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Guidelines Breast  
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## Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

### Adjuvante endokrin-basierte Therapie bei prä- und postmenopausalen Patientinnen



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## Adjuvante endokrine Therapie bei prä- und postmenopausalen Patientinnen

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## Bestimmung des Steroid-Hormonrezeptorstatus

Oxford LoE: 1 GR: A AGO: ++

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

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

**Bei ER negativ / PR positiv (> 10 % Zellen): immunhistochemische Reevaluation erforderlich**

### 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.
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## Adjuvante endokrine Therapie

### Bestimmung des Menopausenstatus

	Oxford	
	LoE	GR
<b>Bestimmung des Menopausenstatus:</b>		
▪ Menstruationsanamnese		++
▪ 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.



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## Adjuvante endokrine Therapie

	Oxford		
	LoE	GR	AGO
▪ <b>Endokrin sensitiv</b>	<b>1a</b>	<b>A</b>	<b>++</b>
▪ <b>fraglich endokrin sensitiv</b>	<b>3b</b>	<b>D</b>	<b>+</b>
▪ <b>Endokrine Therapie sequentiell: nach einer adjuvanten Chemotherapie</b>	<b>2a</b>	<b>B</b>	<b>+</b>
▪ <b>Endokrine Therapie simultan mit T-DM1 / Anti- HER2-Therapie ohne Chemotherapie</b>	<b>2b</b>	<b>B</b>	<b>+</b>
▪ <b>Nicht endokrin sensitiv: keine endokrine Therapie</b>	<b>1a</b>	<b>A</b>	<b>++</b>

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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## Generelle Prinzipien der adjuvanten endokrinen Therapie AGO ++

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

1. Ingle JN: Overview of adjuvant trials of aromatase inhibitors in early breast cancer. *Steroids* 2011;76(8):765-7.
2. Higgins MJ, Liedke PE, Goss PE et al. Extended adjuvant endocrine therapy in hormone dependent breast cancer: the paradigm of the NCIC-CTG MA.17/BIG 1-97 trial. *Crit Rev Oncol Hematol* 2013;86(1):23-32.
3. Regan MM, Neven P, Giobbie-Hurder A et al. BIG 1-98 Collaborative Group; International Breast Cancer Study Group (IBCSG). Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8.1 years median follow-up. *Lancet Oncol* 2011;12(12):1101-8.
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet* 2015;386(10001):1341-52.
5. Rydén L, Heibert Arnlind M, Vitols S et al. Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials. *Breast* 2016;26:106-140.
6. Goss PE, Ingle JN, Pritchard KI et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. *N Engl J Med* 2016;375(3):209.
7. Pan H, Gray R, Braybrooke J et al. 20-year risks of breast recurrence after stopping endocrine therapy 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)

Adjuvante endokrine Therapie bei prämenopausalen Patientinnen (Jahr 1–5)			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>■ <b>Niedriges Rezidivrisiko:</b> <ul style="list-style-type: none"> <li>■ Tamoxifen für 5 Jahre</li> </ul> </li> </ul>	1a	A	++
<ul style="list-style-type: none"> <li>■ <b>Erhöhtes Rezidivrisiko:</b> <ul style="list-style-type: none"> <li>■ OFS 2-5 Jahre* + Tamoxifen für 5 Jahre</li> <li>■ OFS# + AI für 5 Jahre</li> </ul> </li> </ul>	1a	A	++
<ul style="list-style-type: none"> <li>■ <b>GnRHa Monotherapie</b> (Bei relevanten Kontraindikationen für Tam, gegenüber keiner Therapie)</li> </ul>	1a	B	+
<p>OFS: Ovarialfunktions-Suppression;            * Behandlung nur solange sie tolerabel ist und die Pat. eindeutig prämenopausal ist            Bei Z.n. Chemotherapie bei Wiedereintritt der Ovarialfunktion innerhalb von 24 Monaten            Die Applikation einer Chemotherapie war in den Studien ein Surrogatmarker für hohes Rezidivrisiko            # AI NUR in Kombination mit OFS bei prämenopausalen Patientinnen</p>			

