Diagnostik und Therapie primärer und metastasierter Mammakarzinome

Guidelines Breast
Version 2018.1D

Adjuvante zytostatische und zielgerichtete Therapien

FORSCHEN
LEHREN
HEILEN

Guidelines Breast
Version 2018.1D

Adjuvante zytostatische und zielgerichtete Therapien

- **Versionen 2002–2017:**
  Dall / Harbeck / Jackisch /Janni / Loibl / Lux/ von Minckwitz / Möbus / Müller / Nitz / Schneeweiss / Simon / Schütz / Solomeyer / Stickeler / Thomssen / Untch

- **Version 2018:**
  Thill / Untch

Subtyp-spezifische Strategien zur Systemtherapie

Guidelines Breast
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	AGO
▪ **Wenn die Indikation zur Chemotherapie aufgrund der Tumorbiologie gegeben ist, sollte eine neoadjuvante Therapie erwogen werden**	++
▪ **HR+/HER2- mit „niedrigem Risiko"**	
▪ **Endokrine Therapie ohne Chemotherapie**	++
▪ **HR+/HER2- mit „hohem Risiko"**	
▪ **Konventionell dosierte AT-basierte Chemotherapie**	++
▪ **Dosisdichte Chemotherapie**	++
▪ **Anschließend endokrine Therapie**	++
▪ **HER2+**	
▪ **Trastuzumab (plus Pertuzumab neoadjuvant bei hohem Risiko)**	++
▪ **Sequenzielles A/T-basiertes Regime mit simultaner Gabe von T+H**	++
▪ **Anthrazyklin-freies, Platin-haltige Regime**	+
▪ **Anthrazyklin-freies, Taxan-haltige Regime**	+
▪ **Triple-negativ (TNBC)**	
▪ **Konventionell dosierte AT-basierte Chemotherapie**	++
▪ **Dosisdichte Chemotherapie**	++
▪ **Neoadjuvant Platin-haltige Chemotherapie**	+

