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Guidelines Breast  
Version 2025.1E

FORSCHEN  
LEHREN  
HEILEN

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

## Systemic Therapy of Primary Early Breast Cancer - Hormone Receptor-positive, HER2-negative



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## Systemic Therapy of Primary Early Breast Cancer - Hormone Receptor-positive, HER2-negative

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Bauerfeind / Dall / Diel / Fasching / Fersis / Fehm / Friedrich / Friedrichs /  
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Thomssen / Untch / Wöckel

### ■ Version 2025:

Park-Simon / Schmidt

# Strategies for Differentiated Systemic Treatment in the Curative Situation

AGO

If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred; study participation recommended

<ul style="list-style-type: none"> <li>▪ HR+ / HER2- and „low recurrence-risk“               <ul style="list-style-type: none"> <li>▪ Endocrine therapy without chemotherapy</li> </ul> </li> </ul>	++
<ul style="list-style-type: none"> <li>▪ HR+ / HER2- and „high recurrence-risk“               <ul style="list-style-type: none"> <li>▪ endocrine therapy</li> <li>▪ endocrine-based therapy (abemaciclib or ribociclib)</li> <li>▪ Patients with indication for chemo-endocrine therapy*                   <ul style="list-style-type: none"> <li>▪ Conventionally dosed AT-based chemotherapy (q3w)</li> <li>▪ Dose dense chemotherapy (including weekly schedule)</li> </ul> </li> </ul> </li> </ul>	++ + + ++
<ul style="list-style-type: none"> <li>▪ gBRCA1/2mut (HR+ / HER2- or TNBC respectively)               <ul style="list-style-type: none"> <li>▪ Olaparib +/- endocrine therapy</li> </ul> </li> </ul>	++
<ul style="list-style-type: none"> <li>▪ Triple-negative (TNBC)               <ul style="list-style-type: none"> <li>▪ Conventional dosed AT-based chemotherapy (q3w)</li> <li>▪ Sequential AT-based chemotherapy (incl. weekly schedule)</li> <li>▪ Neoadjuvant platinum-containing chemotherapy</li> <li>▪ Neoadjuvant platinum-containing chemotherapy with ICPI (Pembrolizumab)</li> </ul> </li> </ul>	+ ++ + ++
<ul style="list-style-type: none"> <li>▪ HER2+               <ul style="list-style-type: none"> <li>▪ Trastuzumab (plus Pertuzumab in N+ or NACT)                   <ul style="list-style-type: none"> <li>▪ Sequential AT-based chemotherapy with concurrent T + anti-HER2 therapy</li> <li>▪ Anthracycline-free, chemotherapy + anti-HER2 therapy</li> </ul> </li> </ul> </li> </ul>	++ ++ ++

\* see prognosis chapter

## Systematic review of published evidence

PUBMED 1999-2024

ASCO 1999-2024

SABCS 1999-2024

ECCO/ESMO 1999-2024

## General Statements:

Loibl S, André F, Bachelot T et al. (2024) Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol , 35:159–182.

## Trastuzumab in combination with chemotherapy

1. Gianni L, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet 2010: 375; 377
2. Untch M, et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study

groups. J Clin Oncol 2011; 29; 3351

3. Gianni L, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet Oncol 2014; 15; 640
4. Jackisch C, et al. HannaH phase III randomised study: Association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. Eur J Cancer. 2016 Jul;62:62-

#### Pertuzumab + Trastuzumab in combination with chemotherapy

1. Gianni L, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012; 13; 25-32
2. Schneeweiss A, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Annals Oncol 2013; 24; 2278-84
3. Nagayama A, et al. Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis. J Natl Cancer Inst 2014; 106(9): in print
4. Gianni L et al. Five-year analysis of the phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P). J Clin Oncol 33, 2015 (suppl; abstr 505)
5. Loibl S, et al. Dual HER2-blockade with pertuzumab and trastuzumab in HER2-positive early breast cancer: a subanalysis of data from the randomized phase III GeparSepto trial. Ann Oncol. 2017;28:497-504
6. Schneeweiss A et al. Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: Evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer. Eur J Cancer 89:27-35, 2017
7. Hurvitz SA, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2017. pii: S1470-2045(17)30716-7 [Epub ahead of print]
8. Swain SM, et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. Ann Oncol 2017. doi: 10.1093/annonc/mdx773. [Epub ahead of print]
9. Von Minckwitz G, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017

13;377(2):122-131.

#### Her2+ Antrazyklin-freie Chemotherapie:

1. Ramphorstet MS, van der Voort A, Workhoven ED al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2018 Dec;19(12):1630-1640. doi: 10.1016/S1470-2045(18)30570-9.
2. Anna van der Voort, Mette S. van Ramshorst, Erik D. van Werkhoven et al. *J Clin Oncol* 38: 2020 (suppl; abstr 501)

#### TNBC neoadjuvant chemotherapy with ICP

1. Mittendorf EA, Zhang H, Barrios Chet al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. *Lancet.* 2020 Oct 10;396(10257):1090-1100. doi: 10.1016/S0140-6736(20)31953-X.
2. Schmid P, Cortes J, Pusztai L et al. ; KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. *N Engl J Med.* 2020 Feb 27;382(9):810-821. doi: 10.1056/NEJMoa1910549.
3. Schmid P, Cortes J, Dent R et al. KEYNOTE-522: Phase 3 study of pembrolizumab + chemotherapy vs placebo + chemotherapy as neoadjuvant treatment, followed by pembrolizumab vs placebo as adjuvant treatment for early triple-negative breast cancer (TNBC). *ESMO 2021 Abstract #VP7\_2021*

#### Abemaciclib:

1. Rastogi P, O'Shaughnessy J, Martin M, Boyle F, Cortes J, Rugo HS, Goetz MP, Hamilton EP, Huang CS, Senkus E, Tryakin A, Cicin I, Testa L, Neven P, Huober J, Shao Z, Wei R, André V, Munoz M, San Antonio B, Shahir A, Harbeck N, Johnston S. Adjuvant Abemaciclib Plus Endocrine Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative, High-Risk Early Breast Cancer: Results From a Preplanned monarchE Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes. *J Clin Oncol.* 2024 Jan 9:JCO2301994.
2. Goetz MP, Cicin I, Testa L, et al. (2024) Impact of dose reductions on adjuvant abemaciclib efficacy for patients with high-risk early breast cancer: analyses from the monarchE study. *NPJ Breast Cancer* 10:34.
3. Tolaney SM, Guarneri V, Seo Jhet al. (2024) Long-term patient-reported outcomes from monarchE: Abemaciclib plus endocrine therapy as adjuvant therapy for HR+, HER2-, node-positive, high-risk, early breast cancer. *Eur J Cancer*

### Ribociclib:

1. Fasching PA, Stroyakovskiy D, Yardley D et al. (2024) LBA13 Adjuvant ribociclib (RIB) plus nonsteroidal aromatase inhibitor (NSAI) in patients (Pts) with HR+/HER2- early breast cancer (EBC): 4-year outcomes from the NATALEE trial. *Annals of Oncology* 35:S1207.
2. Hortobagyi GN, Lacko A, Sohn J et al. (2024) A phase III trial of adjuvant ribociclib plus endocrine therapy versus endocrine therapy alone in patients with HR-positive/HER2-negative early breast cancer: final invasive disease-free survival results from the NATALEE trial. *Ann Oncol*.

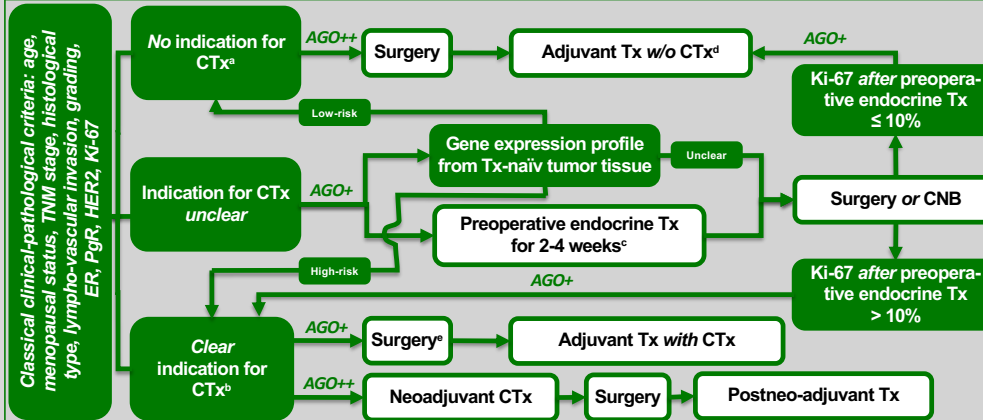
### Olaparib

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.
2. Geyer CE Jr, Garber JE, Gelber RD et al.; OlympiA Clinical Trial Steering Committee and Investigators. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in *BRCA1/2* and high-risk, early breast cancer. *Ann Oncol* 2022;33(12):1250-1268

### Platin salts:

1. Geyer CE, Sikov WM, Huober J et al. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. *Ann Oncol*. 2022 Apr;33(4):384-394.
2. van Mackelenbergh MT, Seither F, Möbus V et al. Effects of capecitabine as part of neo-/adjuvant chemotherapy - A meta-analysis of individual breast cancer patient data from 13 randomised trials including 15,993 patients. *Eur J Cancer* 2022; 166: 185-201
3. Gupta S, Nair NS, Hawaldar RW et al., Addition of platinum to sequential taxan-anthracycline neoadjuvant chemotherapy in patients with triple-negative breast cancer: a phase III randomized controlled trial SABCS 2022, GS5-01. III randomized controlled trial SABCS 2022, GS5-01
4. MasonSRE, WillsonML, EggerSJ, BeithJ, DearRF, GoodwinA. Platinum-based chemotherapy for early triple-negative breast cancer. *Cochrane Database of Systematic Reviews* 2023, Issue 9. Art. No.: CD014805.