#### 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

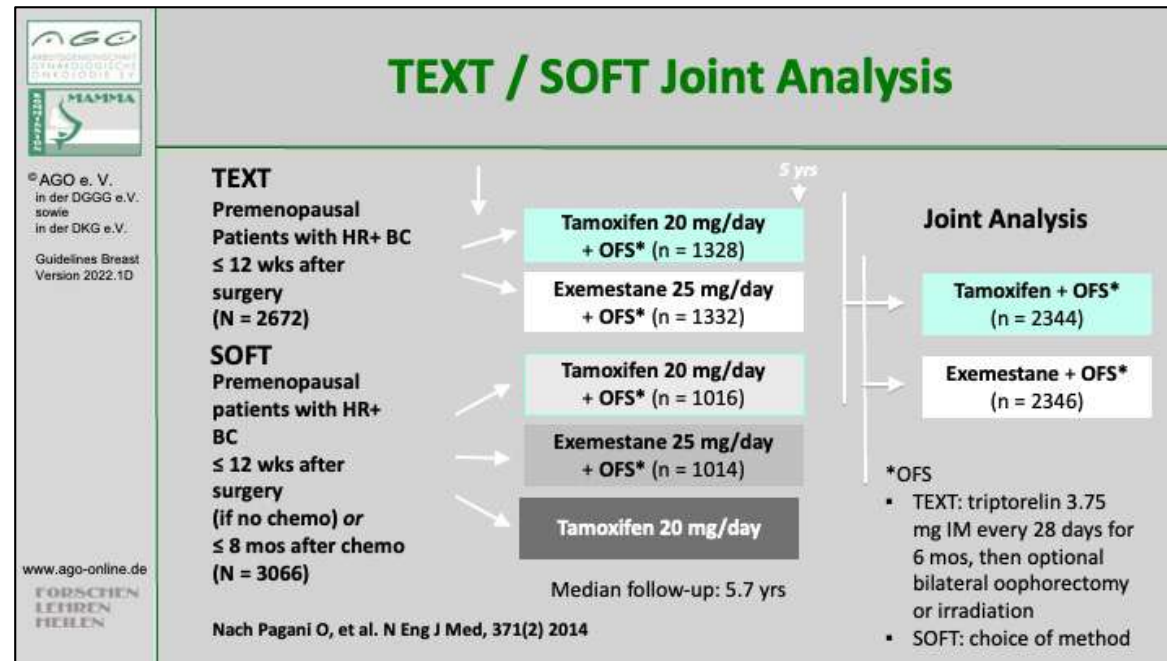
#### GnRH as monotherapy:

1. Cuzick J, 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.

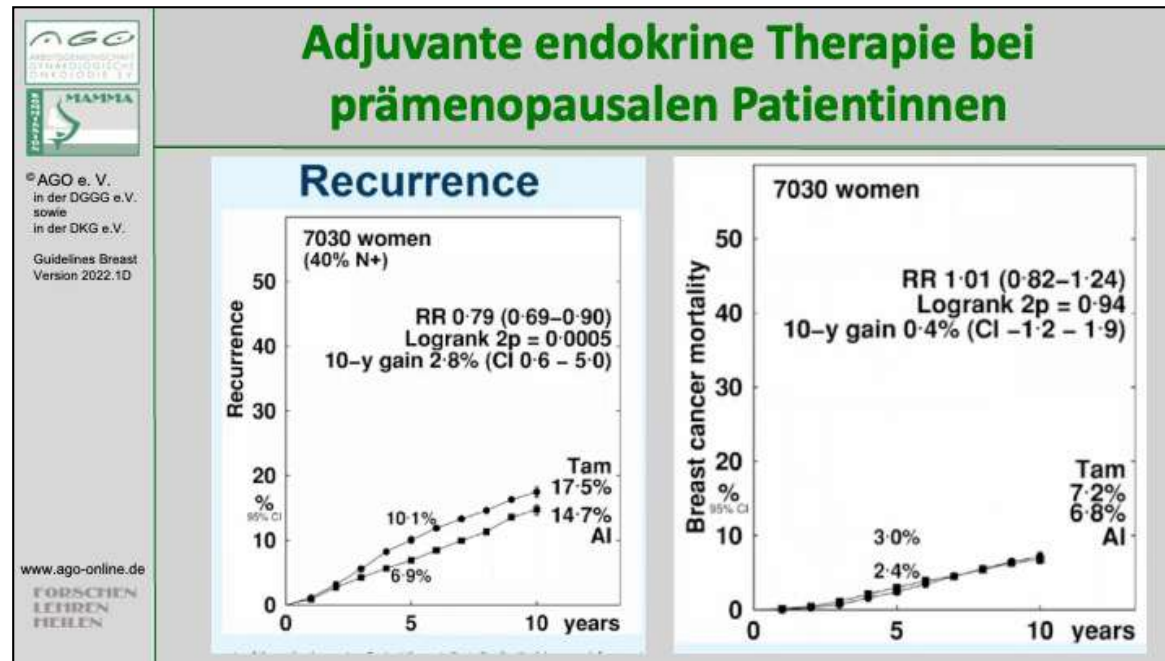
#### Ovarian function suppression (OFS) with Tam/AI and Tam with or without OFS:

1. 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.