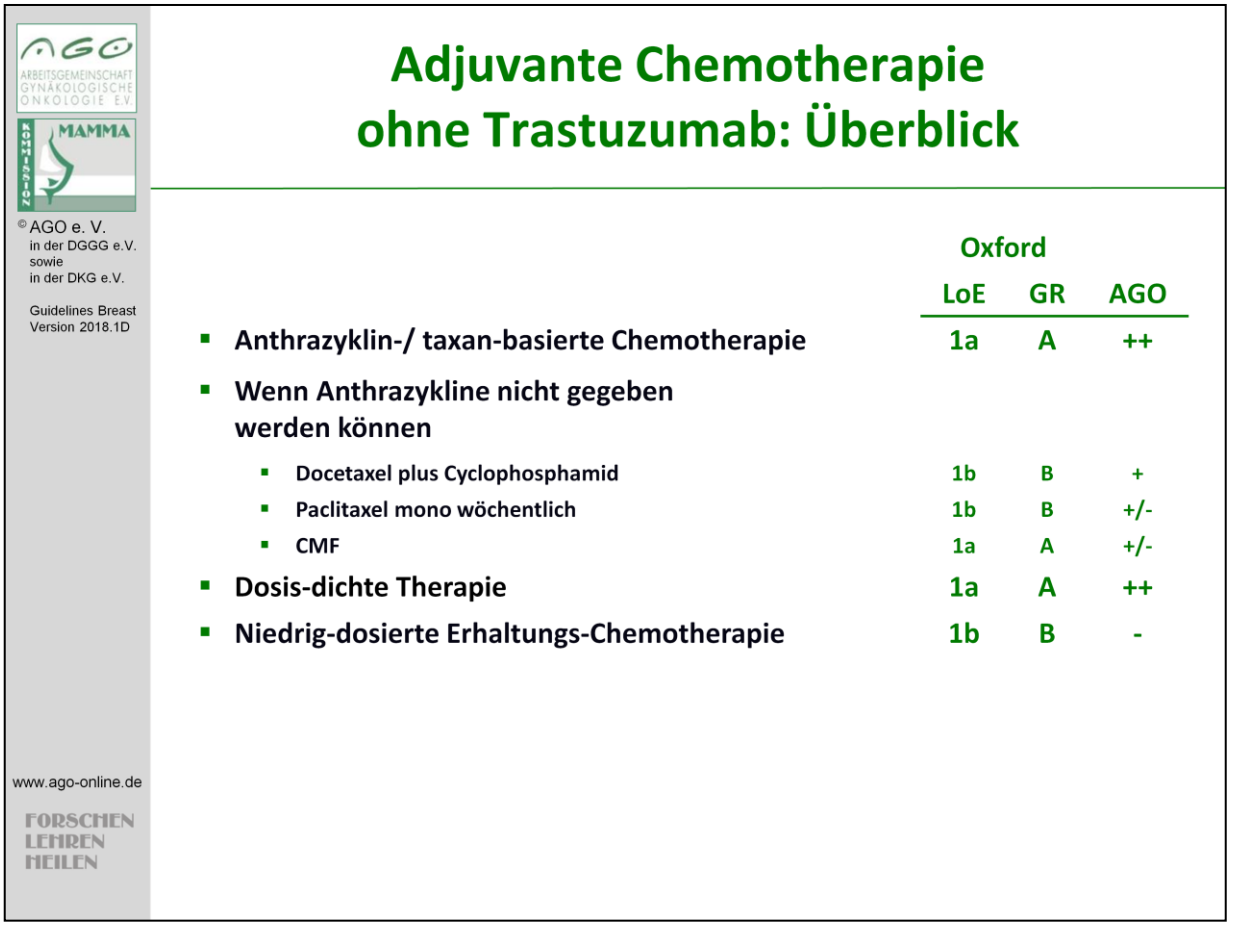
Systematic review of published evidence

PUBMED 1999-2017

ASCO 1999-2017

SABCS 1999-2017

ECCO/ESMO 1999-2017



Statement: Anthracycline/ taxane based chemotherapy

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 diffeent 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

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: Dose-dense in case of high tumor burden

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. 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;28(17):2874-80.
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

