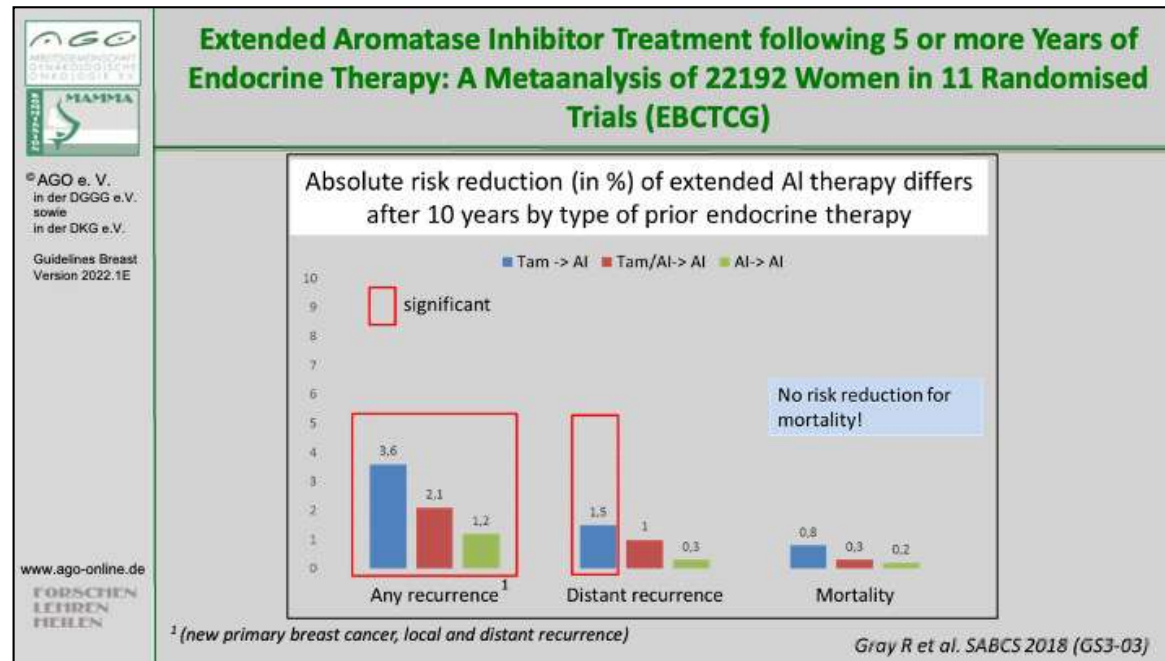
11. Mamounas EP, Bandos H: Ten year results from NRG/NSABP – B42: a randomized , double blinded placebo controlled clinical trial of extended adjuvant endocrine therapy with letrozole in postmenopausal women with hormone receptor + breast cancer who have completed previous adjuvant therapy with an aromatase inhibitor after initial AI containing therapy (upfront or switch) further prolongation of endocrine therapy with AI 2-5years. SABCS 2019, GS4-01

low risk, poor tolerability of the AI

1. Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E et al. Optimal Duration of Extended Adjuvant Endocrine Therapy for early breast cancer; results of the IDEAL trial (BOOG 2006-05). J Natl Cancer Inst 2018;110(1): dx134
2. Mamounas EP, Bandos H, Lembersky BC et al. Use of letrozole after aromatase inhibitor-based therapy in postmenopausal breast cancer (NRG Oncology/NSABP B-42): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20(1):88-99.
3. Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM et al. Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial. Lancet Oncol 2017;18(11):1502-1511.
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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



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Extended Adjuvant Treatment, Overview

Studie	Therapien												De-facto- Vergleich e (Jahre)	HR für DFS	AI- Therapie Jahre 6- 9 (%)	Braun: Tamoxifen Grün: Tamoxifen oder AI Blaue: AI Gestreift: Zeit der randomisierten Intervention vs keine Therapie od. Plazebo *: Rando- misierungs- zeitpunkt § : MA17R nach 5 Jahren AI mit /ohne Tam zuvor
Jahre nach Diagnose	1	2	3	4	5	6	7	8	9	10	11	12				
Studien mit Tamoxifen nach 5 Jahren Tamoxifen																
ATLAS					*								5 vs 10	0,75 - 0,93	0	
ATTOM					*								5 vs 10	0,75 - 0,93	0	
Studien mit AI nach 5 Jahren Tamoxifen																
MA 17					*								5 vs 10	0,57	0	
NSABP B-33					*								5 vs 10	0,68	0	
ABCSG 6a					*								5 vs 8	0,62	0	
Studien mit anreicherter AI-Th. Nach 5 Jahren endokrin inkl. AI																
DATA				*									6 vs 9	0,79	100	
NSABP B-42				*									5 vs 10	0,85	100	
QM 4													5 vs 7	0,78	100	
MA 17R													10 vs 15	0,66	100	
Studien bzgl. optimaler Dauer in Jahr 5-10																
BOCG 2005- 05 IDEAL					*								7,5 vs 10	0,92	88	
ABCSG 16					*								7 vs 10	1,007	49	
SOLE													Cont vs unsteril	1,08	81	



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Decision Criteria for Extended Adjuvant Therapy

Factors indicating a clinical benefit from EAT:

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

Further decision criteria:

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

1. Gnant M, G Steger, R Greil, et al. A prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years of Anastrozole after initial 5 years of adjuvant endocrine therapy - results from 3,484 postmenopausal women in the ABCSG-16 trial. SABCS 2017; GS3-01
2. Li L, Chang B, Jiang X et al. Clinical outcomes comparison of 10 years versus 5 years of adjuvant endocrine therapy in patients with early breast cancer. Clinical outcomes comparison of 10 years versus 5 years of adjuvant endocrine therapy in patients with early breast cancer. BMC Cancer 2018;18:977
3. Goldvaser H, Barnes TA, Šeruga B, et al. Toxicity of extended adjuvant therapy with aromatase inhibitors in early breast cancer: a systematic review and meta-analysis. J Natl Cancer Inst 2018;110(1)djx141
4. van Hellemond I, Geurts SME, Tjan-Heijnen VCG: Current status of extended adjuvant endocrine therapy in early stage breast cancer. Curr Treat Options in Oncol 2018;19:26.
5. Pan H, Gray R, Braybrooke J et al. 20-year risks of breast recurrence after stopping endocrine therapy at 5 years. N Engl J Med 2017;1836-49.
6. Munzone E, Colleoni M: Optimal management of luminal breast cancer: how much endocrine therapy is long enough? Ther Adv Med Oncol 2018;10: 1–11.
7. Dowsett M, Sestak I, Regan MM et al. Integration of clinical variables for the prediction of late distant recurrence in patients with estrogen receptor–positive breast cancer treated with 5 years of endocrine therapy: CTS5. J Clin Oncol 2018 : 36(19): 1941–1948.

8. Sestak I, Buus R, Cuzick J et al. Comparison of the performance of 6 prognostic signatures for estrogen receptor–positive breast cancer: a secondary analysis of a randomized clinical trial. *JAMA Oncol* 2018; 4(4): 545–553.
9. Burstein HJ, Lacchetti C, Anderson H et al. Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer: ASCO clinical practice guideline focused update. *J Clin Oncol*. 2018 Nov 19;JCO1801160. doi: 10.1200/JCO.18.01160
10. Bartlett J, Sgroi DTrans-aTTom: Breast Cancer Index predicts benefit of extended endocrine therapy in HR+ breast cancers treated in the adjuvant tamoxifen-to offer meore (aTTom) trial Abstract 505 ASCO 2019
11. Dennis C Sgroi, et al. Correlative studies of the breast cancer index (HOXB13/IL17BR) and ER, PR, AR, AR/ER ratio and Ki67 for prediction of extended endocrine benefit: A trans-aTTom study, SABCS 2020; GS4-09.

Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT)			
	Oxford LoE	GR	AGO
<p>■ Fertility preservation counselling including referral of all potential patients to appropriate reproductive specialists (further information https://fertiprotekt.com/english)</p>			++
<p>■ CTx + GnRHα (preservation of ovarian function) (GnRHα application > 2 weeks prior to chemotherapy, independent of hormone receptor status)</p>	1a	A	+
<p>■ CTx + GnRHα (preservation of fertility)</p>	2a	B	+/-

Ovarian function protection

1. Gerber B, von Minckwitz G, Stehle H et al.: Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. J Clin Oncol. 2011 Jun 10;29(17):2334-41.
2. 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.
3. Del Mastro L, Rossi G, Lambertini M et al.: New insights on the role of luteinizing hormone releasing hormone agonists in premenopausal early breast cancer patients. Cancer Treat Rev. 2016 Jan;42:18-23.
4. Munholz RR, et al: Gonadotropin-Releasing hormone agonists for ovarian function preservation in premenopausal women undergoing chemotherapy for early stage breast cancer- A systematic Review and Meta Analysis. JAMA Oncol 2016;2:65-73
5. Munster PN, Moore AP, Ismail-Khan R et al.: Randomized Trial Using Gonadotropin-Releasing Hormone Agonist Triptorelin for the Preservation of Ovarian Function During (Neo)Adjuvant Chemotherapy for Breast Cancer. J Clin Oncol. 2012;30(5):533–8.
6. 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.
7. 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

8. Elgindy E, Sibai H, Abdelghani A et al.: Protecting Ovaries During Chemotherapy Through Gonad Suppression: A Systematic Review and Meta-analysis. *Obstet Gynecol*. 2015;126(1):187–95.
9. Sun X, Dongol S, Jiang J et al.: Protection of ovarian function by GnRH agonists during chemotherapy: a meta-analysis. *Int J Oncol*. 2014;44(4):1335–40.

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.

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.

Fertility preservation with assisted reproduction therapy

1. Dittrich R, Hackl J, Lotz L et al.: Pregnancies and live births after 20 transplantations of cryopreserved ovarian tissue in a single center. *Fertil Steril*. 2015 Feb;103(2):462-8.
2. Gamzatova Z, Komlichenko E, Kostareva A et al.: Autotransplantation of cryopreserved ovarian tissue--effective method of fertility preservation in cancer patients. *Gynecol Endocrinol*. 2014 Oct;30 Suppl 1:43-7.

3. Goldrat O, Kroman N, Peccatori FA et al.: Pregnancy following breast cancer using assisted reproduction and its effect on long-term outcome. *Eur J Cancer*. 2015;51(12):1490–6.
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5. 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.
6. 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.

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

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

	Control	GnRH	HR (95%-CI)	P-value
POI ^{1,2}	30.9%	14.1%	0.38; 0.26 to 0.57	< 0.001

¹ premature ovarian insufficiency

² different definitions and time points were used

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

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

Lambertini M et al. J Clin Oncol 2018

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. doi: 10.1200/JCO.2018.78.0858.