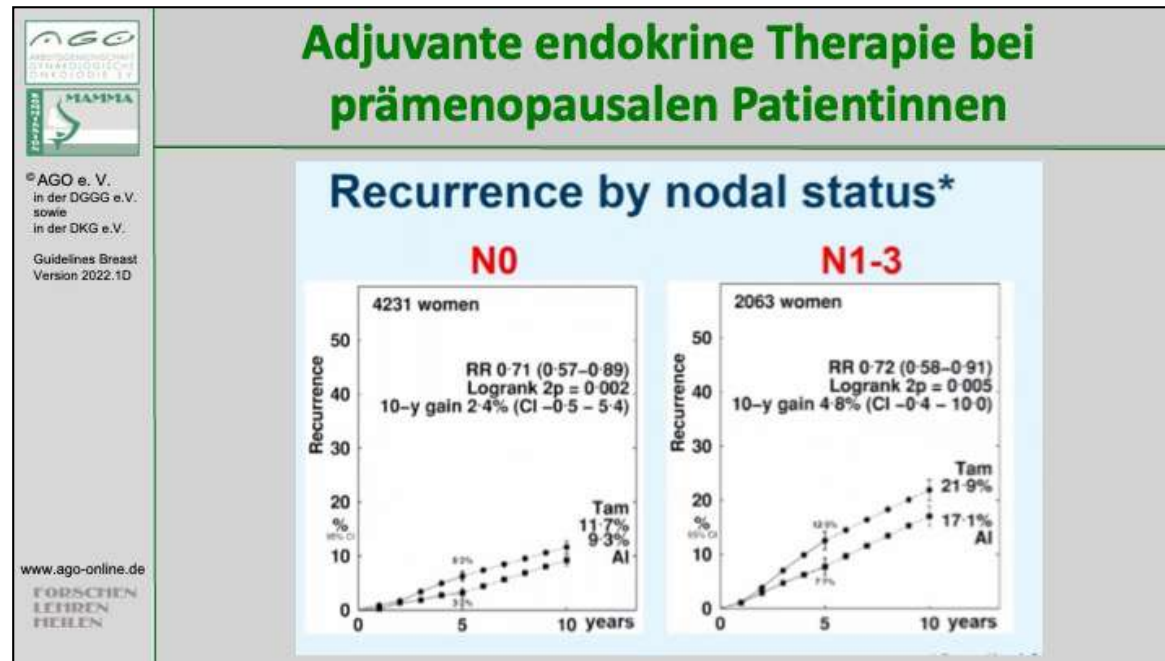
10. Regan MM, Walley BA, Fleming GF et al. Randomized comparisons of adjuvant exemestane + ovarian function suppression versus Tamoxifen + OFS versus tamoxifen in premenopausal women with HR + early breast : update of the TEXT and SOFT trials. SABCS 2021, GS2-05.



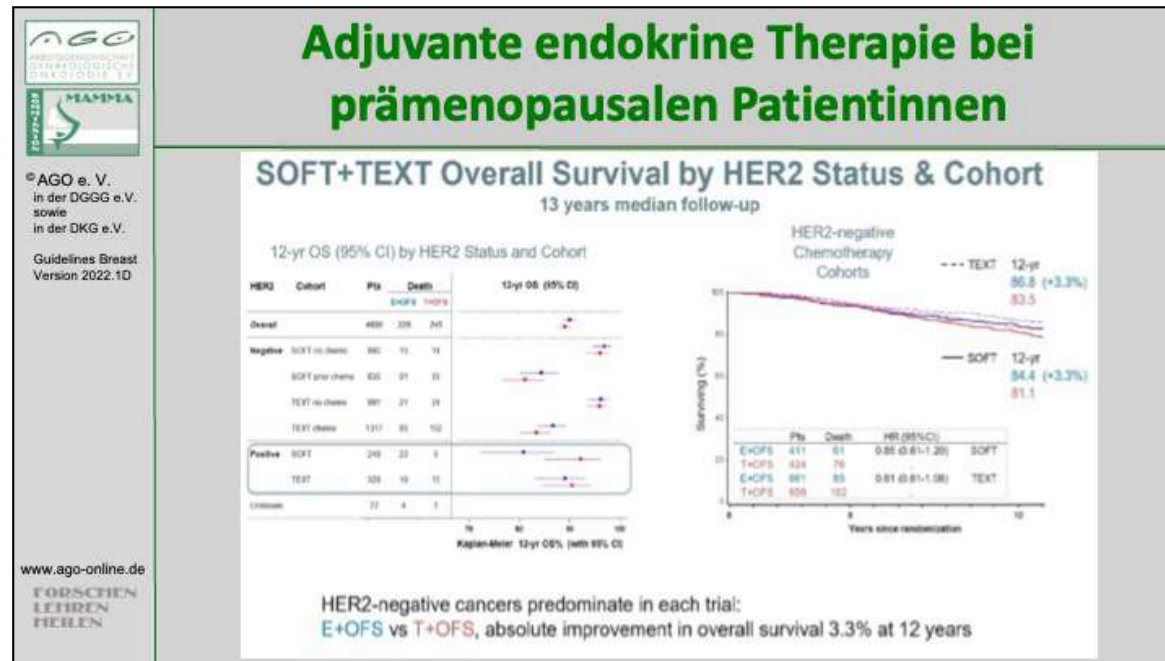
1. Pagani O, Gelber S, Colleoni M, et al. Impact of SERM adherence on treatment effect: International Breast Cancer Study Group Trials 13-93 and 14-93. Breast Cancer Res Treat 2013;142(2):455-9.
2. Francis PA, Regan MM, Fleming GF et al. The SOFT Investigators and the International Breast Cancer Study 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.