## Therapy of HR-positive, HER2-negative Early Breast Cancer



CNB, core needle biopsy; CTx, chemotherapy; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; Tx, therapy; w/o, without; <sup>a</sup>e.g.  $\leq$  cT1c cN0-1 G1-2 Ki-67  $\leq$  5% or -if situation unclear- low-risk gene expression profile; <sup>b</sup>e.g. inoperable tumor or  $\geq$  4 clinically involved axillary nodes or G3 and Ki-67  $\geq$  35% or -if situation unclear- high-risk gene expression profile; <sup>c</sup>standard endocrine Tx; <sup>d</sup>if no change of prognostic factors after surgery; <sup>e</sup>if not done already.

# Assessment of Steroid Hormone Receptor Status

**Oxford LoE: 1**

**GR: A AGO: ++**

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

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

**If ER negative / PR positive (> 10% positive cells): reassess IHC status**  
**If ER low (1-10%): Implications for therapy should be recommended in the pathology report**

## Endocrine responsiveness:

1. Early Breast Cancer Trialists Collaborative Group EBCTCG. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365(9472):1687–717.
2. Traub L, Thill M, Nitschmann S: 20-Jahres-Ergebnisse einer 5-jährigen Hormontherapie bei Mammakarzinom : Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Internist (Berl)*. Springer Medizin 2018;59(4):410–2.
3. Pan H, Gray R, Braybrooke J et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. *N Engl J Med*. 2017;377(19):1836–46.
4. Allison KH, Hammond MEH, Dowsett M, et al: Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. *J Clin Oncol*. 2020 Apr 20;38(12):1346-1366.
5. Panagiotis Malainou C, Stachika N, Damianou A et al. Estrogen-Receptor-Low-Positive Breast Cancer: Pathological and Clinical Perspectives. *Curr Oncol*. 2023 Nov 4;30(11):9734-9745. doi: 10.3390/currenol30110706.
6. Choong GMY, Hoskin TL, Boughey JC, Ingle JN, Goetz MP (2024) The impact of adjuvant endocrine therapy (AET) omission in ER-low (1-10%) early-stage breast cancer. *J Clin Oncol* 42:513.

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

1. Viale G, Regan MM, Maiorano E et al. Prognostic and predictive value of centrally reviewed expression of estrogen and progesterone receptors in a randomized trial comparing letrozole and tamoxifen adjuvant therapy for postmenopausal early breast cancer: BIG 1-98. *J Clin Oncol* 2007;25:3846-52.
2. Cserni G, Fracz M, Kalman E et al. Estrogen receptor negative and progesterone receptor positive breast carcinomas-how frequent are they? *Pathol Oncol Res* 2011;17:663-8.
3. Hefti MM, Hu R, Knblauch NW et al. Estrogen receptor negative/progesterone receptor positive breast cancer is not a reproducible subtype. *Breast Cancer Res* 2013;15:R68.
4. Yi M, Huo L, Koenig KB et al. Which threshold for ER positivity? a retrospective study based on 9639 patients. *Ann Oncol* 2014;25:1004-11.
5. Allison, K. H., et al. (2020). "Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update." *J Clin Oncol* 38(12): 1346-1366.

## Adjuvant Endocrine Therapy

### Assessment of Menopausal Status

#### Assessment of menopausal status:

- Menstruation history
- FSH, E2

Oxford		
LoE	GR	AGO
		++
		++

1. Partridge AH, Ruddy KJ, Gelber S et al. Ovarian reserve in women who remain premenopausal after chemotherapy for early stage breast cancer. *Fertil Steril* 2010;94(2):638-44.
2. Su HI, Chung K, Sammel MD et al. Antral follicle count provides additive information to hormone measures for determining ovarian function in breast cancer survivors. *Fertil Steril* 2011;95(5):1857-9.
3. Furlanetto J , Marme F , Seiler S. Chemotherapy-induced ovarian failure in young women with early breast cancer: Prospective analysis of four randomised neoadjuvant/adjuvant breast cancer trials. *European Journal of Cancer* 152 (2021) 193e203.

## Neoadjuvant Systemic Chemotherapy Clinical Benefit

	Oxford	
	LoE	GR
▪ Leads to improvement of prognosis by individualization of neoadjuvant and post-neoadjuvant therapy	1b	A
▪ Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and number of cycles), if the postneoadjuvant therapy is not stratified according to pathologic response	1a	A
▪ Pathological complete response is associated with improved survival	1b	A
▪ The RCB Score and the class of RCB are subtype independent prognostic factors	2a	B
▪ Can achieve operability in primary inoperable tumors	1b	A
▪ Improved options for breast conserving surgery	1b	A
▪ Decreases rate of axillary lymphadenectomies lymphonodectomies	2b	B
▪ Allows individualization of therapy according to mid-course treatment effect	1b	B

### Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and cycle number)

1. Fisher B, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998; 16; 2672
2. Van der Hage JA, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001; 19; 4224
3. Rastogi P, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008; 26; 778
4. EBCTCG. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol Lancet Oncol. 2018 Jan;19(1):27-39.

### Pathological complete response is associated with improved survival in all subgroups

1. von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012; 30; 1796
2. Fisher B, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998; 16; 2672
3. Van der Hage JA, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for

Research and Treatment of Cancer trial 10902. J Clin Oncol 2001: 19; 4224

4. Rastogi P, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008: 26; 778
5. EBCTCG. Long-term outcomes for neoadjuvant chemotherapy. J Clin Oncol 2010: 28; 3758
6. Cortazar P, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014: 384; 164
7. Berruti A, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: a meta-regression of 29 randomized prospective studies. J Clin Oncol 2014: 32; 3883
8. Yee D, et al. Pathological complete response predicts event-free and distant disease free survival in the I-SPY 2 Trial. SABCS 2017 (abs GS3-08)

#### Can achieve operability in primary inoperable tumors

1. Makhoul I, et al. Neoadjuvant systemic treatment of breast cancer. J Surg Oncol 2011: 103; 348
2. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

#### Improved options for breast conserving surgery

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

#### Reduces the rate of lymphadenectomies

1. Fernandez-Gonzalez S, et al. The Shift From Sentinel Lymph Node Biopsy Performed Either Before or After Neoadjuvant Systemic Therapy in the Clinical Negative Nodes of Breast Cancer Patients. Results, and the Advantages and Disadvantages of Both Procedures. Clin Breast Cancer 2018 Feb;18(1):71-77.
2. Reimer T et al. Avoiding axillary sentinel node biopsy after neoadjuvant systemic therapy in breast cancer: rationale for the prospective, multicentric EUBREAST-01 trial. Cancers 2020:3698; doi:10.3390/cancers12123698

#### Allows individualization of therapy according to mid-course treatment effect

1. Von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in

various intrinsic breast cancer subtypes. J Clin Oncol 2012; 30; 1796

#### Allows individualization of post-neoadjuvant treatment

1. von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012; 30; 1796
2. Berruti A, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: a meta-regression of 29 randomized prospective studies. J Clin Oncol 2014; 32, 3883
3. Marmé F, et al. Utility of the CPS+EG staging system in hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer treated with neoadjuvant chemotherapy. Eur J Cancer 53:65-74, 2016
4. Symmans WF, et al. Long-Term Prognostic Risk After Neoadjuvant Chemotherapy Associated With Residual Cancer Burden and Breast Cancer Subtype. J Clin Oncol 35(10):1049-1060, 2017
5. Loibl S, et al. Risk Assessment after Neoadjuvant Chemotherapy in Luminal Breast Cancer Using a Clinicomolecular Predictor. Clin Cancer Res. 2018;24(14):3358-3365.
6. Masuda N, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med 376, 2147–2159, 2017
7. von Minckwitz G, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019;380(7):617-628.

#### RCB Score and RCB class as prognostic factors

1. Yau C, Osdoit M, van der Noordaa Metz al. Residual cancer burden after neoadjuvant chemotherapy and long term survival outcome in breast cancer: a multicentre pooled analysis of 5161 patients. Lancet Oncol. 2022 Jan;23(1):149-160. doi: 10.1016/S1470-2045(21)00589-1. Epub 2021 Dec 11. PMID: 34902335.

