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Guidelines Breast
Version 2025.1D

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Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Systemische Therapie des primären, frühen Mammakarzinoms – HR-positiv / HER2-negativ



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Systemische Therapie des primären, frühen Mammakarzinoms – HR-positiv / HER2-negativ

■ Versionen 2002–2024:

Bauerfeind / Dall / Diel / Fasching / Fersis / Fehm / Friedrich / Friedrichs /
Gerber / Göring / Hanf / Harbeck / Huober / Jackisch / Lisboa / Loibl / Lück
/ Lux / Maass / von Minckwitz / Möbus / Müller / Nitz / Oberhoff /
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**FORSCHEN
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Strategien der differenzierten Systemtherapie in der kurativen Situation

AGO

Bei Indikation zur Chemotherapie neoadjuvante Applikation bevorzugen; Studienteilnahme empfohlen.

<ul style="list-style-type: none"> ▪ HR+ / HER2- mit „niedrigem Rückfallrisiko“ <ul style="list-style-type: none"> ▪ Endokrine Therapie ohne Chemotherapie 	++
<ul style="list-style-type: none"> ▪ HR+ / HER2- mit „erhöhtem Rückfallrisiko“ <ul style="list-style-type: none"> ▪ Endokrine Therapie ▪ endokrin-basierte Therapie (Abemaciclib oder Ribociclib) ▪ Bei Patientinnen mit Indikation zur chemo-endokrinen Therapie*: <ul style="list-style-type: none"> ▪ Konventionell dosierte AT-basierte Chemotherapie (q3w) ▪ Dosisdichte Chemotherapie (inkl. weekly-Regime) 	++ + + ++
<ul style="list-style-type: none"> ▪ gBRCA1/2^{MUT} (HR+ / HER2- o. TNBC) <ul style="list-style-type: none"> ▪ Olaparib +/- endokrine Therapie 	++
<ul style="list-style-type: none"> ▪ Triple-negative (TNBC) <ul style="list-style-type: none"> ▪ Konventionell dosierte AT-basierte Chemotherapie (q3w) ▪ Dosisdichte sequentielle AT-basierte Chemotherapie (inkl. weekly Schemata) ▪ Neoadjuvante platinhaltige Chemotherapie ▪ Neoadjuvante platinhaltige Chemotherapie mit ICPI (Pembrolizumab) 	+ ++ + ++
<ul style="list-style-type: none"> ▪ HER2+ <ul style="list-style-type: none"> ▪ Trastuzumab (plus Pertuzumab bei N+ oder NACT) <ul style="list-style-type: none"> ▪ Sequentielle AT-basierte Chemotherapie mit simultaner Gabe von T + anti-HER2-Therapie ▪ Anthrazyklin-freie Chemotherapie + anti-HER2-Therapie 	++ ++ ++

* s. Prognosekapitel

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):

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, Puztai 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 Jet 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:

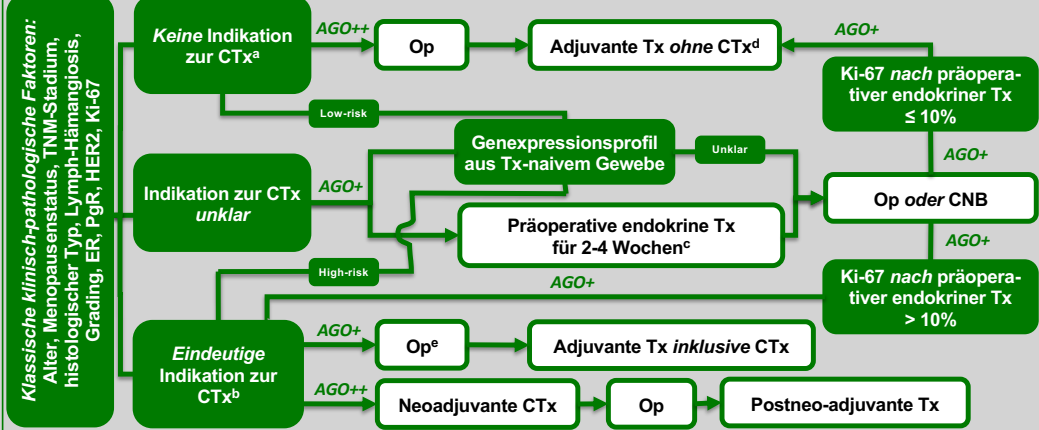
1. Geyer CE, Sikov WM, Huober J et al. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. *Ann Oncol*. 2022 Apr;33(4):384-394.
2. 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