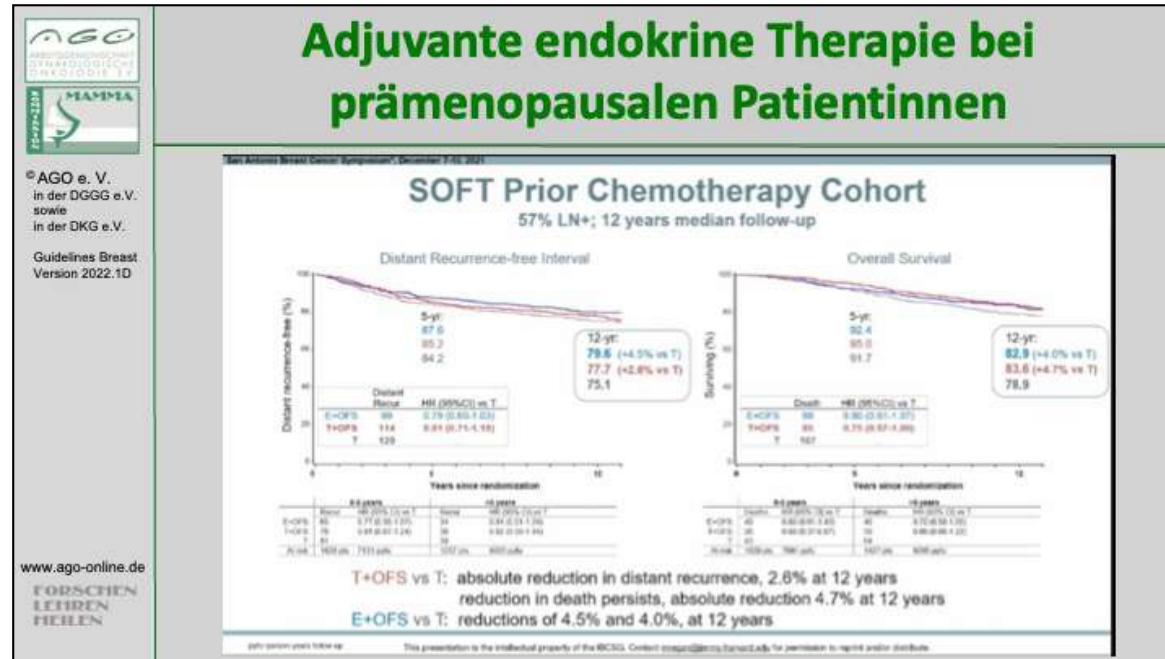


1. Bradley R, Braybrooke J, Gray R et al. Aromatase Inhibitors versus Tamoxifen in premenopausal women with ER + early stage breast cancer treated with ovarian suppression: A patient level meta-analysis of 7.030 women in four randomised trials. SABCS 2021, GS2-04.