## Neoadjuvant Systemic Chemotherapy - Indications

	Oxford		
	LoE	GR	AGO
▪ <b>If similar postoperative adjuvant chemotherapy is indicated</b>	<b>1b</b>	<b>A</b>	<b>++</b>
▪ <b>To allow a risk adapted postoperative therapy</b>	<b>1b</b>	<b>A</b>	<b>++</b>
▪ <b>Inflammatory breast cancer</b>	<b>2b</b>	<b>B</b>	<b>++</b>
▪ <b>Primary inoperable breast cancer</b>	<b>1c</b>	<b>A</b>	<b>++</b>
▪ <b>Large operable breast cancer requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation</b>	<b>1b</b>	<b>B</b>	<b>++</b>

### Inflammatory breast cancer

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011: 22; 515

### Inoperable breast cancer

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011: 22; 515

### Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant

systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

3. EBCTCG. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol 2018 Jan;19(1):27-39.

If similar postoperative adjuvant chemotherapy is indicated

1. Untch M, et al. Neoadjuvant chemotherapy: early response as a guide for further treatment: clinical, radiological, and biological. J Natl Cancer Inst Monogr 2011: 43; 138
2. Loibl S, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012: 13 ; 887

## Neoadjuvant Systemic Therapy

### Timing of Diagnosis, Surgery and Radiotherapy

	Oxford		
	LoE	GR	AGO
<b>Timing of surgery</b> 4-8 weeks after last course of chemotherapy	2a	B	++
<b>Radiotherapy within 2 months after surgery</b>	2b	B	++

#### Initiation of chemotherapy after histologic diagnosis

1. de Melo Gagliato D, Lei X, Giordano SH, et al. Impact of Delayed Neoadjuvant Systemic Chemotherapy on Overall Survival Among Patients with Breast Cancer. *Oncologist*. 2020;25(9):749-757. doi: 10.1634/theoncologist.2019-0744.
2. Hanna TP, King WD, Thibodeau S, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. *BMJ* 2020 Nov 4;371:m4087.doi:10.1136/bmj.m4087

#### Time between surgery and last chemotherapy

1. Cullinane C, Shrestha A, Al Maksoud A, et al. Optimal timing of surgery following breast cancer neoadjuvant chemotherapy: A systematic review and meta-analysis. *J Surg Oncol*. 2021 Jul;47(7):1507-1513.
2. Suleman K, Almalik O, Haque E et al. Does the Timing of Surgery after Neoadjuvant Therapy in Breast Cancer Patients Affect the Outcome? *Oncology*. 2020;98(3):168-173.
3. Grubstein A, Rapson Y, Stemmer SM et al. Timing to imaging and surgery after neoadjuvant therapy for breast cancer. *Clin Imaging*. 2020;71:24-28..
4. Sanford RA, Lei X, Barcenas CH et al. Impact of Time from Completion of Neoadjuvant Chemotherapy to Surgery on Survival Outcomes in Breast Cancer Patients. *Ann Surg Oncol* 2016;23(5):1515-21.

Radiotherapy 2 mths after surgery BCS

1. Silva SB, Pereira AAL, Marta GN, et al. Clinical impact of adjuvant radiation therapy delay after neoadjuvant chemotherapy in locally advanced breast cancer. *Breast*. 2018;38:39-44. doi: 10.1016/j.breast.2017.11.012.

## (Neo-)adjuvant Chemotherapy without Trastuzumab: Overview

	Oxford		
	LoE	GR	AGO
▪ <b>Dose-dense anthracycline / taxane based (incl. weekly) chemotherapy</b>	<b>1a</b>	<b>A</b>	<b>++</b>
▪ <b>Conventional anthracycline / taxane based (q3w)</b>	<b>1a</b>	<b>A</b>	<b>+</b>
▪ <b>„Tailored“ anthracycline-/ taxane based</b>	<b>1b</b>	<b>B</b>	<b>+/-</b>
▪ <b>If anthracyclines are not a preferred option</b>			
▪ <b>Docetaxel plus cyclophosphamide</b>	<b>1b</b>	<b>B</b>	<b>++</b>
▪ <b>Paclitaxel mono weekly</b>	<b>1b</b>	<b>B</b>	<b>+/-</b>
▪ <b>CMF</b>	<b>1a</b>	<b>A</b>	<b>+/-</b>

### indoindocIGStatement: Dosis-dicht Anthrazyklin-/ Taxan-basiert (inkl. weekly) LoE 1a A AGO ++

1. Metzger Filho O, Ballman K, Campbell J, et al. (2025) Adjuvant Dose-Dense Chemotherapy in Hormone Receptor-Positive Breast Cancer. J Clin Oncol.
2. Moylan EJ, Connell LC, O'Reilly S et al. Are dose-dense and triplet chemotherapy regimens optimal adjuvant therapy in the majority of women with node-positive early breast cancer? J Clin Oncol. 2014;32(6):605-6.
3. Lemos Duarte I, da Silveira Nogueira Lima JP, Passos Lima CS et al. Dose-dense chemotherapy versus conventional chemotherapy for early breast cancer: a systematic review with meta-analysis. Breast. 2012;21(3):343-9.
4. Möbus V, Jackisch C, Lück HJ et al. Ten-year results of intense dose-dense chemotherapy show superior survival compared with a conventional schedule in high-risk primary breast cancer: final results of AGO phase III iddEPC trial. Ann Oncol. 2018 Jan 1;29(1):178-185.
5. Gray R, Bradley R, Braybrooke J et al. Increasing the dose density of adjuvant chemotherapy by shortening intervals between courses or by sequential drug administration significantly reduces both disease recurrence and breast cancer mortality: An EBCTCG meta-analysis of 21,000 women in 16 randomised trials. SABCS 2017, abstr. GS1-01
6. Budd GT, Barlow WE, Moore HC et al. SWOG S0221: A Phase III Trial Comparing Chemotherapy Schedules in High-Risk Early-Stage Breast Cancer. J Clin Oncol. 2015 Jan 1;33(1):58-64.
7. Zhou W, Chen S, Xu Fet al. Survival benefit of pure dose-dense chemotherapy in breast cancer: a meta-analysis of randomized

controlled trials. World J Surg Oncol. 2018 Jul 14;16(1):144.

8. Goldvaser H, Majeed H, Ribnikar D et al. Influence of control group therapy on the benefit from dose-dense chemotherapy in early breast cancer: a systemic review and meta-analysis. Breast Cancer Res Treat. 2018 Jun;169(3):413-425.
9. Matikas A, Foukakis T, Moebus V et al. Dose tailoring of adjuvant chemotherapy for breast cancer based on hematologic toxicities: further results from the prospective PANTHER study with focus on obese patients. Ann Oncol. 2019 Jan 1;30(1):109-114.

Statement: Konventionell Anthrazyklin-/ Taxan-basiert (q3w) LoE 1a A AGO +

1. Budd GT, Barlow WE, Moore HC et al. SWOG S0221: A Phase III Trial Comparing Chemotherapy Schedules in High-Risk Early-Stage Breast Cancer. J Clin Oncol. 2015 Jan 1;33(1):58-64.
2. EBCTCG, Peto R, Davies C, Godwin J et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long term outcome among 100,000 women in 123 randomised trials. Lancet 2012;379(9814):432-44
3. Denduluri N, Chavez-MacGregor M, Telli ML et al. Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Clinical Practice Guideline Focused Update. J Clin Oncol. 2018 Aug 10;36(23):2433-2443.

Statement Anthrazyklin verzicht

1. Baybrooke J et al. San Antonio Breast Cancer Symposium 2021
2. Hurvitz et al. NPJ Breast Cancer 2021 Oct 8;7(1):134. doi: 10.1038/s41523-021-00342-5.

Statement: „Tailored“ Anthrazyklin-/ Taxan-basiert LoE 1b B AGO +/-

1. Matikas A, Foukakis T, Moebus V, et al. Dose tailoring of adjuvant chemotherapy for breast cancer based on hematologic toxicities: further results from the prospective PANTHER study with focus on obese patients. Ann Oncol. 2019 Jan 1;30(1):109-114.

Statement: If anthracyclines cannot be given - Docetaxel plus cyclophosphamide

1. Jones S, Holmes FA, O'Shaughnessy J et al. Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. Clin Oncol. 2009;27(8):1177-83.
2. Blum JL, Flynn PJ, Yothers G, et al Anthracyclines in Early Breast Cancer: The ABC Trials-USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology). J Clin Oncol. 2017 Aug 10;35(23):2647-2655.

3. de Gregorio A, Janni W, Friedl TW et al. The impact of anthracyclines in intermediate and high-risk HER2-negative early breast cancer-a pooled analysis of the randomised clinical trials PlanB and SUCCESS C. Br J Cancer. 2022 Jun;126(12):1715-1724.
4. Yu KD, Liu XY, Chen L, et al. Anthracycline-free or short-term regimen as adjuvant chemotherapy for operable breast cancer: A phase III randomized non-inferiority trial. Lancet Reg Health West Pac. 2021 May 13;11:100158

Statement: If anthracyclines cannot be given - Paclitaxel mono weekly

1. Amoroso V, Pedersini R, Sharratt P et al. Should adjuvant weekly Paclitaxel be considered less efficacious than anthracyclines plus cyclophosphamide for lower-risk patients with early-stage breast cancer? J Clin Oncol. 2015 Jan 20;33(3):290.
2. Shulman LN, Berry DA, Cirrincione CT et al. Comparison of doxorubicin and cyclophosphamide versus single-agent paclitaxel as adjuvant therapy for breast cancer in women with 0 to 3 positive axillary nodes: CALGB 40101 (Alliance). J Clin Oncol. 2014 Aug 1;32(22):2311-7.
3. Sparano JA, Wang M, Martino S et al. Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer. N Engl J Med. 2008 Apr 17;358(16):1663-71

Statement: If anthracyclines cannot be given - CMF

1. Perrone F, Nuzzo F, Di Rella F et al. Weekly docetaxel versus CMF as adjuvant chemotherapy for older women with early breast cancer: final results of the randomized phase III ELDA trial. Ann Oncol. 2015;26(4):675-82.

Statement: Low dose maintenance Chemotherapy

1. Colleoni, Viale G, Goldhirsch A. Low-dose oral cyclophosphamide and methotrexate maintenance for hormone receptor-negative early breast cancer: International Breast Cancer Study Group trial 22-00. J Clin Oncol 2016;34:3400-8.