Therapie beim frühen HR-positiven, HER2-negativen Mammakarzinom

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CNB, core needle biopsy; CTx, Chemotherapie; ER, estrogen receptor; PgR, Progesteron-Rezeptor; HER2, humaner epidermaler Wachstumsfaktor-Rezeptor 2; HR, Hormonrezeptor; Op, Operation; Tx, Therapie; ^az. B. \leq cT1c cN0-1 G1-2 Ki-67 \leq 5 % oder - bei unklarer Situation - Genexpressionsprofil low-risk; ^bz. B. primär inoperabler Tumor oder \geq 4 klinisch befallene axilläre Lymphknoten oder G3 und Ki-67 \geq 35 % oder - bei unklarer Situation - Genexpressionsprofil high-risk; ^cendokrine Standardtherapie; ^dsofern postoperativ keine Änderung in Prognosefaktoren; ^esofern noch nicht erfolgt.

Bestimmung des Steroid-Hormonrezeptorstatus

Oxford LoE: 1 GR: A AGO: ++

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

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

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

Bei ER-low (1-10 %) Nennung der Relevanz im histopathologischen Bericht empfohlen.

Endocrine responsiveness:

1. Early Breast Cancer Trialists Collaborative Group EBCTCG. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365(9472):1687–717.
2. Traub L, Thill M, Nitschmann S: 20-Jahres-Ergebnisse einer 5-jährigen Hormontherapie bei Mammakarzinom : Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Internist (Berl)*. Springer Medizin 2018;59(4):410–2.
3. Pan H, Gray R, Braybrooke J et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. *N Engl J Med*. 2017;377(19):1836–46.
4. Allison KH, Hammond MEH, Dowsett M, et al: Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. *J Clin Oncol*. 2020 Apr 20;38(12):1346-1366.
5. Panagiotis Malainou C, Stachika N, Damianou A et al. Estrogen-Receptor-Low-Positive Breast Cancer: Pathological and Clinical Perspectives. *Curr Oncol*. 2023 Nov 4;30(11):9734-9745. doi: 10.3390/currenco30110706.
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.

Adjuvante endokrine Therapie

Bestimmung des Menopausenstatus

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

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

Neoadjuvante systemische Chemotherapie – Klinischer Benefit

	Oxford	
	LoE	GR
▪ Ermöglicht eine Prognoseverbesserung durch Individualisierung der neoadjuvanten und post-neoadjuvanten Behandlung	1b	A
▪ Überleben ist gleich nach neoadjuvanter (präoperativer, primärer) und adjuvanter systemischer Therapie (bei gleichem Regime und gleicher Zyklenzahl, wenn die postneoadjuvante Therapie nicht anhand des pathologischen Ansprechens stratifiziert wird)	1a	A
▪ Pathologische Komplettremission ist mit einem besseren Überleben assoziiert	1b	A
▪ Der RCB Score und die RCB Klasse sind subtypen-unabhängige Prognosefaktoren	2a	B
▪ Kann Operabilität bei primär inoperablen Tumoren erreichen	1b	A
▪ Verbessert die Optionen für eine brusterhaltende Operation	1b	A
▪ Senkt die Rate an axillären Lymphonodektomien	2b	B
▪ Erlaubt Individualisierung der Therapie nach dem Interims-Ansprechen	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; 3541
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)

RCB Score and RCB class as prognostic factors

1. Yau C, Osdoit M, van der Noordaa M et 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

Can achieve operability in primary inoperable tumors

1. Makhoul I, et al. Neoadjuvant systemic treatment of breast cancer. J Surg Oncol 2011: 103; 348

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.