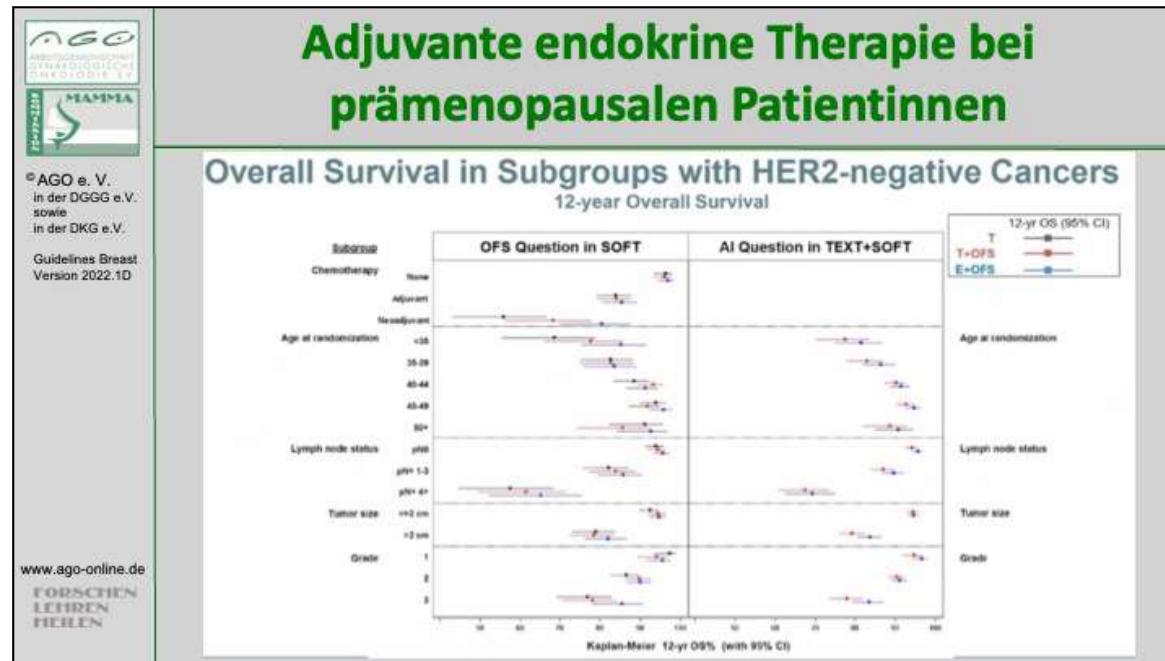


1. Bradley R, Braybrooke J, Gray R et al. Aromatase Inhibitors versus Tamoxifen in premenopausal women with ER + early stage breast cancer treated with ovarian suppression: A patient level meta-analysis of 7.030 women in four randomised trials. SABCS 2021, GS2-04.

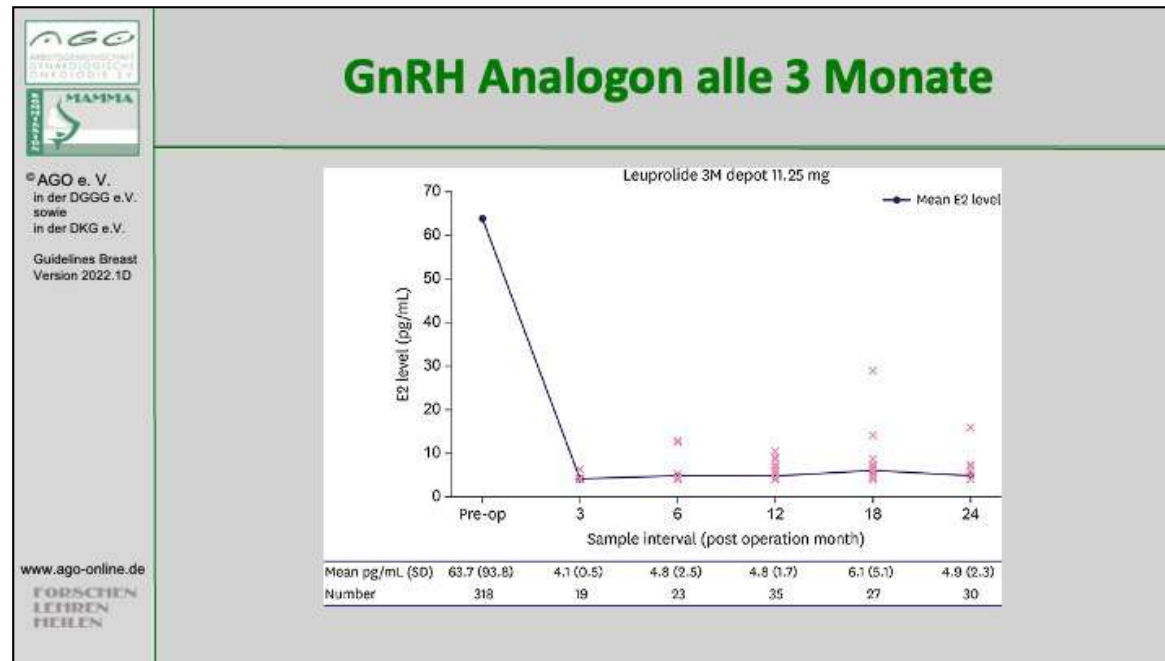




1. Regan MM, Walley BA, Fleming GF et al. Randomized comparisons of adjuvant exemestane + ovarian function suppression versus Tamoxifen + OFS versus tamoxifen in premenopausal women with HR + early breast : update of the TEXT and SOFT trials. SABCS 2021, GS2-05.



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 patients 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>

Adjuvante endokrine Therapie bei postmenopausalen Patientinnen (Jahre 1-5)			
	Oxford		
	LoE	GR	AGO
■ <b>Aromatasehemmer für die ersten 5 Jahre</b>			
■ Nicht-steroidaler AI bei lobulärem Karzinom	1a	A	++
■ Hohes Rezidivrisiko	2b	B	+
■ <b>Sequentielle Therapie für die ersten 5 Jahre*</b>			
■ Tam (2–3 Jahre) gefolgt von AI bis zur Gesamtdauer von 5 Jahren	1a	A	++
■ AI (2–3 Jahre) gefolgt von Tamoxifen bis zur Gesamtdauer von 5 Jahren	1b	C	++
■ <b>Tamoxifen 20 mg/d für die ersten 5 Jahre**</b>	1a	A	+

\* Die endokrine adjuvante Therapie postmenopausaler Patientinnen sollte in den ersten 5 Jahren für 2–3 Jahre einen Aromatasehemmer enthalten  
 \*\* Eine Monotherapie mit Tamoxifen kann im Einzelfall in Abhängigkeit vom Alter, Rückfallrisiko und Kontraindikationslage eingesetzt werden.