## Recommended Dose-dense and / or Dose-escalated, Sequential (Neo-)adjuvant Chemotherapy

	Oxford		
	LoE	GR	AGO
<b>Dose-dense regimen</b>			
▪ A <sub>60</sub> x 4 → Pac <sub>175</sub> x 4 → C <sub>600</sub> x 4 q2w	1b	A	++
▪ A <sub>60</sub> C q2w x 4 → Pac <sub>175</sub> q2w x 4	1b	B	++
▪ E <sub>90</sub> C q2w x 4 → Pac <sub>175</sub> q2w x 4	1b	A	++
▪ E <sub>90</sub> C q2w x 4 → Pac <sub>80</sub> q1w x 12	1b	B	++
▪ NabPac <sub>125</sub> x 8-12 → E <sub>90</sub> C q2(3)w x 4	1b	B	+
<b>Dose-dense and dose-escalated regimen (N ≥ 4+)</b>			
▪ E <sub>150</sub> → Pac <sub>225</sub> → C2000 q2w	1b	A	++

### Statement: Dose-dense regimen

NabPac bei allergischer Reaktion auf Paclitaxel:

1. Michael Untch , Christian Jackisch , Andreas Schneeweiss et al. NAB-Paclitaxel Improves Disease-Free Survival in Early Breast Cancer: GBG 69-GeparSepto. J Clin Oncol. 2019 Sep 1;37(25):2226-2234.doi: 10.1200/JCO.18.01842.
2. Sherko Kuemmel, Oleg Gluz, Matthias Christgen et al. Efficacy of response- and toxicity-guided neoadjuvant chemotherapy in elderly early breast cancer patients: Results of WSG ADAPT elderly sub-trial. AACR; Cancer Res 2020;80(4 Suppl):Abstract nr P2-16-05.
3. Jens-Uwe Blohmer, Theresa Link, Sherko Kümmel et al. Investigating denosumab as an add-on treatment to neoadjuvant chemotherapy and two different nab-paclitaxel schedules in a 2x2 design in primary breast cancer - First results of the GeparX study. AACR; Cancer Res 2020;80(4 Suppl):Abstract nr GS3-01.

### Statement: Dose-dense regimen

A60x4 - Pac175x4 - C600x4 q2w / ACPac / AC-Pac q2w

1. Citron ML, Berry DA, Cirrincione C et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21:1431-9.

Statement: Dose-dense regimen

AC /EC q2w x 4 Pac q2w x 4

1. Citron ML, Berry DA, Cirrincione C et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21:1431-9.
2. Burnell M, Levine MN, Chapman JA et al. Cyclophosphamide, epirubicin, and fluorouracil versus dose-dense epirubicin and cyclophosphamide followed by paclitaxel versus doxorubicin and cyclophosphamide followed by paclitaxel in node-positive or high-risk nodenegative breast cancer. J Clin Oncol 28:77-82, 2010.
3. Del Mastro L, De Placido S, Bruzzi P et al. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2 × 2 factorial, randomised phase 3 trial. Lancet. 2015;385(9980):1863-72
4. Budd GT, Barlow WE, Moore HC et al. SWOG S0221: a phase III trial comparing chemotherapy schedules in high-risk early-stage breast cancer. J Clin Oncol. 2015 Jan 1;33(1):58-64.
5. Gray R, Bradley R, Braybrooke J et al. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. Lancet. 2019 Apr 6;393(10179):1440-1452. doi: 10.1016/S0140-6736(18)33137-4. Epub 2019 Feb 8

Statement: Dose-dense regimen

EC q2w / Pac q1w

EC q3w / Pac q1w

1. Sparano JA, Zhao, F Martino S et al. Long-Term Follow-Up of the E1199 Phase III Trial Evaluating the Role of Taxane and Schedule in Operable Breast Cancer. J Clin Oncol 2015;33:2353-60.
2. Jones RL, Walsh G, Ashley S et al. A randomized pilot phase II study of doxorubicin and cyclophosphamide (AC) or epirubicin and cyclophosphamide (EC) given 2 weekly with pegfilgrastim (accelerated) vs 3 weekly (standard) for women with early breast cancer. Br J Cancer 2009;100:305-10.
3. Budd GT, Barlow WE, Moore HC et al. SWOG S0221: a phase III trial comparing chemotherapy schedules in high-risk early-stage breast cancer. J Clin Oncol. 2015 Jan 1;33(1):58-64.

EBCTCG Metaanalyse

1. Gray R, Bradley R, Braybrooke J et al. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. *Lancet*. 2019 Apr 6;393(10179):1440-1452. doi: 10.1016/S0140-6736(18)33137-4. Epub 2019 Feb 8

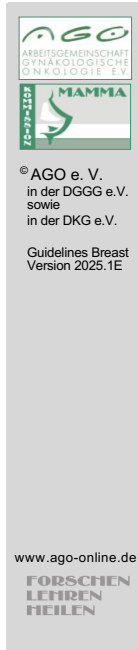
Statement: Dose-dense and dose-escalated regimen (N ≥ 4+)

E-Pac-C q2w

1. Möbus V, Jackisch C, Lück HJ et al. Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. *J Clin Oncol*. 2010 Jun 10;28(17):2874-80.
2. Möbus V, Jackisch C, Lück HJ et al. AGO Breast Study Group (AGO-B) Ten-year Results of Intense Dose-dense chemotherapy show superior survival compared to a conventional schedule in High-risk Primary Breast Cancer: Final results of AGO Phase III iddEPC trial. *Ann Oncol*. 2017 Oct 24. doi: 10.1093/annonc/mdx690. [Epub ahead of print]

Negative Trial

1. Swain SM, Tang G, Geyer CE Jr et al. Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial. *J Clin Oncol*. 2013 Sep 10;31(26):3197-204.
2. Möbus V, von Minckwitz G, Jackisch C et al. German Breast Group (GBG), the AGO Breast Study Group (AGO-B) and NOGGO Study Groups. German Adjuvant Intergroup Node-positive Study (GAIN): a phase III trial comparing two dose-dense regimens (iddEPC versus ddEC-PwX) in high-risk early breast cancer patients. *Ann Oncol*. 2017 Aug 1;28(8):1803-1810.



## Recommended Conventional Regimens for (Neo-)adjuvant Chemotherapy

		Oxford		
		LoE	GR	AGO
<b>Anthrazyklin-/ taxan-based regimen</b>				
▪	*EC q3w x 4 → Pac q1w x 12	2b	B	++
▪	AC q3w x 4 → Pac q1w x 12	1b	A	++
▪	AC → D qw3	1b	A	+
▪	*EC → D qw3	1b	B	+
▪	DAC	1b	A	+ <sup>a</sup>
	A <sub>60</sub> C q3w x 4 → D <sub>100</sub> x 4			
	E <sub>90</sub> C q3w x 4 → D <sub>100</sub> x 4			
	D <sub>75</sub> A <sub>50</sub> C q3w x 6			
<b>Anthrazyklin-free regimen</b>				
▪	6 x DC corresponds to EC → D or 3 x (F)EC → 3 x Doc	1b	B	+
▪	4 x DC >> 4 x AC	1b	B	+
▪	Pac mono	1b	B	+/-
▪	CMF	1a	A	+/-
	D <sub>75</sub> C <sub>600</sub> x 6			
	D <sub>75</sub> C <sub>600</sub> x 4			
	P <sub>80</sub> q1w x 12			
<b>Taxan-free regimen</b>				
▪	EC (q3-2w) x 4-6	2b <sup>(a)</sup>	B	+
	E <sub>90</sub> C <sub>600</sub> x 4-6			

\* Extrapolation from doxorubicin trials

### Statement: Anthracycline/ taxane based regimen

\*EC  $\square$  Pw E90C q3w x 4  $\square$  P80 qw1 x 12

1. Sparano JA, Zhao, F Martino S et al. Long-Term Follow-Up of the E1199 Phase III Trial Evaluating the Role of Taxane and Schedule in Operable Breast Cancer. J Clin Oncol 2015;33:2353-60.

### Statement: Anthracycline/ taxane based regimen

AC  $\square$  Pw A60Cq3w x 4  $\square$  P80qw1 x 12

1. Mamounas EP, Bryant J, Lembersky B et al. Paclitaxel After Doxorubicin Plus Cyclophosphamide As Adjuvant Chemotherapy for Node-Positive Breast Cancer: Results From NSABP B-28 J Clin Oncol 2005;23:3686-3696.
2. Sparano JA, Zhao, F Martino S et al. Long-Term Follow-Up of the E1199 Phase III Trial Evaluating the Role of Taxane and Schedule in Operable Breast Cancer. J Clin Oncol 2015;33:2353-60

### Statement: Anthracycline/ taxane based regimen

AC  $\square$  D A60C q3w x 4  $\square$  D100 qw3 x 4

EC  $\square$  D E90C q3w x 4  $\square$  D100 qw3 x 4

1. Denduluri N, Chavez-MacGregor M, Telli ML et al. Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast

Cancer: ASCO Clinical Practice Guideline Focused Update. J Clin Oncol. 2018 Aug 10;36(23):2433-2443.

Statement: Anthracycline/ taxane based regimen

DAC D75A50C q3w x 6

1. Swain SM, Tang G, Geyer CE Jr et al. Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial. J Clin Oncol. 2013;31(26):3197-204.
2. Blum JL, Flynn PJ, Yothers G et al. Anthracyclines in Early Breast Cancer: The ABC Trials-USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology). J Clin Oncol. 2017;35(23):2647-2655.
3. Braybrooke J, Bradley R, Gray R et al., Taxane with anthracycline versus taxane without anthracycline: An individual patient-level meta-analysis of 16,500 women with early-stage breast cancer in 13 randomised trials, SABCs 2021, GS2-06

Statement: Anthracycline-free regimen

DC D75 C600 x4 corresponds to (F)EC D or

1. Nitz U, Gluz O, Clemens M, et al; West German Study Group PlanB Investigators. West German Study PlanB Trial: Adjuvant Four Cycles of Epirubicin and Cyclophosphamide Plus Docetaxel Versus Six Cycles of Docetaxel and Cyclophosphamide in HER2-Negative Early Breast Cancer. J Clin Oncol. 2019 Apr 1;37(10):799-808. doi: 10.1200/JCO.18.00028. Epub 2019 Feb 20. PMID: 30785826.
2. de Gregorio A, Janni W, Friedl TW et al. The impact of anthracyclines in intermediate and high-risk HER2-negative early breast cancer-a pooled analysis of the randomised clinical trials PlanB and SUCCESS C. Br J Cancer. 2022 Jun;126(12):1715-1724.
3. Yu KD, Liu XY, Chen L, et al. Anthracycline-free or short-term regimen as adjuvant chemotherapy for operable breast cancer: A phase III randomized non-inferiority trial. Lancet Reg Health West Pac. 2021 May 13;11:100158

Statement: Anthracycline-free regimen

DC >> 4 x AC

1. Jones S, Holmes FA, O'Shaughnessy J et al. Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. J Clin Oncol. 2009;27(8):1177-83.

