

Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Adjuvante zytostatische und zielgerichtete Therapien



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Adjuvante zytostatische und zielgerichtete Therapien

- **Versionen 2002 – 2018:**
 Dall / Harbeck / Jackisch / Janni / Loibl / Lux/
 von Minckwitz / Möbus / Müller / Nitz /
 Schneeweiss / Simon / Schütz / Solomeyer /
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- **Version 2019:**
 Schmidt / Thomssen

250



Systematic review of published evidence

PUBMED 1999-2018

ASCO 1999-2018

SABCS 1999-2018

ECCO/ESMO 1999-2018

 	<h1>Subtyp-spezifische Strategien zur Systemtherapie</h1>	
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<ul style="list-style-type: none"> Bei Indikation zur Chemotherapie neoadjuvante Applikation bevorzugt 		
<ul style="list-style-type: none"> HR+/HER2- mit „niedrigem Risiko“ 		
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Endokrine Therapie ohne Chemotherapie 		++
<ul style="list-style-type: none"> HR+/HER2- mit „hohem Risiko“ 		
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Konventionell dosierte AT-basierte Chemotherapie (q3w) 		+
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Dosisdichte Chemotherapie (inkl. weekly-Regime) 		++
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Anschließend endokrine Therapie 		++
<ul style="list-style-type: none"> HER2+ 		
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Trastuzumab (plus Pertuzumab neoadjuvant bei hohem Risiko) 		++
<ul style="list-style-type: none"> <ul style="list-style-type: none"> <ul style="list-style-type: none"> Sequentielles A/T-basiertes Regime mit simultaner Gabe von T + anti HER2-Th. 		++
<ul style="list-style-type: none"> <ul style="list-style-type: none"> <ul style="list-style-type: none"> Anthrazyklin-freies, Platin-haltige Regime 		+
<ul style="list-style-type: none"> <ul style="list-style-type: none"> <ul style="list-style-type: none"> Anthrazyklin-freies, Taxan-haltige Regime 		+
<ul style="list-style-type: none"> Triple-negativ (TNBC) 		
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Konventionell dosierte AT-basierte Chemotherapie (q3w) 		+
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Dosisdichte sequentielle A/T-basierte Chemotherapie (inkl. weekly Schemata) 		++
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Neoadjuvante Platin-haltige Chemotherapie 		+

Systematic review of published evidence

PUBMED 1999-2018

ASCO 1999-2018

SABCS 1999-2018

ECCO/ESMO 1999-2018

Dosisdichte Paclitaxel

Schema	ED [mg/m ²]	Gaben	kumulativ	mg/m ² /Wo
<u>Konventionelle Dosisdichte</u>				
EC-Pac q3w	175	4	700	58,33
<u>Dosis-dichte Schemata</u>				
ddEC-ddPac q2w	175	4	700	87,5
ddEC-Pw q1w	80	12	960	80

Adjuvante Chemotherapie ohne Trastuzumab: 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 Anthrazykline nicht gegeben werden können			
■ Docetaxel plus Cyclophosphamid	1b	B	+
■ Paclitaxel mono wöchentlich	1b	B	+/-
■ CMF	1a	A	+/-
■ Niedrig-dosierte Erhaltungs-Chemotherapie	1b	B	-

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

1. Moylan EJ et al. Are dose-dense and triplet chemotherapy regimens optimal adjuvant therapy in the majority of women with node-positive early breast cancer? J Clin Oncol. 2014;32(6):605-6.
2. Lemos Duarte I 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 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 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 F, Zeng X. 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 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 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: „Tailored“ Anthrazyklin-/ Taxan-basiert LoE 1b B AGO +/-

1. Matikas A, Foukakis T, Moebus V, Greil R, Bengtsson NO, Steger GG, Untch M, Johansson H, Hellström M, Malmström P, Gnant M, Loibl S, Bergh J. 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 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.