Neoadjuvante systemische Chemotherapie – Indikationen

	Oxford		
	LoE	GR	AGO
▪ Wenn die gleiche postoperative adjuvante Chemotherapie indiziert ist	1b	A	++
▪ Um eine risikoadaptierte postoperative Therapie durchzuführen	1b	A	++
▪ Inflammatorisches Mammakarzinom	2b	B	++
▪ Primär inoperables Mammakarzinom	1c	A	++
▪ Große operable Mammakarzinome, die primär eine Mastektomie und adjuvante Chemotherapie erfordern, mit dem Ziel der Brusterhaltung	1b	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

Neoadjuvante systemische Therapie Zeitablauf von Diagnosestellung, Operation und Radiotherapie

	Oxford		
	LoE	GR	AGO
Zeitpunkt der Operation nach NACT			
▪ 4-8 Wochen nach dem letzten Chemotherapiezyklus	2a	B	++
Radiotherapie innerhalb von 2 Monaten nach der Operation	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-) Adjuvante Chemotherapie: Überblick

	Oxford		
	LoE	GR	AGO
▪ Dosis-dicht Anthrazyklin-/ Taxan-basiert (inkl. weekly)	1a	A	++
▪ Konventionell Anthrazyklin-/ Taxan-basiert (q3w)	1a	A	+
▪ „Tailored“ Anthrazyklin-/ Taxan-basiert	1b	B	+/-
▪ Wenn auf Anthrazykline verzichtet werden soll			
▪ Docetaxel plus Cyclophosphamid	1b	B	++
▪ Paclitaxel mono wöchentlich	1b	B	+/-
▪ CMF	1a	A	+/-

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. 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.
3. 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.
4. 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
5. 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.
6. 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.
7. 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.

8. 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

Empfohlene dosis-dichte und / oder dosis-eskalierte, sequentielle (neo-) adjuvante Chemotherapie

	Oxford		
	LoE	GR	AGO
Dosis-dichte Regime			
▪ A ₆₀ x 4 → Pac ₁₇₅ x 4 → C ₆₀₀ x 4 q2w	1b	A	++
▪ A ₆₀ C q2w x 4 → Pac ₁₇₅ q2w x 4	1b	B	++
▪ E ₉₀ C q2w x 4 → Pac ₁₇₅ q2w x 4	1b	A	++
▪ E ₉₀ C q2w x 4 → Pac ₈₀ q1w x 12	1b	B	++
▪ NabPac ₁₂₅ x 8-12 → E ₉₀ C q2(3)w x 4	1b	B	+
Dosis-dichtes und dosis-eskaliertes Regime (N ≥ 4+)			
▪ E ₁₅₀ → Pac ₂₂₅ → C ₂₀₀₀ 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. 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, Cirincione 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, Cirincione 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.

Empfohlene konventionelle Regime für die (neo-) adjuvante Chemotherapie

		Oxford		
		LoE	GR	AGO
<u>Anthrazyklin-/ Taxan-basierte Regime</u>				
▪	*EC q3w x 4 → Pac q1w x 12	2b	B	++
▪	AC q3w x 4 → Pac q1w x 12	1b	A	++
▪	AC → D q3w	1b	A	+
▪	*EC → D q3w	1b	B	+
▪	DAC	1b	A	+ ^a
<u>Anthrazyklin-freie Regime</u>				
▪	6 x DC entspricht EC → D oder 3 x (F)EC-3 x Doc	1b	B	+
▪	4 x DC >> 4 x AC	1b	B	+
▪	Pac mono	1b	B	+/-
▪	CMF	1a	A	+/-
<u>Taxan-freie Schemata</u>				
▪	EC (q3-2w) x 4-6	2b ^(a)	B	+

* Extrapoliert von Studien mit Doxorubicin

Statement: Anthracycline/ taxane based regimen

*EC q3w Pw E90C q3w x 4 P80 q1w 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 q3w Pw A60Cq3w x 4 P80q1w 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 q3w D A60C q3w x 4 D100 qw3 x 4

EC q3w D E90C q3w x 4 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

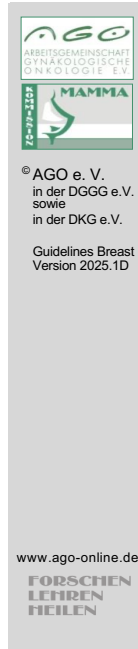
CMF 600/40/600 mg q3w x 6

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.



Neoadjuvante endokrine Therapie (NET) - Gute klinische Praxis -

- **Geeignet für Patientinnen, die**
 - inoperabel sind.
 - keine Chemotherapie haben möchten / können.
- **Datenlage in der Prämenopause im Gegensatz zur Postmenopause begrenzt.**
- **Die optimale Dauer der endokrinen Therapie ist mind. 4-6 Monate oder bis best response bzw. Progress.**
- **Die Wahl der endokrinen Therapie richtet sich nach dem Menopausenstatus.**
- **Eine Ki-67 Analyse nach zwei- bis vierwöchiger, präoperativer endokriner Therapie kann das Ansprechen auf eine endokrine Therapie vorhersagen (prognostische / prädiktive 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).