#### AI for first 5 years:

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 2015;386(10001):1341-52.
2. Rydén L, Heibert 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.
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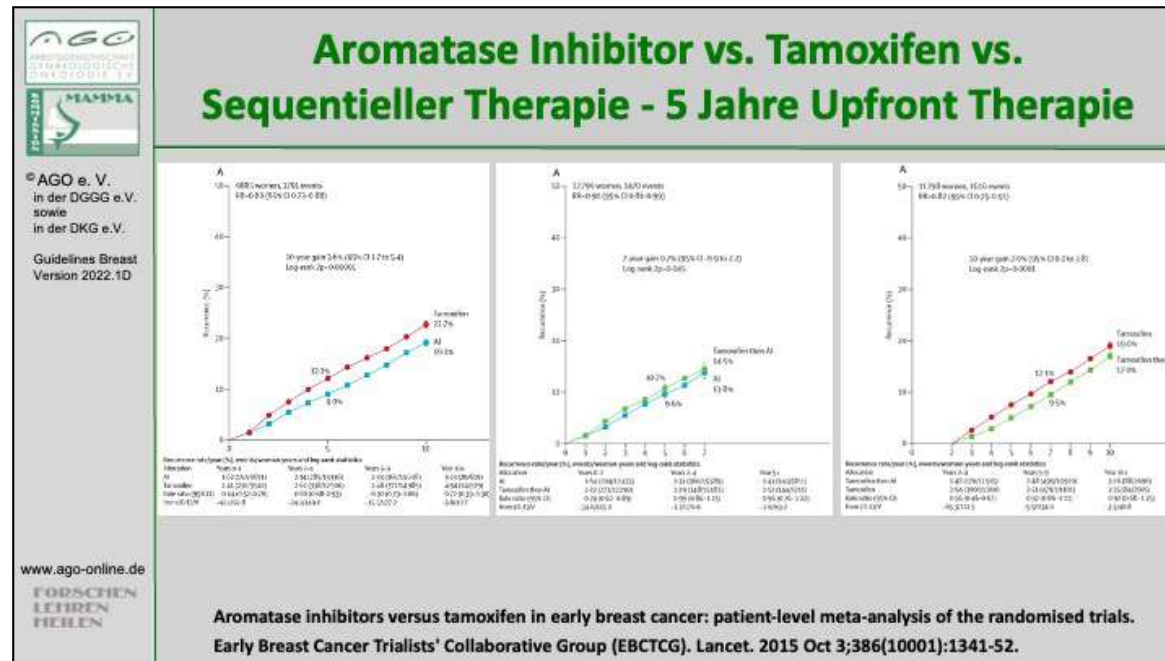
Tamoxifen 20 mg/d for first 5 yrs:

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



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

	Oxford		
	LoE	GR	AGO
<b>Bei erhöhtem Rückfallrisiko und Patientinnencharakteristika analog zu den Studien</b>			
▪ Abemaciclib für 2 Jahre*	1b	B	+
▪ Olaparib für 1 Jahr bei <i>gBRCA1/2</i> Mutation**	1b	B	+
▪ Palbociclib für 1-2 Jahre	1b	B	-


\* entsprechend der MonarchE-Studie

\*\* entsprechend der OlympiA-Studie

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
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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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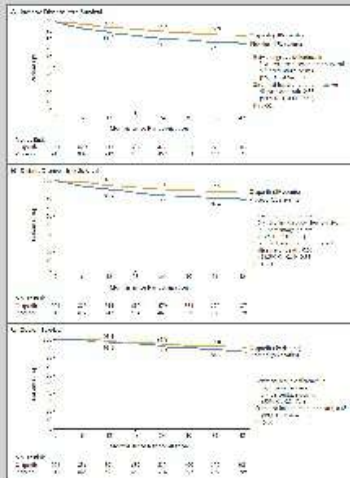
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## PARP-Inhibition zusätzlich zu einer standardmäßigen endokrinen Therapie in der adjuvanten / post-neoadjuvanten Situation

Studie	Gruppe	ParP	Ende	Standard	Standard	Standard	Standard	Standard
Tutt ANJ	Standard	100%	100%	100%	100%	100%	100%	100%
	ParP	100%	100%	100%	100%	100%	100%	100%
Garber JE	Standard	100%	100%	100%	100%	100%	100%	100%
	ParP	100%	100%	100%	100%	100%	100%	100%
Kaufman B	Standard	100%	100%	100%	100%	100%	100%	100%
	ParP	100%	100%	100%	100%	100%	100%	100%