Statement: If anthracyclines cannot be given - Paclitaxel mono weekly


1. Amoroso V 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 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 et al. N Engl J Med. 2008 Apr 17;358(16):1663-71

Statement: If anthracyclines cannot be given - CMF

1. Perrone 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 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;34:3400-8



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Gray R et al., SABCS 2017, abstr. GS1-01

Early Breast Cancer Trialists' Cooperative Group (EBCTCG)

Increasing the dose-density of adjuvant chemotherapy: an EBCTCG meta-analysis


Same chemotherapy drugs and doses (**n = 10,004**)

Recurrence-free survival: 10-y Gain 4.3% (95%-C.I. 2.2 – 6.5)
(RR = 0.83; 95%-C.I. 0.76 – 0.91; 2p=0.0004)

Overall survival: 10-y Gain 2.8% (95%-C.I. 0.8 – 4.8)
(RR = 0.86; 95%-C.I. 0.77 – 0.95; 2p=0.004)

ER negative: **10-y Gain 4.7%** (95%-C.I. 2.3 – 7.1)
ER positive: **10-y Gain 3.1%** (95%-C.I. 1.5 – 4.7)

1. Gray R 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



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Empfohlene dosis-dichte und / oder dosis-eskalierte, sequentielle adjuvante Chemotherapie*

	Oxford		
	LoE	GR	AGO
Dosis-dichte Regime			
▪ A ₆₀ x4 → Pac ₁₇₅ x4 → C ₆₀₀ x4 q2w	1b	A	++
▪ A ₆₀ C q2w x4 → Pac ₁₇₅ q2w x 4	1b	B	++
▪ E ₉₀ C q2w x4 → Pac ₁₇₅ q2w x 4	1b	A	++
▪ E ₉₀ C q2w x4 → Pac ₈₀ q1w x 12	1b	B	++
Dosis-dichtes und dosis-eskaliertes Regime (N ≥ 4+)			
▪ E ₁₅₀ → Pac ₂₂₅ → C ₂₅₀₀ q2w	1b	A	++

* G-CSF obligat

Statement: Dose-dense regimen

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

1. Citron ML 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 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 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 node-negative breast cancer. J Clin Oncol 28:77-82, 2010.

3. Del Mastro L 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, Hobday TJ, Stewart JA, Isaacs C, Salim M, Cho JK, Rinn KJ, Albain KS, Chew HK, Burton GV, Moore TD, Srkalovic G, McGregor BA, Flaherty LE, Livingston RB, Lew DL, Gralow JR, Hortobagyi GN. 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.

Statement: Dose-dense regimen

EC q2w / Pac q1w

EC q3w / Pac q1w

1. Sparano JA 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 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 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


Statement: Dose-dense and dose-escalated regimen ($N \geq 4+$)

E-Pac-C q2w

1. Moebus V 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 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 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 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.



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Empfohlene konventionelle Regime für die adjuvante Chemotherapie

*Extrapoliert von Studien mit Doxorubicin

Anthrazyklin-/ taxan-basierte Regime

- *EC q3w x 4 → Pac q1w x 12
- AC q3w x 4 → Pac q1w x 12
- AC → D qw3
- *EC → D qw3
- DAC

A₆₀C q3w x 4 → D₁₀₀ x 4

E₉₀C q3w x 4 → D₁₀₀ x 4

D₇₅A₅₀C q3w x 6

Oxford		
LoE	GR	AGO

2b	B	++
1b	A	++
1b	A	+
1b	B	+
1b	A	+

Anthrazyklin-freie Regime

- DC entspricht EC → D
- DC >> 4 x AC
- Pac mono
- CMF

D₇₅ C₆₀₀ x 6

D₇₅ C₆₀₀ x 4

P₈₀ q1w x 12

1b	B	+
1b	B	+
1b	B	+/-
1a	A	+/-

Taxan-freie Schemata (bei pN0)

- FE₁₀₀C x 6

F₅₀₀E₁₀₀C₅₀₀ x 6

2b ^(a)	B	+
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Statement: Anthracycline/ taxane based regimen

*EC → Pw E90C q3w x 4 → P80 qw1 x 12

1. Sparano JA 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 → Pw A60Cq3w x 4 → P80qw1 x 12

1. Mamounas EP 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 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 → D A60C q3w x 4 → D100 qw3 x 4

EC → 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 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 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.