NET bei Patienten mit endokrin-sensitivem Mammakarzinom

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ▪ Postmenopausale Patienten <ul style="list-style-type: none"> ▪ Verbessert die Optionen für brusterhaltende Operationen ▪ Aromataseinhibitoren (mindestens 6 Monate) ▪ Prämenopausale Patientinnen <ul style="list-style-type: none"> ▪ Tamoxifen ▪ Aromataseinhibitoren + LHRHa ▪ Simultane chemo-endokrine Therapie ▪ Ki-67 Analyse nach kurzer (2-4 W.) präoperativer endokriner Therapie (Tam/AI +/-GnRHa) (prognost./prädikt. Information) ▪ Prognostischer Score: <ul style="list-style-type: none"> ▪ PEPI: pTN-Stadium, ER-Expression und Ki-67 Expression nach neoadjuvanter endokriner Therapie 	 1b 1a* 2b 1b 1b 1b 1b	 A B C C A B B	 + + + +/- - + +

* Keine Langzeitergebnisse zur neoadjuvanter endokriner Therapie (vs. adjuvante endokrine Therapie)

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
5. 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

6. 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.
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.
8. 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
9. 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.
10. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. *Breast* 2009; 18; 339
11. 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).

Prognostic scores following NST

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
4. 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.

Neoadjuvante Chemotherapie – Vorgehen je nach Ansprechen

	Oxford		
	LoE	GR	AGO
Frühes Therapieansprechen:			
▪ Fortführung der neoadjuvanten Therapie	1b	A	++
Bei keiner Änderung:			
▪ Komplettierung der NACT, anschl. Operation	2b	C	++
▪ Fortsetzen der NACT mit einem nicht-kreuzresistenten Schema	2b	B	+
▪ AC oder EC x 4 → D x 4 oder Pw x 12	2b	B	+
▪ DAC x 2 → NX x 4	1b	B	+
Bei Progression:			
▪ Reevaluation der Tumorbiologie	5	D	+/-
▪ Abbruch der NACT und Operation oder Bestrahlung	4	D	++
▪ Zusätzliche adj. Chemotherapie mit nicht-kreuzresistenten Schemata	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

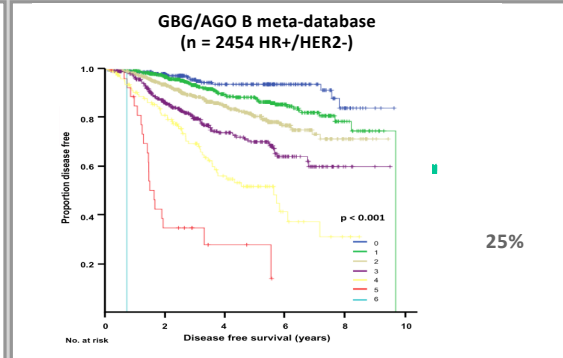
1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012; 19; 1508

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	
IIB	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	
IIB	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-/Adjuvante Therapie HR+ / HER2-

	Oxford		
	LoE	GR	AGO
▪ Endokrine Therapie nach Menopausenstatus	1a	A	++
▪ Abemaciclib für 2 Jahre + endokrine Therapie ¹	1b	B	+
▪ Ribociclib (400 mg) für 3 Jahre + AI +/- GnRHa ²	1b	B	+
▪ Olaparib für 1 Jahr + endokrine Therapie (gBRCA1/2 ^{MUT}) ³			
▪ Adjuvant: ≥ 4 befallene Lymphknoten	1b	A	++
▪ Postneoadjuvant: non-pCR und CPS-EG Score ≥ 3	1b	A	++
▪ CDK4/6i in Sequenz, Beginn mit Olaparib	5	D	+
▪ Capecitabin (bei non-pCR)	1b	A	+/-

1 entsprechend Einschlusskriterien der monarchE-Studie,

2 entsprechend Einschlusskriterien der Natalee-Studie

3 entsprechend Einschlusskriterien der OlympiA-Studie

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.
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.
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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6. Mayer EL, Dueck AC, Martin M, et al. Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2021 Feb;22(2):212-222.
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8. García-Sáenz JA, Marmé F, Untch M et al. (2024) Patient-reported outcomes in high-risk HR+ /HER2- early breast cancer patients treated with endocrine therapy with or without palbociclib within the randomized PENELOPE(B) study. Eur J Cancer 196:113420.
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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.
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Statement Capecitabine (bei non-pCR; 8 Kurse)

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Results From a Randomized Trial. J Clin Oncol. 2022 Jan 12;JCO2102054.