1. 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

 <b>CDK4/6 Inhibitoren zusätzlich zu einer standardmäßigen endokrinen Therapie in der adjuvanten / post-neoadjuvanten Situation</b>				
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	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 <sub>CDKi</sub>	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. doi: 10.1016/j.annonc.2021.09.015
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

Erweiterte adjuvante endokrine Therapie (EAT) bei prämenopausalen Patientinnen (Jahre 6–10)			
	Oxford		
	LoE	GR	AGO
<b>Bei erhöhtem Rückfallrisiko</b>			
▪ 5 Jahre Tamoxifen nach 5 Jahren Tamoxifen	1a	A	++
▪ 2,5–5 Jahre AI nach 5 Jahren Tamoxifen prämenopausal, bei im Verlauf eindeutig nachgewiesener postmenopausaler Situation	1b	B	+
▪ 5 Jahre Tamoxifen nach 5 Jahre endokriner Therapie + OFS	5	D	+

#### 5 years Tamoxifen after 5 years Tamoxifen:

1. Davies C, Pan H, Godwin J et al. Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381(9869):805-16. Erratum in: Lancet. 2013;381(9869):804.
2. Gray RG, Rea D, Handley K et al. ATTom: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6953 women with early breast cancer. J Clin Oncol 2013; 31 (18 suppl):5.
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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.

Erweiterte adjuvante endokrine Therapie (EAT) bei postmenopausalen Patientinnen (Jahre 6–10)			
	Oxford		
	LoE	GR	AGO
<b>Bei erhöhtem Rückfallrisiko:</b>			
▪ Nach 5 Jahren Tamoxifen, Tamoxifen für 5 Jahre	1a	A	+
▪ Nach 5 Jahren Tamoxifen, AI für 2 bis 5 Jahre	1a	A	++
▪ Nach initialer AI-haltiger Therapie (upfront oder Switch) Verlängerung der endokrinen Therapie mit AI für 2 bis 5 * Jahre			
▪ höheres Rückfall-Risiko und bei guter Verträglichkeit des AIs	1a	A	+
▪ niedriges Rückfall-Risiko, schlechte Verträglichkeit des AIs	1a	A	-
▪ Therapiepausen des AI bis zu 3 Monaten möglich unter kontinuierlicher EAT mit AI	1b	B	+/-
* Kein Einfluss auf das Gesamtüberleben (OS)			

#### 5 years Tamoxifen after 5 years Tamoxifen:

1. Davies C, Pan H, Godwin J et al. Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381(9869):805-16. Erratum in: Lancet. 2013;381(9869):804.
2. Gray RG, Rea D, Handley K et al. ATTOM: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6953 women with early breast cancer. J Clin Oncol 2013; 31 (18 suppl):5.
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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.
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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*

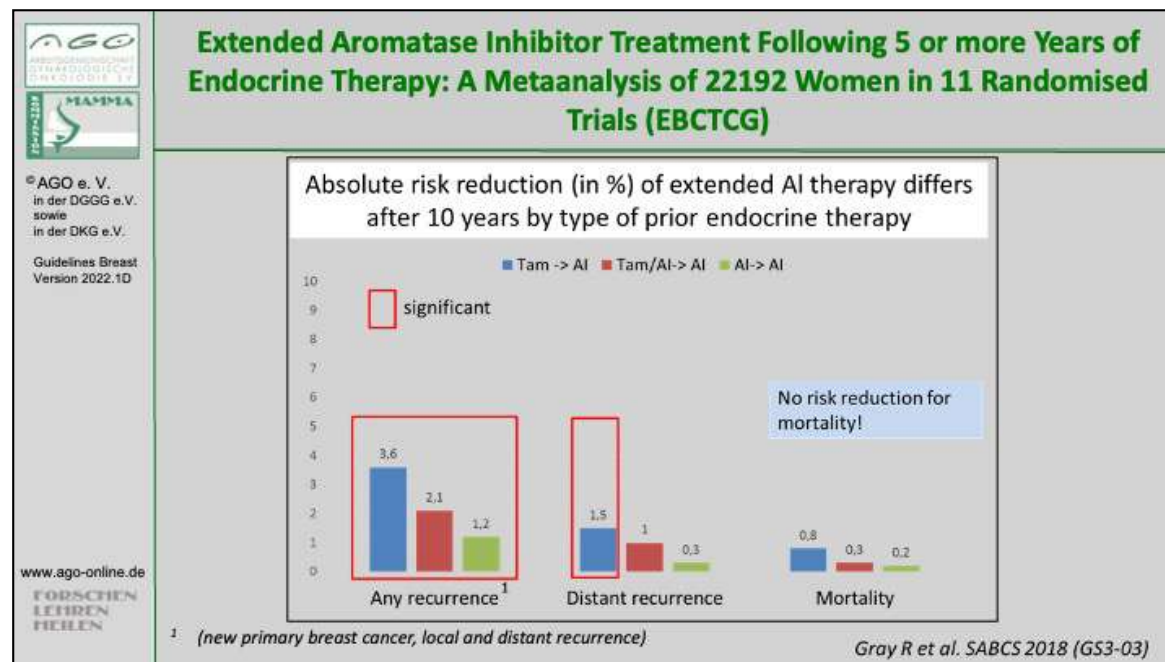
#### low risk, poor tolerability of the AI