Statement: Anthracycline-free regimen

DC → D75 C600 x4 corresponds to EC → D

1. Harbeck N et al. No age-related outcome disparities according to 21-gene recurrence score groups in early breast cancer patients treated by adjuvant chemotherapy in the prospective WSG PlanB trial. SABCS 2017, abstr.P1-06-06

Statement: Anthracycline-free regimen

DC >> 4 x AC

1. Jones S 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.

Statement: Anthracycline-free regimen

Pac mono 80 mg q1w x 4-6

1. Shulman LN 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 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)

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



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Adjuvante Chemotherapie: Andere Medikamente

Oxford		
LoE	GR	AGO
1a	B	+/-
1b ^a	B	-
2b	C	+
5	D	+
1b	A	--

- **Capecitabine-haltige Therapie bei TNBC**
 - generell
 - postneoadjuvant bei non-pCR
- **Platin-haltige adjuvante Therapie bei TNBC**
- **Hinzunahme von 5-Fluorouracil zu EC/AC-Pac**

Statement: Capecitabine containing regimen in TNBC

1. O'Shaughnessy J et al. Patients with Slowly Proliferative Early Breast Cancer Have Low Five-Year Recurrence Rates in a Phase III Adjuvant Trial of Capecitabine. Clin Cancer Res. 2015;21:4305-11
2. Jiang Y et al. First efficacy results of capecitabine with anthracycline-and taxane-based adjuvant therapy in high-risk early breast cancer: a meta-analysis. PLoS ONE 2012;7(3): e32474.
3. Joensuu H et al. Adjuvant Capecitabine in Combination With Docetaxel, Epirubicin, and Cyclophosphamide for Early Breast Cancer: The Randomized Clinical FinXX Trial. JAMA Oncol. 2017;3(6):793-800.
4. Martín M, Barrios CH, Torrecillas L et al. Efficacy results from CIBOMA/2004-01_GEICAM/2003-11 study: A randomized phase III trial assessing adjuvant capecitabine after standard chemotherapy for patients with early triple negative breast cancer. San Antonio Breast Cancer Symposium 2018, abstr. GS2-04.

Statement: Capecitabine containing regimen in TNBC in general:

1. Martín M, Barrios CH, Torrecillas L et al. Efficacy results from CIBOMA/2004-01_GEICAM/2003-11 study: A randomized phase III trial assessing adjuvant capecitabine after standard chemotherapy for patients with early triple negative breast cancer. San

Antonio Breast Cancer Symposium 2018, abstr. GS2-04.

Statement: Capecitabine containing regimen in TNBC as postneoadjuvant therapy if non-pCR:

1. Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, Kuroi K, Im SA, Park BW, Kim SB, Yanagita Y, Ohno S, Takao S, Aogi K, Iwata H, Jeong J, Kim A, Park KH, Sasano H, Ohashi Y, Toi M. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med. 2017 Jun 1;376(22):2147-2159.

Statement: 5- Fluorouracile added to EC/AC=>Pac


1. Del Mastro L 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

Statement: Platinum containing regimen in TNBC

1. Joensuu H, Gligorov J. Adjuvant treatments for triple-negative breast cancers. Ann Oncol. 2012;23 Suppl 6:vi40-5.
2. Alba E et al. A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from the GEICAM/2006-03, multicenter study. Breast Cancer Res Treat 2012: 136; 487
3. Von Minckwitz G et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol 2014: 15; 747
4. Ando M, et al. Randomized phase II study of weekly paclitaxel with and without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA breast cancer without HER2 overexpression. Breast Cancer Res Treat 2014: 145; 401
5. Petrelli F et al. The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat 2014: 144; 223
6. Sikov WM et al. Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast

Cancer: CALGB 40603 (Alliance). J Clin Oncol 2015; 33; 13

7. Loibl S, O'Shaughnessy J, Untch M et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. Lancet Oncol. 2018 Apr;19(4):497-509.
8. Gluz O Nitz U, Liedtke C et al. Comparison of Neoadjuvant Nab-Paclitaxel+Carboplatin vs Nab-Paclitaxel+Gemcitabine in Triple-Negative Breast Cancer: Randomized WSG-ADAPT-TN Trial Results. J Natl Cancer Inst. 2018 Jun 1;110(6):628-637.

Adjuvante Therapie mit Trastuzumab +/- Pertuzumab			
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	LoE	GR	AGO
	1a	A	++
	Trastuzumab		
	▪ Trastuzumab + Pertuzumab		
	▪ N+ und/oder HR-		
	▪ N- und HR+		
	1b	B	+
	1b	B	+/-
	▪ Trastuzumab bei nodal-negativer Erkrankung (wenn Chemotherapie als indiziert angesehen wird)		
	▪ 10 mm		
	▪ > 5–10 mm		
	▪ ≤ 5 mm		
	1a	A	++
	2b	B	+
	2b	B	+/-

Statement Trastuzumab + Pertuzumab (N+ and/or HR- / N- and HR+)

1. von Minckwitz G et al; APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017;377(2):122-131.


Statements:Trastuzumab in node-negative disease (if chemotherapy is indicated)

1. Piccart-Gebhart MJ, et al.; Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353(16):1659-72.
2. Smith I et al.; HERA study team. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet. 2007;369(9555):29-36.
3. Goldhirsch A et al.; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet. 2013;382(9897):1021-8.
4. Cameron D et al.; Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017;389(10075):1195-1205.

5. Perez EA et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol*. 2014;32(33):3744-52.
6. Jackisch C et al. HannaH phase III randomised study: Association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. *Eur J Cancer*. 2016;62:62-75.
7. Jackisch C et al. Efficacy and safety of subcutaneous or intravenous trastuzumab in patients with HER2-positive early breast cancer after 5 years' treatment-free follow-up: Final analysis from the phase III, open-label, randomized HannaH study. *SABCS 2017*, abstr. PD3-11
8. Denduluri N et al. Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor (Her2)-negative and adjuvant targeted therapy for Her2-positive breast cancers: an American Society of Clinical Oncology Guideline adaptation of the Cancer Care Ontario Clinical Practice Guideline. *J Clin Oncol* 2016 Jul;34(20):2416-27.

Statements: >10 mm/> 5-10 mm/ <= 5mm

1. Denduluri N et al. Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor (Her2)-negative and adjuvant targeted therapy for Her2-positive breast cancers: an American Society of Clinical Oncology Guideline adaptation of the Cancer Care Ontario Clinical Practice Guideline. *J Clin Oncol* 2016;34(20):2416-27.
2. O'Sullivan CC et al. Efficacy of Adjuvant Trastuzumab for Patients With Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer and Tumors ≤ 2 cm: A Meta-Analysis of the Randomized Trastuzumab. *J Clin Oncol*. 2015;33(24):2600-8.
3. de Nonneville A et al. Benefit of adjuvant chemotherapy with or without trastuzumab in pT1ab node-negative human epidermal growth factor receptor 2-positive breast carcinomas: results of a national multi-institutional study. *Breast Cancer Res Treat*. 2017;162(2):307-316.