Statement: Anthracycline-free regimen

Pac mono 80 mg q1w x 4-6

1. Shulman LN, Burstein HJ, Winer EP et al. Comparison of doxorubicin and cyclophosphamide versus single-agent paclitaxel as adjuvant therapy for breast cancer in women with 0 to 3 positive axillary nodes: CALGB 40101 (Alliance). J Clin Oncol. 2014;32:2311-7.

Statement: Anthracycline-free regimen

CMF 600/40/600 mg q3w x 6

1. Perrone F, Nuzzo F, Di Rella F et al. Weekly docetaxel versus CMF as adjuvant chemotherapy for older women with early breast cancer: final results of the randomized phase III ELDA trial. Ann Oncol. 2014;26:675-82

Statement: Taxan-freie Schemata (bei pN0)

EC/AC q2w/q3w oder FE100C x 6 q3w

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 May 14-20;365(9472):1687-717.
2. Thomssen C, Vetter M, Kantelhardt EJ et al. on behalf of the NNBC-3 Study Group Adjuvant therapy with FEC and docetaxel in high risk node-negative breast cancer patients identified by tumor-biological (uPA/PAI-1) or clinico-pathological risk assessment. A joint trial of AGO-Breast Study Group, German Breast Group and EORTC Pathology and Biomarker Group (NNBC 3-Europe). Submitted
3. van Rossum AGJ, Kok M, van Werkhoven E, et al; MATADOR Trialists' Group. Adjuvant dose-dense doxorubicin-cyclophosphamide versus docetaxel-doxorubicin-cyclophosphamide for high-risk breast cancer: First results of the randomised MATADOR trial (BOOG 2004-04). Eur J Cancer. 2018 Oct;102:40-48.
4. Kerbrat P, Desmoulins I, Roca L, et al. Optimal duration of adjuvant chemotherapy for high-risk node-negative (N-) breast cancer patients: 6-year results of the prospective randomised multicentre phase III UNICANCER-PACS 05 trial (UCBG-0106). Eur J Cancer. 2017 Jul;79:166-175. doi: 10.1016/j.ejca.2017.03.004. Epub 2017 May 11. PMID: 28501763..
5. Shulman LN, Cirrincione CT, Berry DA et al. Six Cycles of Doxorubicin and Cyclophosphamide or Paclitaxel Are Not Superior to Four Cycles As Adjuvant Chemotherapy for Breast Cancer in Women With Zero to Three Positive Axillary Nodes: Cancer and Leukemia Group B 40101. Journal of Clinical Oncology 2012; 30: 4071-4076.

## Neoadjuvant endocrine Therapy (NET) - Good clinical practice -

- **Suitable for patients who are**
  - inoperable
  - not able or willing to undergo chemotherapy
- **Data for premenopausal in contrast to postmenopausal patients is limited**
- **Optimale duration of NET is at least 4-6 months or until best response or progression**
- **Choice of endocrine therapy is based on the menopausal status**
- **Ki-67 analysis after preoperative short term endocrine therapy for 2 to 4 weeks may predict response to endocrine treatment (prognostic / predictive evaluation)**

1. Brett B, Savva C, Mirshekar-Syahkal B, Hill M, Douek M, Copson E, Cutress R (2024) Surgical outcomes of neoadjuvant endocrine treatment in early breast cancer: meta-analysis. BJS Open 8.
2. Lerebours F, Cabel L, Pierga JY. Neoadjuvant Endocrine Therapy in Breast Cancer Management: State of the Art. Cancers (Basel). 2021 Feb 21;13(4):902.
3. Sella T, Weiss A, Mittendorf EA, et al. Neoadjuvant Endocrine Therapy in Clinical Practice: A Review. JAMA Oncol. 2021 Nov 1;7(11):1700-1708.
4. Harbeck N. Adapted adjuvant therapy of luminal early breast cancer in 2020. Curr Opin Obstet Gynecol. 2021 Feb 1;33(1):53-58.
5. Harbeck N, Gluz O, Kümmel S et al., Endocrine therapy alone in patients with intermediate or high-risk luminal early breast cancer (0-3 lymph nodes), Recurrence Score <26 and Ki67 response after preoperative endocrine therapy: Primary outcome results from the WSG-ADAPT HR+/HER2- trial. SABCS 2020 GS4-04.
6. Smith I et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy on postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentric, parallel-group, randomized phase 3 trial. Lancet Oncol. 2020 Nov;21(11):1443-1454
7. Nitz U et al. The run-in phase of the prospective WSG-ADAPT HR+/Her2- trial demonstrates the feasibility of a study design combining static and dynamic biomarker assessments for individualized therapy in early breast cancer. Ther Adv Med Oncol. 2020 Nov 23;12:1758835920973130

8. Madigan LI et al. Neoadjuvant endocrine therapy in locally advanced estrogen and progesterone receptor-positive breast cancer: determining the optimal endocrine agent and treatment duration in postmenopausal women-a literature review and proposed guidelines. *Breast Cancer Res.* 2020 Jul 20;22(1):77.
9. Kurozumi S et al. Impact of combining the progesterone receptor and preoperative endocrine prognostic index (PEPI) as a prognostic factor after neoadjuvant endocrine therapy using aromatase inhibitors in postmenopausal ER positive and HER2 negative breast cancer. *PLoS One.* 2018;13(8):e0201846.
10. Ellis MJ et al. Ki67 proliferation index as a tool for chemotherapy decisions during and after neoadjuvant aromatase inhibitor treatment of breast cancer: results from the American College of Surgeons Oncology Group Z1031 Trial (Alliance). *J Clin Oncol.* 2017;35(10):1061–9
11. Spring LM, et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol.* 2016 Nov 1;2(11):1477-1486.
12. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. *Breast* 2009; 18; 339
13. Nitz UA, Gluz O, Kümmel S et al. Endocrine therapy response and 21-Gene Expression Assay for therapy guidance in HER+/Her2- Early Breast Cancer. *J Clin Oncol* 2022;40(23):2557-2567).

## Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>▪ <b>Postmenopausal patients:</b> <ul style="list-style-type: none"> <li>▪ Optimizes the option for breast conserving therapy</li> <li>▪ Aromatase inhibitors (at least 6 months)</li> </ul> </li> </ul>	1b	A	+
	1a*	B	+
<ul style="list-style-type: none"> <li>▪ <b>Premenopausal patients</b> <ul style="list-style-type: none"> <li>▪ Tamoxifen</li> <li>▪ Aromatase inhibitors + LHRHa</li> </ul> </li> </ul>	2b	C	+
	1b	C	+/-
<ul style="list-style-type: none"> <li>▪ <b>Concurrent chemo-endocrine therapy</b></li> </ul>	1b	A	-
<ul style="list-style-type: none"> <li>▪ <b>Ki-67 analysis after preoperative short term endocrine therapy for 2 to 4 weeks (Tam / AI ± GnRha) (prognostic / predictive evaluation information)</b></li> </ul>	1b	B	+
<ul style="list-style-type: none"> <li>▪ <b>Prognostic score:</b> <ul style="list-style-type: none"> <li>▪ PEPI: pTN-Stage, ER expression and Ki-67 expression after neoadjuvant endocrine therapy</li> </ul> </li> </ul>	1b	B	+

\* No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)

### Postmenopausal patients:

#### Aromatase inhibitors (for up to 6 months)

1. Smith I, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol 2005; 23; 5108
2. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009; 18; 339
3. Ellis MJ, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype--ACOSOG Z1031. J Clin Oncol 2011; 29; 2342
4. Spring LM et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA oncology 2016;2(11):1477-86.
5. Madigan LI et al. Neoadjuvant endocrine therapy in locally advanced estrogen and progesterone receptor-positive breast cancer: determining the optimal endocrine agent and treatment duration in postmenopausal women-a literature review and proposed guidelines. Breast Cancer Res. 2020 Jul 20;22(1):77. doi: 10.1186/s13058-020-01314-6

### AI and fulvestrant

1. Lerebours F, et al. Randomized phase 2 neoadjuvant trial evaluating anastrozole and fulvestrant efficacy for postmenopausal, estrogen receptor-positive, human epidermal growth factor receptor 2-negative breast cancer patients: Results of the UNICANCER CARMINA 02 French trial (UCBG 0609). *Cancer*. 2016 Oct;122(19):3032-40.

#### Concurrent chemo-endocrine therapy

1. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. *Breast* 2009: 18; 339  
Von Minckwitz G, et al. Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: a randomized, controlled, open phase IIb study. *J Clin Oncol* 2001: 15; 3506
2. Fontein DB, et al. Efficacy of six month neoadjuvant endocrine therapy in postmenopausal, hormone receptor-positive breast cancer patients--a phase II trial. *Eur J Cancer* 2014: 50; 2190
3. Rimawi M, et al. A phase III trial evaluating pCR in patients with HR+, HER2-positive breast cancer treated with neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) +/- estrogen deprivation: NRG oncology/NSABP B-52. *San Antonio Breast Cancer Symposium 2016:Abstract S3-06*.
4. Spring LM, et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol*. 2016 Nov 1;2(11):1477-1486.