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.
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#### 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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# Erweiterte, adjuvante endokrine Therapie im Überblick

Studie	Therapien												De-facto-Vergleich e (Jahre)	HR für DFS	AI- Therapie Jahre 5- 8 (%)	<u>Braun:</u> Tamoxifen  <u>Grün:</u> Tamoxifen oder AI  <u>Blau:</u> AI  <u>Gestreift:</u> Zeit der randomisierten Intervention vs. keine Therapie od. Placebo  *: 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	15					
Studien mit Tamoxifen nach 5 Jahren Tamoxifen																
ATLAS					*								5 vs 10	0,75 – 0,99 I	0	
ATTOM					*								5 vs 10	0,75 – 0,99 I	0	
Studien mit AI nach 5 Jahren Tamoxifen																
MA. 17					*								5 vs 10	0,97	0	
NSAPB B-33					*								5 vs 10	0,68	0	
ABCSG 6a					*								5 vs 8	0,62	0	
Studien mit erweiterter 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																
BODG 2006- DS IDEAL					*								7,5 vs 10	0,92	88	
ABCSG 16					*								7 vs 10	1,007	49	
SOLE													Cont vs unbebr	1,08	81	



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## Entscheidungskriterien für die erweiterte adjuvante Behandlung

**Kriterien, die auf einen klinischen Benefit hinweisen:**

- Alleinige adjuvante Therapie mit Tamoxifen
- Z. n. Chemotherapie (höheres Risiko)
- Positiver Lymphknotenstatus
- T2/T3-Tumoren
- hohes Rückfall-Risiko nach immunhistochemischen Kriterien oder Multi-Gen Assays
- Erhöhter CTS5-Score
- BCI (H/I) (Breast Cancer Index)

**Weitere Entscheidungsfaktoren:**

- Patientenwunsch
- bisherige gute Verträglichkeit der AI-Therapie bzw. Nebenwirkungen
- Knochengesundheit
- jüngeres Alter
- Adhärenz

1. Gnant M, G Steger, R Greil, et al. A prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years of Anastrozole after initial 5 years of adjuvant endocrine therapy - results from 3,484 postmenopausal women in the ABCSG-16 trial. SABCS 2017; GS3-01
2. Li L, Chang B, Jiang X et al. Clinical outcomes comparison of 10 years versus 5 years of adjuvant endocrine therapy in patients with early breast cancer. Clinical outcomes comparison of 10 years versus 5 years of adjuvant endocrine therapy in patients with early breast cancer. BMC Cancer 2018;18:977
3. Goldvaser H, Barnes TA, Šeruga B, et al. Toxicity of extended adjuvant therapy with aromatase inhibitors in early breast cancer: a systematic review and meta-analysis. J Natl Cancer Inst 2018;110(1)djx141
4. van Hellemond I, Geurts SME, Tjan-Heijnen VCG: Current status of extended adjuvant endocrine therapy in early stage breast cancer. Curr Treat Options in Oncol 2018;19:26.
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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.

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	<ul style="list-style-type: none"> <li>▪ <b>Angebot zur Beratung über Fertilitätserhaltung inkl. assistierter Reproduktion</b> (Information: <a href="https://fertiprotekt.com">https://fertiprotekt.com</a>)</li> <li>▪ <b>CTx + GnRHa</b> (zur Prophylaxe des ovariellen Funktionsausfalls) (GnRHa Applikation &gt; 2 Wochen vor Chemotherapie, unabhängig vom Hormonrezeptorstatus)</li> <li>▪ <b>CTx + GnRHa</b> (zur Erhöhung der Schwangerschaftsrate)</li> </ul>	<b>Oxford</b> <b>LoE GR AGO</b>		
		<b>++</b>		
		<b>1a</b>	<b>A</b>	<b>+</b>
		<b>2a</b>	<b>B</b>	<b>+/-</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
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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.
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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

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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 <sup>1,2</sup>	30.9%	14.1%	0.38; 0.26 to 0.57	< 0.001

- <sup>1</sup> premature ovarian insufficiency
- <sup>2</sup> different definitions and time points were used
- <sup>3</sup> in most trials POI and not pregnancy was defined as the primary endpoint

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

Lambertini M et al. J Clin Oncol 2018

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