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Adjuvante Therapie mit Trastuzumab

	Oxford	
	LoE	GR
		AGO
Beginn der Therapie		
▪ Simultan mit Taxanen	1a	A
▪ Sequentiell bis zu 3 Monaten nach Chemotherapie	1b	B
▪ s.c. = i.v.	1b	B
Dauer		
▪ Für 1 Jahr	1b	A
▪ Für 0,5 Jahre	1b	A
▪ Für 2 Jahre	1b	A

Statement: Start of treatment simultaneously with taxanes

1. Smith I, et al.; HERA study team. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet*. 2007;369(9555):29-36.
2. Goldhirsch A et al.; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. *Lancet*. 2013;382(9897):1021-8.
3. Cameron D et al.; Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet*. 2017;389(10075):1195-1205.
4. Perez EA et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol*. 2014;32(33):3744-52.
5. Joensuu H et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. *J Clin Oncol*. 2009 Dec 1;27(34):5685-92. Epub 2009 Nov 2.
6. Yin W et al. Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: a meta-analysis of published randomized controlled trials. *PLoS One*. 2011;6(6):e21030.

7. Perez E et al. Sequential Versus Concurrent Trastuzumab in Adjuvant Chemotherapy for Breast Cancer. J Clin Oncol 2011;29:4491-4497
8. Slamon D et al.; Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273-83.
9. Perez EA et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol. 2014;32(33):3744-52.

Statement s.c.

1. Gligorov J et al.; SafeHer Study Group. Safety and tolerability of subcutaneous trastuzumab for the adjuvant treatment of human epidermal growth factor receptor 2-positive early breast cancer: SafeHer phase III study's primary analysis of 2573 patients. Eur J Cancer. 2017;82:237-246.
2. Pivot X et al.; PrefHer Study Group. Efficacy and safety of subcutaneous trastuzumab and intravenous trastuzumab as part of adjuvant therapy for HER2-positive early breast cancer: Final analysis of the randomised, two-cohort PrefHer study. Eur J Cancer. 2017;86:82-90.

Statement: Duration

Duration Trastuzumab 1 year

Duration Trastuzumab 2 year

Duration Trastuzumab 0.5 years


1. Goldhirsch A et al.; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive

breast cancer (HERA): an open-label, randomised controlled trial. *Lancet*. 2013;382(9897):1021-8.

2. Cameron D et al.; Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet*. 2017;389(10075):1195-1205.
3. Pivot X et al.; PHARE trial investigators. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol*. 2013;14(8):741-8.
4. Joensuu H et al. A randomized phase III study of a adjuvant trastuzumab for a duration of 9 weeks versus 1 year, combined with adjuvant taxane-anthracycline chemotherapy, for early HER2-positive breast cancer (the SOLD study). *SABCS 2017*, abstr. GS3-04
5. Pivot X, Romieu G, Debled M et al. PHARE randomized trial final results comparing 6 to 12 months of trastuzumab in adjuvant early breast cancer. *San Antonio Breast Cancer Symposium 2018*, GS2-07.
6. Earl HM, Vallier AL, Dunn J et al. [Trastuzumab-associated cardiac events in the Persephone trial](#). *Br J Cancer*. 2016 Dec 6;115(12):1462-1470.
7. Conte P, Frassoldati A, Bisagni G et al. Nine weeks versus 1 year adjuvant trastuzumab in combination with chemotherapy: final results of the phase III randomized Short-HER study. *Ann Oncol*. 2018 Dec 1;29(12):2328-2333.

Metaanalysis:

1. Inno A, Barni S, Ghidini A et al. One year versus a shorter duration of adjuvant trastuzumab for HER2-positive early breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2018 Oct 13. doi: 10.1007/s10549-018-5001-x. [Epub ahead of print] Review.