#### Preoperative ET and Ki67 measurement:

1. Lerebours F, Cabel L, Pierga JY. Neoadjuvant Endocrine Therapy in Breast Cancer Management: State of the Art. *Cancers (Basel)*. 2021 Feb 21;13(4):902.
2. Sella T, Weiss A, Mittendorf EA, et al. Neoadjuvant Endocrine Therapy in Clinical Practice: A Review. *JAMA Oncol*. 2021 Nov 1;7(11):1700-1708.
3. Harbeck N. Risk-adapted adjuvant therapy of luminal early breast cancer in 2020. *Curr Opin Obstet Gynecol*. 2021 Feb 1;33(1):53-58.
4. Smith I et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy on postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentric, parallel-group, randomized phase 3 trial. *Lancet Oncol*. 2020 Nov;21(11):1443-1454
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7. Kurozumi S et al. Impact of combining the progesterone receptor and preoperative endocrine prognostic index (PEPI) as a prognostic factor after neoadjuvant endocrine therapy using aromatase inhibitors in postmenopausal ER positive and HER2 negative breast cancer. *PLoS One.* 2018;13(8):e0201846.
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1. Ellis MJ et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. *J Natl Cancer Inst.* 2008;100(19):1380–8.
2. Marmé F, et al. Utility of the CPS+EG staging system in hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer treated with neoadjuvant chemotherapy. *Eur J Cancer* 53:65-74, 2015
3. Ellis MJ et al. Ki67 proliferation index as a tool for chemotherapy decisions during and after neoadjuvant aromatase inhibitor treatment of breast cancer: results from the American College of Surgeons Oncology Group Z1031 Trial (Alliance). *J Clin Oncol.* 2017;35(10):1061–9
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## Neoadjuvant Chemotherapy Treatment Strategies Based on Clinical Response

	Oxford		
	LoE	GR	AGO
<b>In case of early response</b>			
▪ Completion of neoadjuvant chemotherapy	1b	A	++
<b>In case of no change:</b>			
▪ Completion of neoadjuvant chemotherapy (NACT) followed by surgery	2b	C	++
▪ Continuation of NACT with non cross-resistant regimen	2b	B	+
▪ AC or EC x 4 → D x 4 or Pw x 12	2b	B	+
▪ DAC x 2 → NX x 4	1b	B	+
<b>In case of disease progression</b>			
▪ Re-evaluation of tumorbiological factors	5	D	+/-
▪ Stop NACT and proceed to surgery or radiotherapy	4	D	++
▪ Additional adjuvant chemotherapy with non cross-resistant regimen	4	D	+/-

### Completion of neoadjuvant chemotherapy

1. Von Minckwitz G, et al. Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: a randomized, controlled, open phase IIb study. J Clin Oncol 2001; 19; 3506
2. Von Minckwitz G, et al. Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. J Natl Cancer Inst 2008; 100; 542
3. Von Minckwitz G, et al. Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. J Natl Cancer Inst 2008; 100; 552
4. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012; 19; 1508

### In case of no change:

#### Completion of NACT, followed by surgery

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012; 19; 1508

2. Smith IC, et al. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol 2002; 20; 1456
3. Von Minckwitz G, et al. Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. J Natl Cancer Inst 2008; 100; 542
4. Von Minckwitz G, et al. Response-guided neoadjuvant chemotherapy for breast cancer. J Clin Oncol. 2013; 31; 3623-30

#### Continuation of NST with non-cross-resistant regimen

##### AC or EC x 4->D x 4 or Pw x 12

1. Bear HD, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2003; 21; 4165
2. Bear HD, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2006; 24; 2019

##### DAC2x -> NX x 4

1. Von Minckwitz G, et al. Response-guided neoadjuvant chemotherapy for breast cancer. J Clin Oncol. 2013; 31; 3623-30

#### In case of progressive disease:

##### Stop of NACT and immediate surgery or radiotherapy

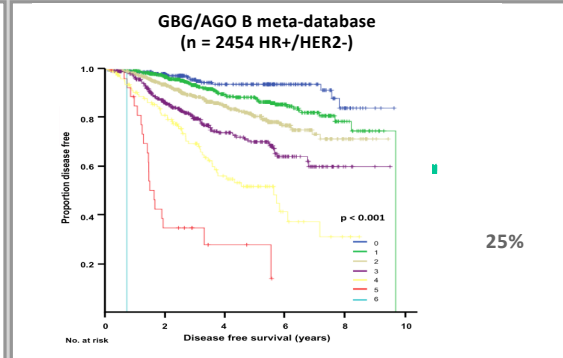
1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012; 19; 1508

Additional adjuvant chemotherapy with non-cross-resistant regimen

1. Mittendorf EA, et al. Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. J Clin Oncol 29, 1956, 2011
2. Lee S-J et al. A phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after neoadjuvant chemotherapy (CREATE-X/JBCRG-04). San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, TX. Abstract: S1-07
3. Colleoni M, Gray KP, Gelber S et al. Low-Dose Oral Cyclophosphamide and Methotrexate Maintenance for Hormone Receptor-Negative Early Breast Cancer: International Breast Cancer Study Group Trial 22-00. J Clin Oncol 2016;34(28):3400-8.

## How to Calculate CPS+EG Score?

Point assignment for CPS+EG score			
Clinical Stage			
I	0	T1N0, T0N1mi, T1N1mi	
IIA	0	T0N1, T1N1, T2N0	
IIIB	1	T2N1, T3N0	
IIIA	1	T0-2N2	
IIIB	2	T4N0-2	
Pathologic Stage			
0	0	T0/eN0	
I	0	T1N0, T0N1mi, T1N1mi	
IIA	1	T0N1, T1N1, T2N0	
IIIB	1	T2N1, T3N0	
IIIA	1	T0-2 N2	
IIIB	1	T4 ND-N2	
Tumor Biologic Factors			
ER negative	1		
Nuclear grade 3	1		



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

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

## Postneo-/Adjuvant Therapy HR+ / HER2-

	Oxford		
	LoE	GR	AGO
▪ Endocrine therapy according to menopausal state	1a	A	++
▪ Abemaciclib for 2 y + endokrine therapy <sup>1</sup>	1b	B	+
▪ Ribociclib (400 mg) for 3 y + AI +/- GnRHa <sup>2</sup>	1b	B	+
▪ Olaparib for 1 y + endokrine therapy (gBRCA1/2 <sup>MUT</sup> ) <sup>3</sup>			
▪ Adjuvant: ≥ 4 involved lymph nodes	1b	A	++
▪ Postneoadjuvant: non-pCR and CPS-EG Score ≥ 3	1b	A	++
▪ CDK4/6i in sequence, starting with olaparib	5	D	+
▪ Capecitabin (bei non-pCR)	1b	A	+/-

- 1 Corresponding to monarchE-study  
 2 Corresponding to Natalee-study  
 3 Corresponding to OlympiA-study

### Statement ER and/or PgR positiv (pCR und non-pCR) Endokrine Therapie nach Menopausenstatus (s. Kap. 10)

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 May 14-20;365(9472):1687-717.
2. 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 Oct 3;386(10001):1341-1352.

### Statement CDK4/6 inhibitors

1. Fasching PA, Stroyakovskiy D, Yardley Det al. (2024) LBA13 Adjuvant ribociclib (RIB) plus nonsteroidal aromatase inhibitor (NSAI) in patients (Pts) with HR+/HER2- early breast cancer (EBC): 4-year outcomes from the NATALEE trial. Annals of Oncology 35:S1207.
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3. Rastogi P, O'Shaughnessy J, Martin M, Boyle F, Cortes J, Rugo HS, Goetz MP, Hamilton EP, Huang CS, Senkus E, Tryakin A, Cicin I, Testa L, Neven P, Huober J, Shao Z, Wei R, André V, Munoz M, San Antonio B, Shahir A, Harbeck N, Johnston S. Adjuvant Abemaciclib Plus Endocrine Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative, High-Risk Early Breast Cancer: Results From a Preplanned monarchE Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes. J Clin Oncol. 2024

Jan 9:JCO2301994.

4. Johnston SRD, Harbeck N, Hegg R et al.; monarchE Committee Members and Investigators Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol. 2020 Dec 1;38(34):3987-3998.
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#### Statement Olaparib gBRCAmt

1. Tutt ANJ, Garber JE, Kaufman B, et al.; OlympiA Clinical Trial Steering Committee and Investigators. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021 Jun 24;384(25):2394-2405.
2. Geyer CE Jr, Garber JE, Gelber RD et al.; OlympiA Clinical Trial Steering Committee and Investigators. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. Ann Oncol 2022;33(12):1250-1268

#### Statement Capecitabine (bei non-pCR; 8 Kurse)

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3. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med. 2017 Jun 1;376(22):2147-2159.

	monarchE	PALLAS	PENELOPE <sup>B</sup>	NATALLEE
n	5,637	5,600	1,250	5101
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib	Ribociclib
% of pts. with NACT	95%	n.r.	100%	88%
Duration of CDK4/6i treatment	24 months	24 months	12 mths	36 months
Follow-up	54.0 months	24 months	43 months	44.2 months
Discontinuation rate	28%	42%	20%	36.2%
Discontinuation rate due to AE <sub>CDKi</sub>	17%	27%	5%	20%
IDFS-HR (95%-CI)	0.680 (0.599-0.720) p < 0.0001	0.96 (0.81-1.14) p = 0.65	0.93 (0.74-1.16) p = 0.525	0.715 (0.609-0.840) p < 0.0001
2-yrs IDFS	92.7% vs. 89.9%	n.r.	88% vs. 78%	93.5% vs. 92.0%
3-yrs IDFS	89.2% vs. 84.4%	88.2% vs. 88.5%	81% vs. 78%	90.7% vs. 87.6%
4-yrs IDFS	85.8% vs. 79.4%	84.2% vs. 84.5%	73% vs. 72%	88.5% vs. 83.6%
5-yrs IDFS	83.6% vs. 76%			