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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.



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FORSCHEN
LEHREN
HEILEN

Adjuvant / Post-Neoadjuvant Treatment with CDK4/6i

	monarchE	PALLAS	PENELOPE ^B	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 _{CDKi}	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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6. Rastogi P, O'Shaughnessy J, Martin M et al. (2024) 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* 42:987–993. <https://doi.org/10.1200/JCO.23.01994>

7. 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.

Adjuvante endokrine Therapie

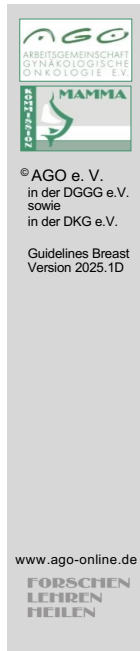
	Oxford		
	LoE	GR	AGO
▪ Endokrin sensitiv	1a	A	++
▪ Fraglich endokrin sensitiv (1-10 %)	2b	D	+
▪ Endokrine Therapie sequentiell: nach einer adjuvanten Chemotherapie	2a	B	+
▪ Endokrine Therapie simultan mit Therapie ohne Chemotherapie	2b	B	+
▪ Nicht endokrin sensitiv	1a	A	--

- Loibl S, André F, Bachelot T (2024) Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 35:159–182.
- 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. https://doi.org/10.1200/JCO.2024.42.16_suppl.513
- Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of randomised trials. La et a. ncet 2005;365:1687-717.
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premenopausal women with endocrine-responsive early breast cancer: an exploratory analysis of TEXT and SOFT. *Ann Oncol* 2017;28:2225-2232.

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14. Burstein HJ, Curigliano G, Thürlimann B et al: Panelists of the St Gallen Consensus Conference. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. *Ann Oncol.* 2021 Oct;32(10):1216-1235.
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Generelle Prinzipien der adjuvanten endokrinen Therapie



- **Die adjuvante endokrine Therapie wird in die initiale Therapie (Jahre 1–5) und die erweiterte adjuvante Therapie (EAT, Jahre 6–10+) eingeteilt. Die initiale adjuvante Therapie umfasst auch die endokrin-basierte Therapie.**
- **Standard Therapiedauer der adjuvanten Therapie: 5 Jahre**
- **Erweiterte Therapiedauer und initial endokrin-basierte Therapie nach individueller Nutzen-Risiko-Abwägung.**
- **Dauer, Wahl & Sequenz von AI oder Tam oder die Kombination mit GnRHa hängen v. a. vom Menopausenstatus, der Verträglichkeit und dem Rückfall-Risiko ab.**

1. Ingle JN: Overview of adjuvant trials of aromatase inhibitors in early breast cancer. Steroids 2011;76(8):765-7.
2. Higgins MJ, Liedke PE, Goss PE et al. Extended adjuvant endocrine therapy in hormone dependent breast cancer: the paradigm of the NCIC-CTG MA.17/BIG 1-97 trial. Crit Rev Oncol Hematol 2013;86(1):23-32.
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14. Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E et al: Relevant factors for the optimal duration of extended endocrine therapy in early breast cancer. *Breast Cancer Res Treat* 2018;168:413-420.
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16. Johnston, SRD; Harbeck, N; Hegg, R et al-: Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). *J Clin Oncol* 2020; 38:3987-3998.
17. Johnston SRD, Toi M, O'Shaughnessy J, Rastogi P et al_ Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2023 Jan;24(1):77-90. doi: 10.1016/S1470-2045(22)00694-5. Epub 2022 Dec 6. PMID: 36493792
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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*