 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	Adjuvante Therapie mit Trastuzumab +/- Pertuzumab: Chemotherapieregime		
	Oxford		
	LoE	GR	AGO
Trastuzumab simultan mit			
▪ Paclitaxel / Docetaxel nach AC / EC	1b	A	++
▪ P q1w 12 x ohne A bei pT < 2 cm, pN0	2b	B	+
▪ Docetaxel und Carboplatin	1b	A	+
Trastuzumab + Pertuzumab simultan mit			
▪ Mit Paclitaxel q1w (oder Docetaxel q3w) nach EC /AC	1b	B	++
▪ Mit Docetaxel + Carboplatin	1b	B	+
▪ Mit Taxan dosis-dicht	2b	B	+*
Radiotherapie simultan zu Trastuzumab	2b	B	+

Statement: with paclitaxel/docetaxel after AC/EC

1. Perez E et al. Sequential Versus Concurrent Trastuzumab in Adjuvant Chemotherapy for Breast Cancer. J Clin Oncol 2011;29:4491-4497.
2. Cameron D et al.; Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017;389(10075):1195-1205.

Statement: P q1w12 without A in pT < 2 cm pN0

1. Tolaney SM et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med. 2015;372(2):134-41.
2. Tolaney SM et al. Seven-year (yr) follow-up of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC). Journal of Clinical Oncology 2017;35:15 suppl: 511-511

Statement: with docetaxel and carboplatin

1. Valero V et al. Multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab as first-line chemotherapy for patients with HER2-gene-amplified metastatic breast cancer (BCIRG 007 study): two highly active therapeutic regimens. J Clin Oncol. 2011;29(2):149-56.
2. Burstein HJ et al. Choosing the Best Trastuzumab-Based Adjuvant Chemotherapy Regimen: Should We Abandon Anthracyclines? Journal of Clinical Oncology 2012;18(30):2179-2182

Statement: Trastuzumab + Pertuzumab simultaneously with Paclitaxel q1w or Docetaxel q3w (after EC or AC)

1. von Minckwitz G et al.; APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017;377(2):122-131.

Statement: Trastuzumab + Pertuzumab simultaneously with Docetaxel and Carboplatin q3w

1. von Minckwitz G et al.; APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017;377(2):122-131.
2. 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

Statement: Trastuzumab + Pertuzumab simultaneously with taxanes dose-dense

1. von Minckwitz G et al.; APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017;377(2):122-131

Statement: radiotherapy concurrent with trastuzumab

1. M. Y. Halyard, T. M. Pisansky, L. J. Solin et al. Trastuzumab can be administered concurrent to adjuvant radiotherapy of the breast or thoracic wall. Adjuvant radiotherapy (RT) and trastuzumab in stage I-IIA breast cancer: Toxicity data from North Central Cancer Treatment Group Phase III trial N9831 J Clin Oncol. 2009;27(16):2638-44



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Adjuvante Therapie mit weiteren zielgerichteten Substanzen

Oxford		
LoE	GR	AGO
1b^a	B	-
1b	B	-
1b^a	B	-
1b	B	--

- **Lapatinib**
 - (verzögerte adjuvante Therapie)
- **Lapatinib + Trastuzumab**
- **Bevacizumab**

Statement: with Lapatinib

Delayed adjuvant treatment

1. Moreno-Aspitia A et al. RC0639: phase II study of paclitaxel, trastuzumab, and lapatinib as adjuvant therapy for early stage HER2-positive breast cancer. Breast Cancer Res Treat. 2013;138(2):427-35.
2. Goss PE et al.; TEACH investigators. Adjuvant lapatinib for women with early-stage HER2-positive breast cancer: a randomised, controlled, phase 3 trial. Lancet Oncol. 2013;14(1):88-96.
3. Perez EA et al. Disease-free survival (DFS) in the lapatinib alone arm and expanded results of the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) in the adjuvant treatment of HER2-positive early breast cancer (EBC) ESMO 2014

Statement: with Lapatinib + Trastuzumab

1. Piccart-Gebhart M et al. Adjuvant Lapatinib and Trastuzumab for Early Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: Results From the Randomized Phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial. J Clin Oncol. 2016 1;34(10):1034-42.