IDFS: invasive disease-free survival



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- 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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- 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
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Human Epidermal Growth Factor Receptor 2-Negative, High-Risk Early Breast Cancer: Results From a Preplanned monarchE Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes. *J Clin Oncol* 42:987–993. <https://doi.org/10.1200/JCO.23.01994>

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## Adjuvant Endocrine Therapy

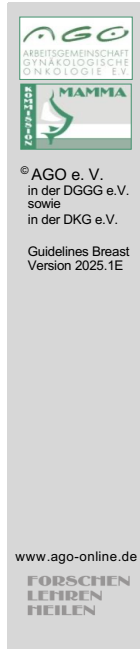
	Oxford		
	LoE	GR	AGO
▪ Endocrine responsive	1a	A	++
▪ Endocrine doubtful responsiveness (1-10%)	2b	D	+
▪ Endocrine therapy sequentially after CT	2a	B	+
▪ Endocrine therapy simultaneous to anti-HER2 therapy (w/o chemotherapy)	2b	B	+
▪ Not sensitiv to endocrine therapy	1a	A	--

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## General Principles in Adjuvant Endocrine Therapy

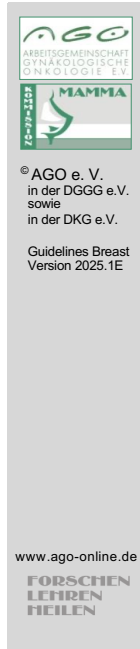


- **Adjuvant endocrine therapy is divided into initial therapy (years 1-5), extended adjuvant therapy (EAT, years 6-10+) and adjuvant endocrine-based treatment.**
- **Standard treatment duration is 5 years.**
- **Extended therapy and initial adjuvant endocrine-based therapy should be considered based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

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20. De Censi A. et al., 10 Year Results of Phase 3 Trial of low-dose Tamoxifen in noninvasive Breast Cancer, *SABCS, 2022, GS408.*

## General Principles in Adjuvant Endocrine Therapy



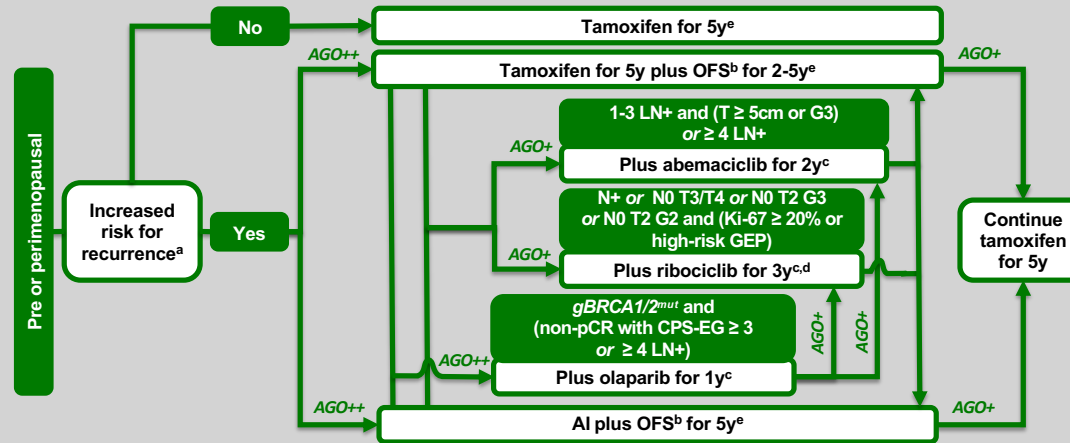
- **Switch to another better tolerated endocrine treatment (Tam or AI) or Tam low dose is better than stopping endocrine therapy altogether.**
- **AI should be used as first treatment in patients, in case of high risk of recurrence.**
- **To date, there is no sufficiently validated biomarker for identification of patients at risk for early versus late recurrence.**
  
- **Bisphosphonates (see also chapter on bone health)**
  - **Osteoprotection**
  - **Improvement of prognosis**
  
- **Women who undergo medical or surgical a hormone ablation are to be equated with postmenopausal women.**

1. Dachverband Osteologie e.V. (2023) Prophylaxe, Diagnostik und Therapie der OSTEOPOROSE bei postmenopausalen Frauen und bei Männern ab dem 50.Lebensjahr: Langfassung V 2.1. <https://register.awmf.org/de/leitlinien/detail/183-001>. Accessed 19 January 2025
2. Ingle JN: Overview of adjuvant trials of aromatase inhibitors in early breast cancer. Steroids 2011;76(8):765-7.
3. 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.
4. 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.
5. 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.
6. 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.
7. Goss PE, Ingle JN, Pritchard KI et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med 2016;375(3):209.
8. Pan H, Gray R, Braybrooke J et al. 20-year risks of breast recurrence after stopping endocrine therapy art 5 years. N Engl J Med

2017;1836-49.

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. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. Johnston, SRD; Harbeck, N; Hegg, R et al-: Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). *J Clin Oncol* 2020; 38:3987-3998.
18. Johnston SRD, Toi M, O'Shaughnessy J, Rastogi P et al\_ Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2023 Jan;24(1):77-90. doi: 10.1016/S1470-2045(22)00694-5. Epub 2022 Dec 6. PMID: 36493792
19. Hortobagyi G, Stroyakovskiy D, Yardley D, et al. Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2– early breast cancer: final invasive disease–free survival (iDFS) analysis from the NATALEE trial. *SABCS, 2023, GS03-03*
20. Importance of endocrine treatment adherence and persistence in breast cancer survivorship: a systematic review. Eliassen FM, Blåfjelldal V, Helland T, et al. *BMC Cancer.* 2023 Jul 4;23(1):625.
21. De Censi A. et al., 10 Year Results of Phase 3 Trial of low-dose Tamoxifen in noninvasive Breast Cancer, *SABCS, 2022, GS408*

# Adjuvant Endocrine-based Therapy in Premenopausal Patients



AI, aromatase inhibitor; CPS-EG, clinical pathological stage + estrogen receptor status and grade score; *gBRCA1/2<sup>mut</sup>*, germline *BRCA1/2* mutation; GEP, gene expression signature; LN, lymph node; non-pCR, no pathological complete response; OFS, ovarian function suppression; y, years; <sup>a</sup>administration of chemotherapy was a surrogate marker for higher risk of recurrence in clinical trials; <sup>b</sup>OFS in case of remaining or recurring ovarian function within 24 months after chemotherapy induced amenorrhea; <sup>c</sup>only HER2-negative; <sup>d</sup>only combined with AI + OFS; <sup>e</sup>in case patients wish to become pregnant interruption of adjuvant endocrine therapy after 18 months for a maximum of 2 years is possible without short-term survival disadvantage with a median F/U of only 3.5 years (AGO+).

## Premenopausal Patients

### Initial Adjuvant Endocrine Therapy (Year 1-5)

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>▪ <b>Low recurrence risk:</b></li> <li>▪ Tamoxifen for 5 years</li> <li>▪ <b>Increased recurrence risk:</b></li> <li>▪ OFS 2-5 years* + tamoxifen for 5 years</li> <li>▪ OFS# + AI for 5 years</li> <li>▪ <b>GnRHa monotherapie</b> (If severe contraindications for Tam exist, compared to no therapy)</li> </ul>	1a	A	++
	1a	A	++
	1a	B	+

OFS: ovarian function suppression;

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

# in premenopausal women AI only in combination with OFS

#### Tamoxifen 5-10 yrs:

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365:1687-717.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011;378:771-84.
3. Davies C, Pan H, Godwin J et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381:805-806.
4. Tormey DC, Gray R, Falkson HC: Postchemotherapy adjuvant tamoxifen therapy beyond five years in patients with lymph node-positive breast cancer. Eastern Cooperative Oncology Group. *J Natl Cancer Inst* 1996;88:1828-33.
5. Goel S, Sharma R, Hamilton A et al: LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. *Cochrane Database Syst Rev.* 2009 7;(4):CD004562.

#### GnRH as monotherapy:

1. Cuzick J, Ambroisine L, Davidson N et al: Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in

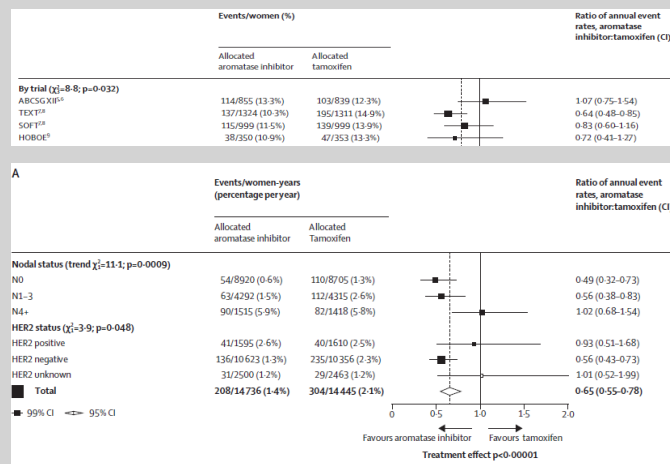
premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. *Lancet* 2007; 369:1711-23.