Generelle Prinzipien der adjuvanten endokrinen Therapie

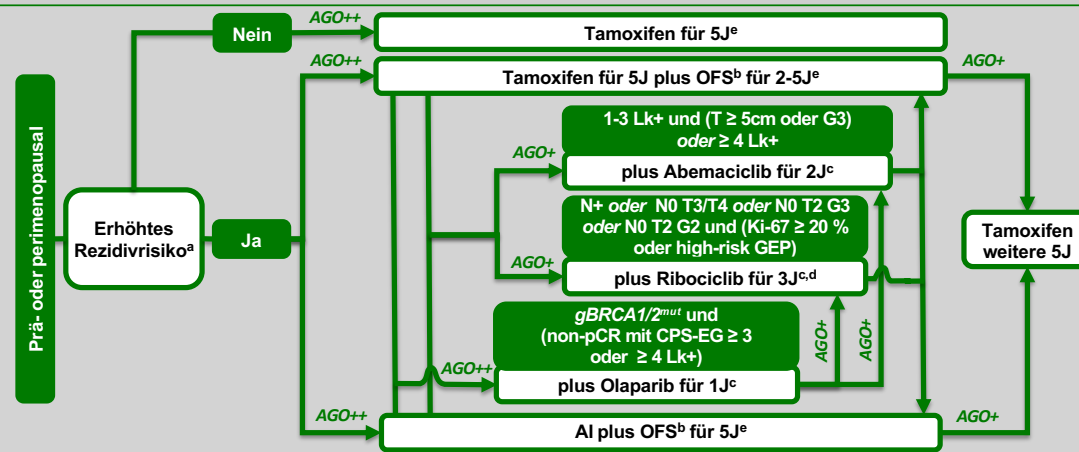
- **Der Wechsel auf eine andere endokrine Therapie (Tam oder AI) oder Tamoxifen low dose ist besser, als die Therapie zu stoppen.**
- **Beginn mit AI bei erhöhtem Rückfall-Risiko.**
- **Es existiert kein ausreichend validierter Biomarker für einen frühen versus einen späten Rückfall.**
- **Bisphosphonate (siehe auch Kapitel Knochengesundheit)**
 - **Osteoprotektion**
 - **Verbesserung der Prognose**
- **Frauen, die medikamentös oder operativ eine Hormonablation erfahren, sind postmenopausalen Frauen gleichzusetzen.**

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 at 5 years. N Engl J Med

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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;36(36):4097-4116. doi: 10.1200/JCO.2018.011160
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.
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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*

Adjuvante endokrin-basierte Therapie in der Prämenopause



AI, Aromataseinhibitor; CPS-EG, Clinical-Pathological Stage + Estrogen receptor status and Grade Score; *gBRCA1/2^{mut}*, Keimbahn *BRCA1/2* Mutation; GEP, Genexpressionsprofil; J, Jahre; Lk, Lymphknoten; non-pCR, keine pathologische Komplettremission; OFS, ovarian function suppression; ²Die Applikation einer Chemotherapie war in den Studien ein Surrogatmarker für ein höheres Rezidivrisiko; ³OFS bei erhaltener Ovarialfunktion bzw. Wiedereintritt der Ovarialfunktion innerhalb von 24 Monaten nach Chemotherapie-induzierter Ovarialinsuffizienz; ⁴nur HER2-negativ; ⁵nur in Kombination mit AI + OFS; ⁶Unterbrechung der adjuvanten endokrinen Therapie nach 18 Monaten für max. 2 Jahre bei Kinderwunsch ohne Überlebensnachteil mit einem medianen F/U von nur 3,5 Jahren möglich (AGO+).

Adjuvante endokrine Therapie bei prämenopausalen Patientinnen (Jahr 1-5)

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ▪ Niedriges Rezidivrisiko: <ul style="list-style-type: none"> ▪ Tamoxifen für 5 Jahre 	1a	A	++
<ul style="list-style-type: none"> ▪ Erhöhtes Rezidivrisiko: <ul style="list-style-type: none"> ▪ OFS 2-5 Jahre* + Tamoxifen für 5 Jahre ▪ OFS# + AI für 5 Jahre 	1a	A	++
<ul style="list-style-type: none"> ▪ GnRHa Monotherapie (Bei relevanten Kontraindikationen für Tam, gegenüber keiner Therapie) 	1a	B	+