Statement: Low dose maintenance Chemotherapy

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

Colleoni et al., J Clin Oncol 2016, 34: 3400-8

rand. phase 3-study of IBCSG: trial 22-00

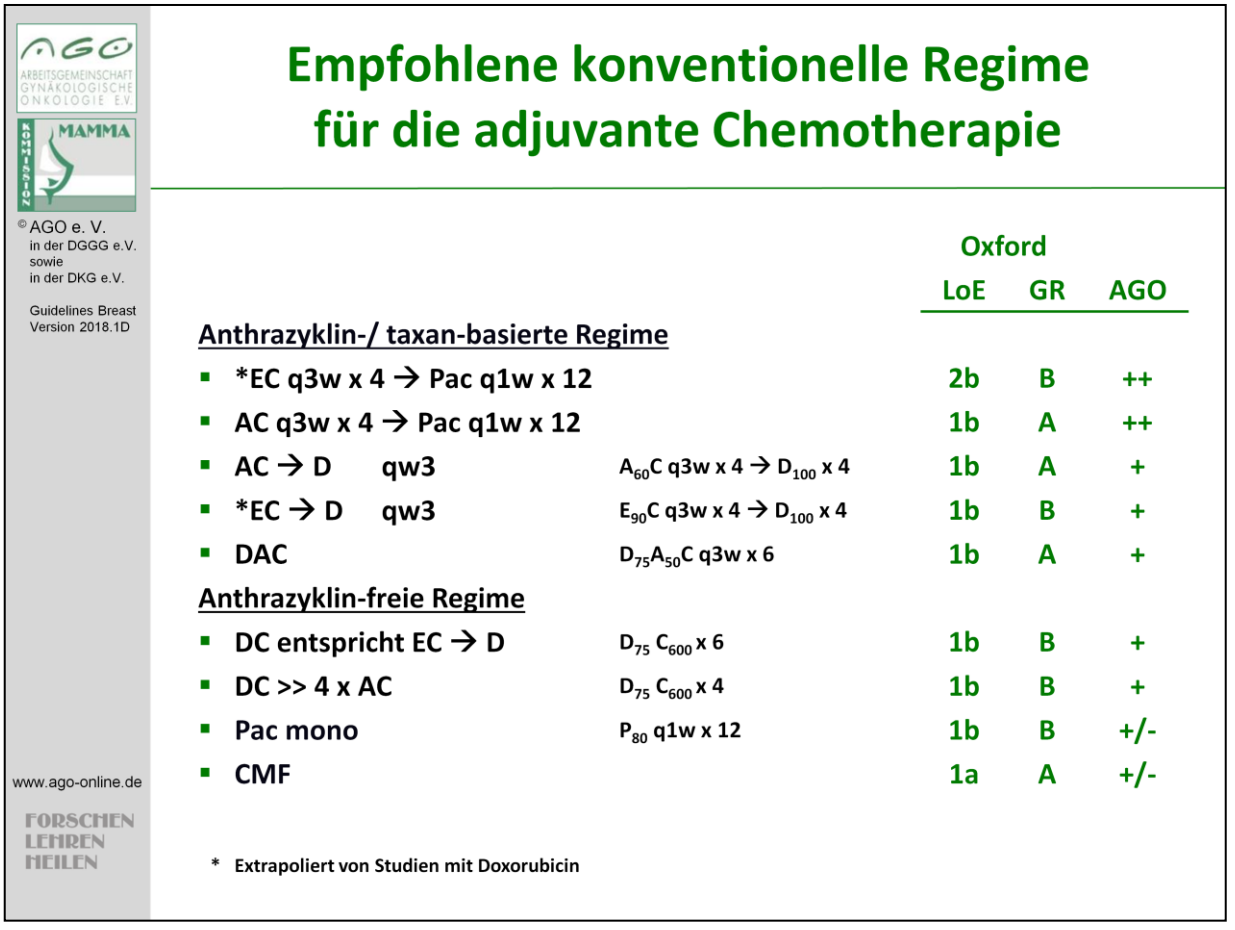
n = 1086 pat., HR neg.,

DFS as primary endpoint

OP -> adj. CT -> R -> Cyclophos. 50 mg p.o. cont. plus
Mtx 2.5 mg 2 x tgl. p.o. d 1 + 2, q1w
versus
control (nil)

Results:
FU 6.9 yrs.,
n.s. DFS difference,
more side effects (14% WHO3/4) in the CM-arm

1. Colleoni et al. Low-dose oral cyclophosphamide and methotrexate maintenance for hormone receptor-negative early nreast cancer: International Breast Cancer Study Group trial 22-00. J Clin Oncol 2016;34:3400-8



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

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: Anthracykline-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

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

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	Oxford LoE	GR	AGO
Dosis-dichte Regime			
▪ E_{90}-Pac_{175}-C_{600} q2w	1b	A	++
▪ AC q2w x4→ Pac q2w x 4	1b	B	++
▪ EC q2w x4→ Pac q2w x 4	1b	A	++
▪ EC q2w x4 → Pac q1w x 12	1b	B	++
Dosis-dichte und dosis-eskalierte Regime (N ≥ 4+)			
▪ E_{150}-Pac_{225}-C_{2500} q2w	1b	A	++

*G-CSF obligat

Statement: Dose-dense regimen

AC q2w x 4 Pac q2w x 4

1. 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 nodenegative breast cancer. J Clin Oncol 28:77-82, 2010.
2. 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: Dose-dense regimen

E90-Pac175-c600 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

EC q3w / Pac q2w

EC q2w / Pac q1w

1. 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.

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 ≥ 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.

Adjuvante Chemotherapie: andere Medikamente

	Oxford		
	LoE	GR	AGO
▪ Capecitabin-haltige Therapie bei TNBC	1a	B	+/-
▪ Platin-haltige Therapie bei TNBC	5	D	+/-
▪ Hinzunahme von 5-Fluorouracil zu EC/AC	1b	A	--

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.

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.

Statement: 5- Fluorouracile added to EC/AC

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

Adjuvante Therapie mit Trastuzumab +/- Pertuzumab

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

Adjuvante Therapie mit Trastuzumab

Guidelines Breast
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	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 2 Jahre	1b	A	-
▪ Für 0,5 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.