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

1. Gnant M, Mlineritsch B, Schippinger W et al: Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009;360(7):679-91.
2. Shiba E, Yamashita H, Kurebayashi J et al. A randomized controlled study evaluating safety and efficacy of leuprorelin acetate every-3-months depot for 2 versus 3 or more years with tamoxifen for 5 years as adjuvant treatment in premenopausal patients with endocrine-responsive breast cancer. *Breast Cancer* 2016;23(3):499-509.
3. 6. Kim HA, Lee JW, Nam SJ et al. Adding Ovarian Suppression to Tamoxifen for Premenopausal Breast Cancer: A Randomized Phase III Trial. *J Clin Oncol.* 2019, <https://doi.org/10.1200/JCO.19.0012>
4. Regan MM, Walley BA, Fleming GF et al. Randomized comparisons of adjuvant exemestane + ovarian function suppression versus Tamoxifen + OFS versus tamoxifen in premenopausal women with HR + early breast : update of the TEXT and SOFT trials. *SABCS 2021, GS2-05.*
5. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. *Lancet Oncol.* 2022 Mar;23(3):382-392. doi: 10.1016/S1470-2045(21)00758-0.
6. Francis PA, Fleming GF, Láng I, et al.; SOFT Investigators and the International Breast Cancer Study Group (a division of ETOP IBCSG Partners Foundation). Adjuvant Endocrine Therapy in Premenopausal Breast Cancer: 12-Year Results From SOFT. *J Clin Oncol.* 2022 Dec 9;JCO2201065. doi: 10.1200/JCO.22.01065.
7. Paganí O, Walley BA, Fleming GF et al. SOFT and TEXT Investigators and the International Breast Cancer Study Group (a division of ETOP IBCSG Partners Foundation). Adjuvant Exemestane With Ovarian Suppression in Premenopausal Breast Cancer: Long-Term Follow-Up of the Combined TEXT and SOFT Trials. *J Clin Oncol.* 2022 Dec 15;JCO2201064. doi: 10.1200/JCO.22.01064.
8. Johansson A, Dar H, van't Veer et al. Twenty-years benefit from adjuvant goserelin and tamoxifen in premenopausal patients with breast cancer in a controlled clinical trial. *J Clin Oncol* 2022;40:4071-4082.

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

## Adjuvant Endocrine Therapy in Premenopausal Patients (OFS + TAM / AI)



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

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

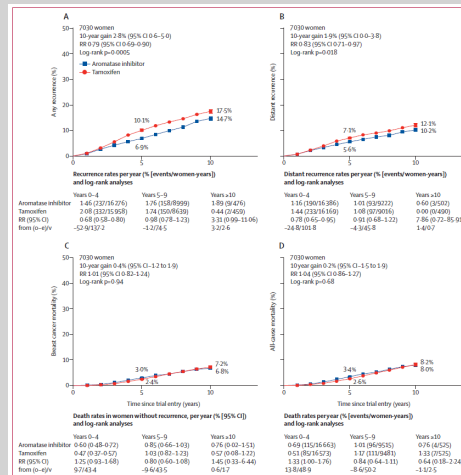
# Adjuvant Endocrine Therapy in Premenopausal Patients (OFS + TAM / AI)

Any recurrence

Breast cancer mortality

Distant recurrence

All-case mortality



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

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

## Premenopausal Patients

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

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

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

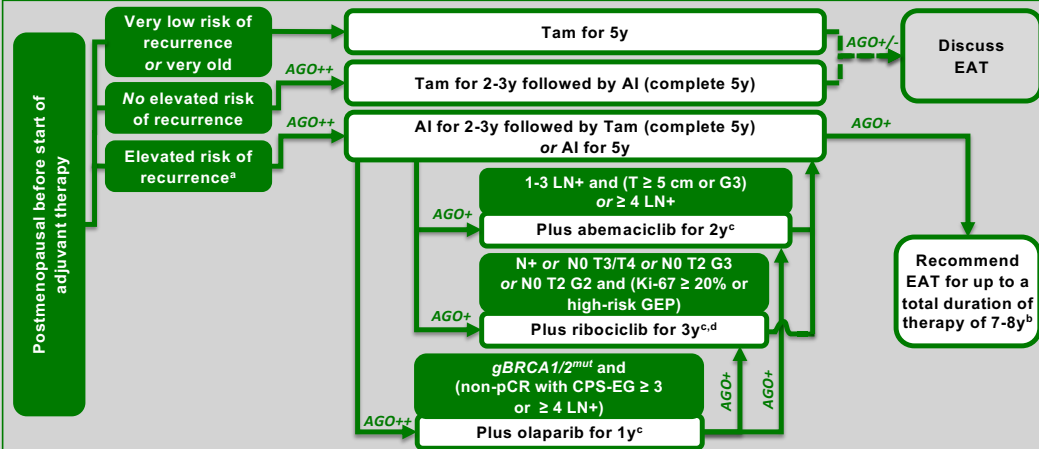
1. Davies C, Pan H, Godwin J et al. Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381(9869):805-16.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

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

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

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

# Adjuvant Endocrine-based Therapy in Postmenopausal Patients



AI, aromatase inhibitor; CPS-EG, clinical pathological stage + estrogen receptor status and grade score; EAT, extended adjuvant therapy; *gBRCA1/2<sup>mut</sup>*, germline *BRCA1/2* mutation; GEP, gene expression signature; LN, lymph node; non-pCR, no pathological complete response; Tam, tamoxifen; y, years; -decision criteria may include: condition after neo(adjuvant) chemotherapy (indicating high risk), positive lymph node status, T2/T3 tumors, elevated risk of recurrence based on immuno-histochemical criteria or based on multi-gene expression assays, regarding EAT high CTSS-Score; -up to date no impact on overall survival; -only HER2 negative; -only combined with AI.

## Postmenopausal Patients

### Initial Adjuvant Endocrine Therapy (Years 1-5)

- **Aromatase inhibitor (AI) for first 5 years**
  - High risk of recurrence
- **Sequential therapy for first 5 years \***
  - Tam (2-3 yrs.) followed by AI to complete 5 years
  - AI (2-3 yrs.) followed by tamoxifen to complete 5 years
- **Tamoxifen 20 mg/d for 5 years\*\***

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

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

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

#### AI for first 5 years:

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

#### Especially in case of lobular cancer

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

#### High risk of recurrence:

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

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

Sequential therapy for first 5 years:

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

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

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

Tamoxifen 20 mg/d for first 5 yrs:

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

early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials. *Breast*. 2016;26:106-14.

Patient care/ adherence and side effects

1. Inwa 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.

## Postmenopausal Patients

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

	Oxford		
	LoE	GR	AGO
<b>In case of high risk of recurrence</b>			
▪ 5 years tamoxifen after 5 years tamoxifen	1a	A	+
▪ 2–5 years AI after 5 years tamoxifen	1a	A	++
▪ After initial AI-containing therapy (upfront or switch), prolongation of endocrine therapy with AI in total for 7-8 years*			
▪ High-risk of recurrence and good tolerability of AI, good bone health	1a	A	+
▪ Low-risk, poor tolerability of AI	1a	A	-
▪ Interruption of endocrine treatment up to 3 months during EAT with AI	1b	B	+/-
* 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.
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3. Petrelli F, Coinu A, Cabiddu M et al. Five or more years of adjuvant endocrine therapy in breast cancer: a meta-analysis of published randomised trials. *Breast Cancer Res Treat* 2013;140(2):233-40.
4. Burstein HJ, Lacchetti C, Anderson H et al. Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer: ASCO clinical practice guideline focused update. *J Clin Oncol*. 2018 Nov 19;JCO1801160. doi: 10.1200/JCO.18.01160
5. 10 years or less of extended adjuvant endocrine therapy for postmenopausal breast cancer patients: A systematic review and network meta-analysis. Petrelli F, Cavallone M, Dottorini L.. *Eur J Cancer*. 2023 Nov;193:113322. doi: 10.1016/j.ejca.2023.113322.
6. Tailoring the optimal duration of the extended adjuvant endocrine therapy in patients with early-stage breast cancer. A systematic review and meta-analysis of randomized clinical trials. Pala L, De Pas T, Pagan E, et al. *Breast*. 2023 Jun;69:258-264. doi:

10.1016/j.breast.2023.02.012.

### 2–5 years AI after 5 years Tamoxifen

1. Goss PE, Ingle JN, Martino S et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005;97(17):1262-71.
2. Jin H, Tu D, Zhao N et al. Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover. *J Clin Oncol* 2012;30(7):718-21.
3. Jakesz R, Greil R, Gnant M et al. Austrian Breast and Colorectal Cancer Study Group. Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. *J Natl Cancer Inst*. 2007;99(24):1845-53. Erratum in: *J Natl Cancer Inst* 2008;100(3):226.
4. Mamounas EP, Jeong JH, Wickerham DL et al. Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial. *J Clin Oncol* 2008;26(12):1965-71.
5. Burstein HJ, Lacchetti C, Anderson H et al. Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer: ASCO clinical practice guideline focused update. *J Clin Oncol*. 2018 Nov 19;JCO1801160. doi: 10.1200/JCO.18.01160
6. Gnant M, G Steger, R Greil, et al. A prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years of Anastrozole after initial 5 years of adjuvant endocrine therapy - results from 3,484 postmenopausal women in the ABCSG-16 trial. *SABCS 2017; GS3-01*
7. Gray R (EBCTCG ) et al. Extended aromatase inhibitor treatment following 5 or more years of endocrine therapy: a metaanalysis of 22192 women in 11 randomised trials. *SABCS 2018;GS3-03*
8. Zackariah C, Kollias J, Bingham J et al. Extended duration of adjuvant aromatase inhibitor in breast cancer: a meta-analysis of randomized controlled trials. *Gland Surg* 2018;7(5):449-457.
9. Mamounas EP, Bandos H, Lembersky BC et al. Use of letrozole after aromatase inhibitor-based therapy in postmenopausal breast cancer (NRG Oncology/NSABP B-42): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019;20(1):88-99.
10. Del Mastro L, Masutti M, Bisagni G: Extended therapy with letrozole as adjuvant treatment of postmenopausal patients with early-

stage breast cancer: a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2021; 22: 1458–67


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

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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 CTSS-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

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