OFS: Ovarialfunktions-Suppression;
 * Behandlung nur solange sie tolerabel ist und die Pat. eindeutig prämenopausal ist
 Bei Z. n. Chemotherapie bei Wiedereintritt der Ovarialfunktion innerhalb von 24 Monaten
 Die Applikation einer Chemotherapie war in den Studien ein Surrogatmarker für hohes Rezidivrisiko
 # AI NUR in Kombination mit OFS bei prämenopausalen Patientinnen

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, Ambrosine L, Davidson N et al: Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in

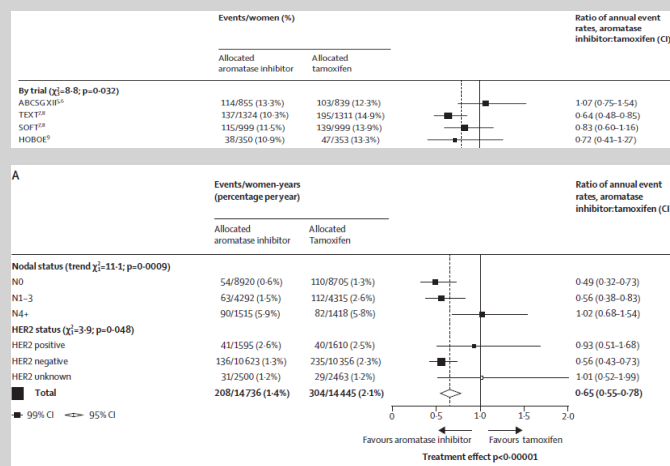
premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. *Lancet* 2007; 369:1711-23.

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

1. 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.

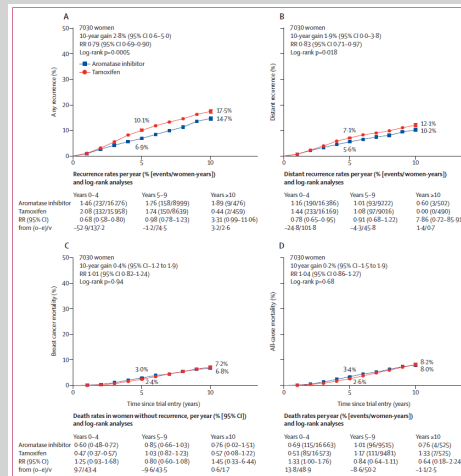
Adjuvant Endocrine Therapy in Premenopausal Patients (OFS + TAM / AI)

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

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

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

5 years Tamoxifen after 5 years Tamoxifen:

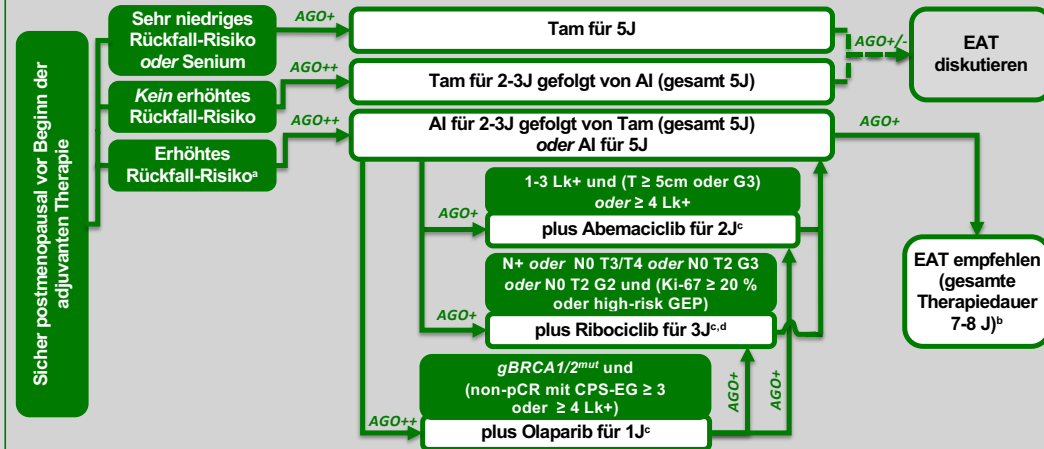
1. Davies C, Pan H, Godwin J et al. Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381(9869):805-16.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