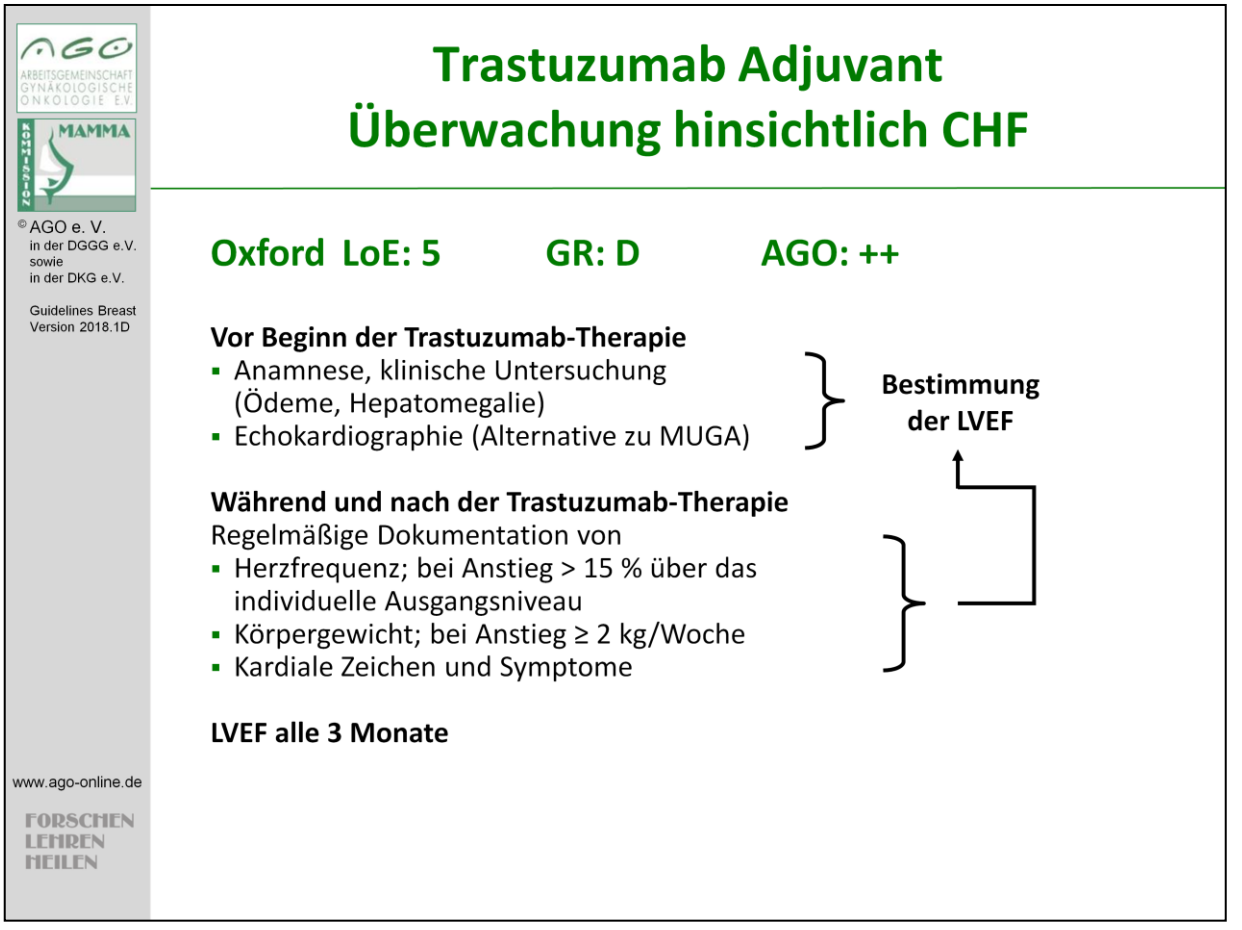
Statement: Duration

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

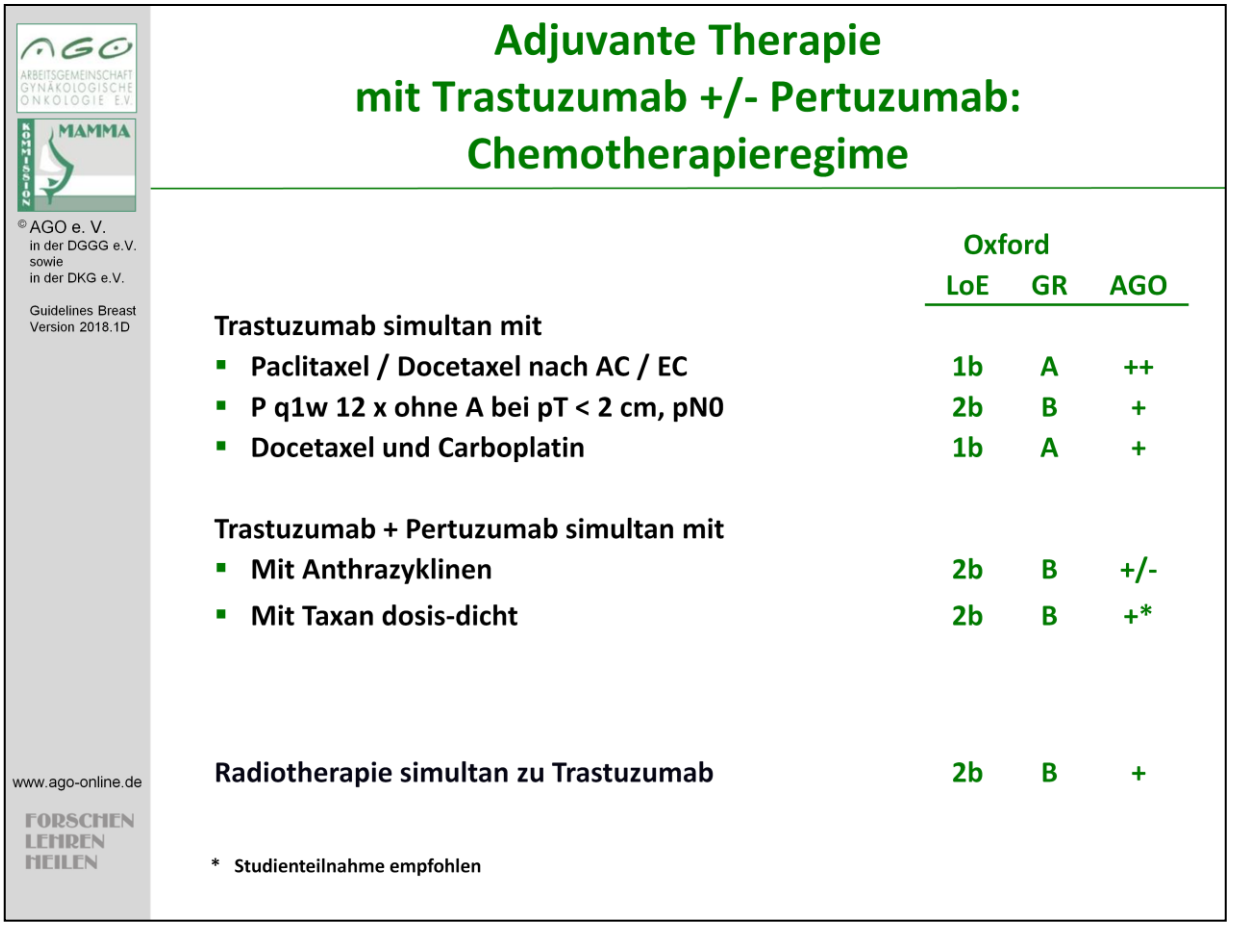


Statement: Cardiac Monitoring

1. Perez EA et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol. 2008;26(8):1231-8.
2. Mackey JR et al. Cardiac management during adjuvant trastuzumab therapy: recommendations of the Canadian Trastuzumab Working Group. Curr Oncol. 2008;15(1):24-35.
3. Chavez-MacGregor M et al. Cardiac Monitoring During Adjuvant Trastuzumab-Based Chemotherapy Among Older Patients With Breast Cancer. J Clin Oncol. 2015;33(19):2176-83.

Statement Cardiac monitoring trastuzumab/pertuzumab

1. Yu AF et al. Cardiac Safety of Paclitaxel Plus Trastuzumab and Pertuzumab in Patients With HER2-Positive Metastatic Breast Cancer. Oncologist. 2016;21(4):418-24.