Statement: Bevacizumab

1. Cameron D et al. Adjuvant bevacizumab-containing therapy in triple-negative breast cancer (BEATRICE): primary results of a randomised, phase 3 trial. *Lancet Oncol.* 2013;14(10):933-42.
2. Slamon D et al.. BETH: A Randomized Phase III Study Evaluating Adjuvant Bevacizumab Added to Trastuzumab/Chemotherapy for Treatment of HER2+ Early Breast Cancer. *SABCS 2013*
3. Miller KD, O'Neill A, Gradishar W et al. Double-Blind Phase III Trial of Adjuvant Chemotherapy With and Without Bevacizumab in Patients With Lymph Node-Positive and High-Risk Lymph Node-Negative Breast Cancer (E5103). *J Clin Oncol.* 2018 Sep 1;36(25):2621-2629.

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	LoE	GR	AGO
HR positiv (pCR und non-pCR)*			
▪ Endokrine Therapie nach Menopausenstatus (s. Kap. 10)	1a	A	++
▪ Capecitabin (bei non-pCR)	3b	C	+/-
HER2 positiv (bei pCR)			
▪ Low risk: Trastuzumab (bis 12 Mon. komplett)	2a	C	++
▪ High risk (z.B. HR-/N+): Trastuzumab + Pertuzumab (bis 12 Mon. komplett)	2b	C	+
HER2 positiv (bei non-pCR)			
▪ T-DM1 (bis zu 14 Gaben anti-HER2-Therapie komplett)	1b	B	+
▪ Neratinib nach 1 Jahr Trastuzumab (nur bei HR-positiv)	4	C	+/-
▪ Trastuzumab + Pertuzumab (bis 12 Mon. komplett)	2b	C	+/-
Tripelnegativ (TNBC) (bei non-pCR)			
▪ Capecitabin (bis zu 8 Kurse)	1b	B	+

*Studienteilnahme empfohlen

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.

etc.

Statement HER2 positiv (bei pCR): Low risk: Trastuzumab (bis 12 Mon. komplett)

1. Goldhirsch A et al.; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet. 2013;382(9897):1021-8.

etc.

Statement HER2 positiv (bei pCR): pN+ oder HR-: Trastuzumab + Pertuzumab (bis 12 Mon. komplett)

1. von Minckwitz G, Procter M, de Azambuja E, et al. APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017 Jul 13;377(2):122-131.

Statement HER2 positiv (bei non-pCR) T-DM1 (bis 12 Mon. anti-HER2-Therapie komplett)


1. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2018 Dec 5. doi: 10.1056/NEJMoa1814017.

Statement HER2 positiv (bei non-pCR) Neratinib nach 1 Jahr Trastuzumab (nur bei HR-positiv)

1. Martin M et al.; ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(12):1688-1700

Statement Tripelnegativ (TNBC) (bei non-pCR) Capecitabine (8 Kurse)

1. 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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Biosimilars

Generelle Überlegungen

Biosimilars, die in der Therapie (z.B. Trastuzumab) und Supportivtherapie des Mammakarzinoms (z.B. GCSF) eingesetzt werden, müssen vor dem Einsatz in der täglichen Routine den von den Zulassungsbehörden (EMA, FDA) geforderten Entwicklungs- und Zulassungsprozess erfolgreich durchlaufen haben.*

* Nach: Thill M et al. Einführung und Verwendung von biosimilaren Antikörpern in der Therapie des Mammakarzinoms. Geburtshilfe Frauenheilkd 2018;78(1):41-44

1. Thill M et al. Einführung und Verwendung von biosimilaren Antikörpern in der Therapie des Mammakarzinoms. Geburtshilfe Frauenheilkd 2018;78(1):41-44
2. Thill M. New frontiers in oncology: biosimilar monoclonal antibodies for the treatment of breast cancer. Expert Rev Anticancer Ther. 2015;15(3):331-8.
3. Tabernero J et al. Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers. ESMO Open. 2017;1(6):e000142.
4. Jacobs I, Ewesuedo R, Lula S, Zacharchuk C. Biosimilars for the Treatment of Cancer: A Systematic Review of Published Evidence. BioDrugs. 2017;31(1):1-36.