Adjuvante endokrin-basierte Therapie in der Postmenopause



AI, Aromataseinhibitor; CPS-EG, Clinical-Pathological Stage + Estrogen receptor status and Grade Score; EAT, erweiterte adjuvante endokrine Therapie; gBRCA1/2^{mut}, Keimbahn BRCA1/2 Mutation; GEP, Genexpressionsprofil; J, Jahre; Lk, Lymphknoten; Tam, Tamoxifen; ^aEntscheidungskriterien können sein: Z. n. Chemotherapie, positiver Lymphknotenstatus, Tumoren ≥ T2, hohes Rückfallrisiko nach immunohistochemischen Kriterien oder Multigen-Assays, für EAT zusätzlich erhöhter CTSS-Score; ^bkein Einfluss auf das Gesamtüberleben; ^cnur HER2-negativ; ^dnur in Kombination mit AI.

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

	Oxford		
	LoE	GR	AGO
▪ Aromatasehemmer für die ersten 5 Jahre			
▪ Hohes Rezidivrisiko	1a	A	++
	2b	B	+
▪ Sequentielle Therapie für die ersten 5 Jahre*			
▪ Tam (2–3 Jahre) gefolgt von AI bis zur Gesamtdauer von 5 Jahren	1a	A	++
	1a	A	++
▪ AI (2–3 Jahre) gefolgt von Tamoxifen bis zur Gesamtdauer von 5 Jahren	1b	C	++
▪ Tamoxifen 20 mg/d für die ersten 5 Jahre**	1a	A	+

* Die endokrine adjuvante Therapie postmenopausaler Patientinnen sollte in den ersten 5 Jahren für 2-3 Jahre einen Aromatasehemmer enthalten

** Eine Monotherapie mit Tamoxifen kann im Einzelfall in Abhängigkeit vom Alter, Rückfallrisiko und Kontraindikationslage eingesetzt werden.

AI for first 5 years:

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

Especially in case of lobular cancer

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

High risk of recurrence:

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

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

Sequential therapy for first 5 years:

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

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

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

Tamoxifen 20 mg/d for first 5 yrs:

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

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

Patient care/ adherence and side effects

1. Inwa 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.

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

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

* Kein Einfluss auf das Gesamtüberleben (OS)

5 years Tamoxifen after 5 years Tamoxifen:

1. Davies C, Pan H, Godwin J et al. Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381(9869):805-16. Erratum in: Lancet. 2013;381(9869):804.
2. Gray RG, Rea D, Handley K et al. ATTom: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6953 women with early breast cancer. J Clin Oncol 2013; 31 (18 suppl):5.
3. Petrelli F, Coinu A, Cabiddu M et al. Five or more years of adjuvant endocrine therapy in breast cancer: a meta-analysis of published randomised trials. Breast Cancer Res Treat 2013;140(2):233-40.
4. Burstein HJ, Lacchetti C, Anderson H et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update. J Clin Oncol. 2018 Nov 19;JCO1801160. doi: 10.1200/JCO.18.01160
5. 10 years or less of extended adjuvant endocrine therapy for postmenopausal breast cancer patients: A systematic review and network meta-analysis. Petrelli F, Cavallone M, Dottorini L.. Eur J Cancer. 2023 Nov;193:113322. doi: 10.1016/j.ejca.2023.113322.
6. Tailoring the optimal duration of the extended adjuvant endocrine therapy in patients with early-stage breast cancer. A systematic review and meta-analysis of randomized clinical trials. Pala L, De Pas T, Pagan E, et al. Breast. 2023 Jun;69:258-264. doi:

10.1016/j.breast.2023.02.012.

2–5 years AI after 5 years Tamoxifen

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

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


11. Mamounas EP, Bandos H: Ten year results from NRG/NSABP – B42: a randomized , double blinded placebo controlle clinical trial of extended adjuvant endocrine therapy with letrozole in postmenopuasal women with hormone receptor + breast cancer who have completed prevoius adjuvant therapy with an aromatase inhibitor after initial AI containing therapy (upfront or switch) further prolongation of endocrine therapy with AI 2-5years. SABCS 2019, GS4-01
12. Tjan-Heijnen VCG, Lammers SWM, Geurts SME et al. Extended adjuvant aromatase inhibition after sequential endocrine therapy in postmenopausal women with breast cancer: follow-up analysis of the randomised phase 3 DATA trial. *ClinicalMedicine*. 2023 Mar 20;58:101901. doi: 10.1016/j.eclim.2023.101901. eCollection 2023 Apr.

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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