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 anthracyclines

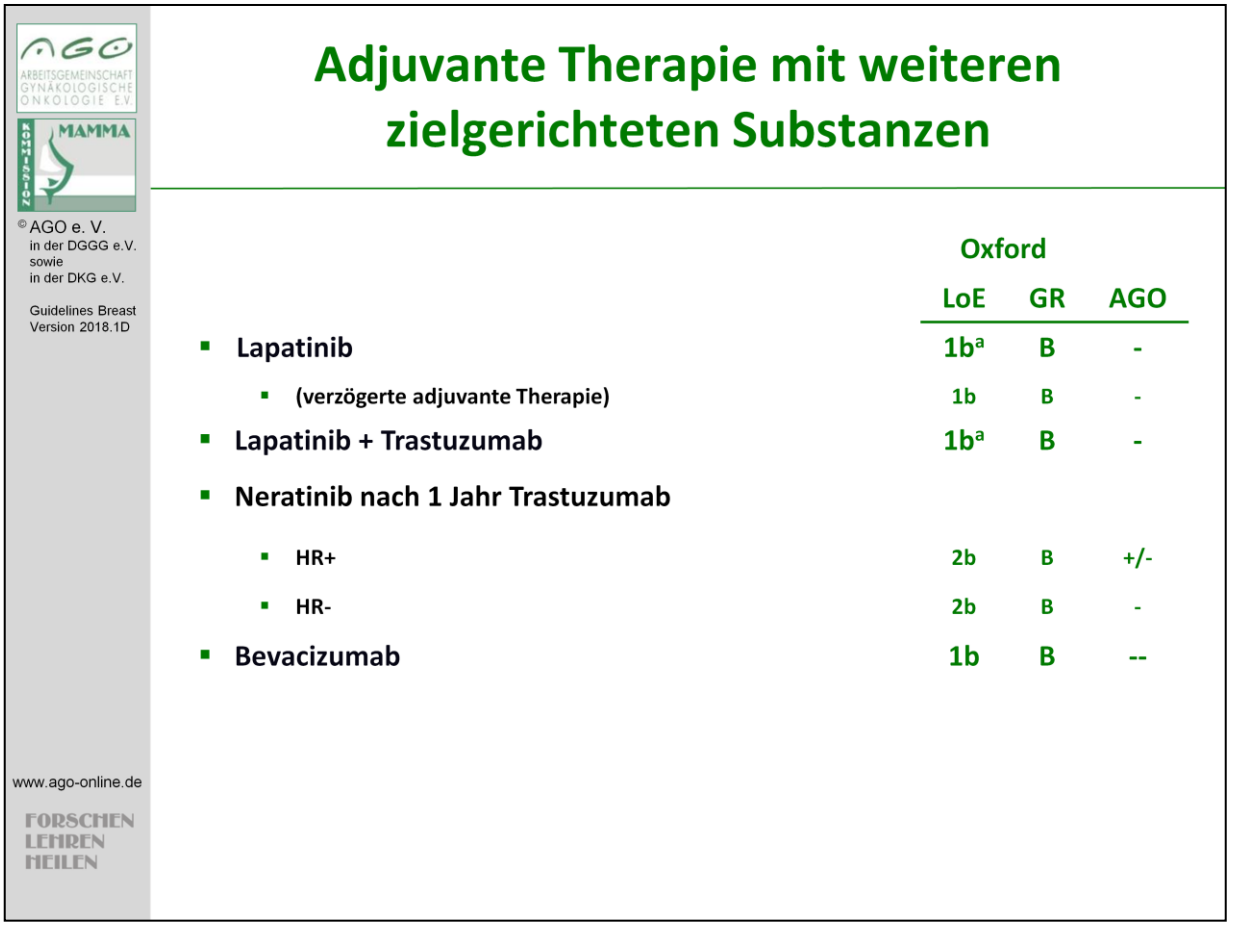
1. von Minckwitz G et al.J; APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017;377(2):122-131.

Statement: Trastuzumab + Pertuzumab simultaneously with 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, L. B. Marks, L. J. Pierce, A. Dueck, E. A. Perez. 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



Statement: with Lapatinib

Delayed adjvuvant 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

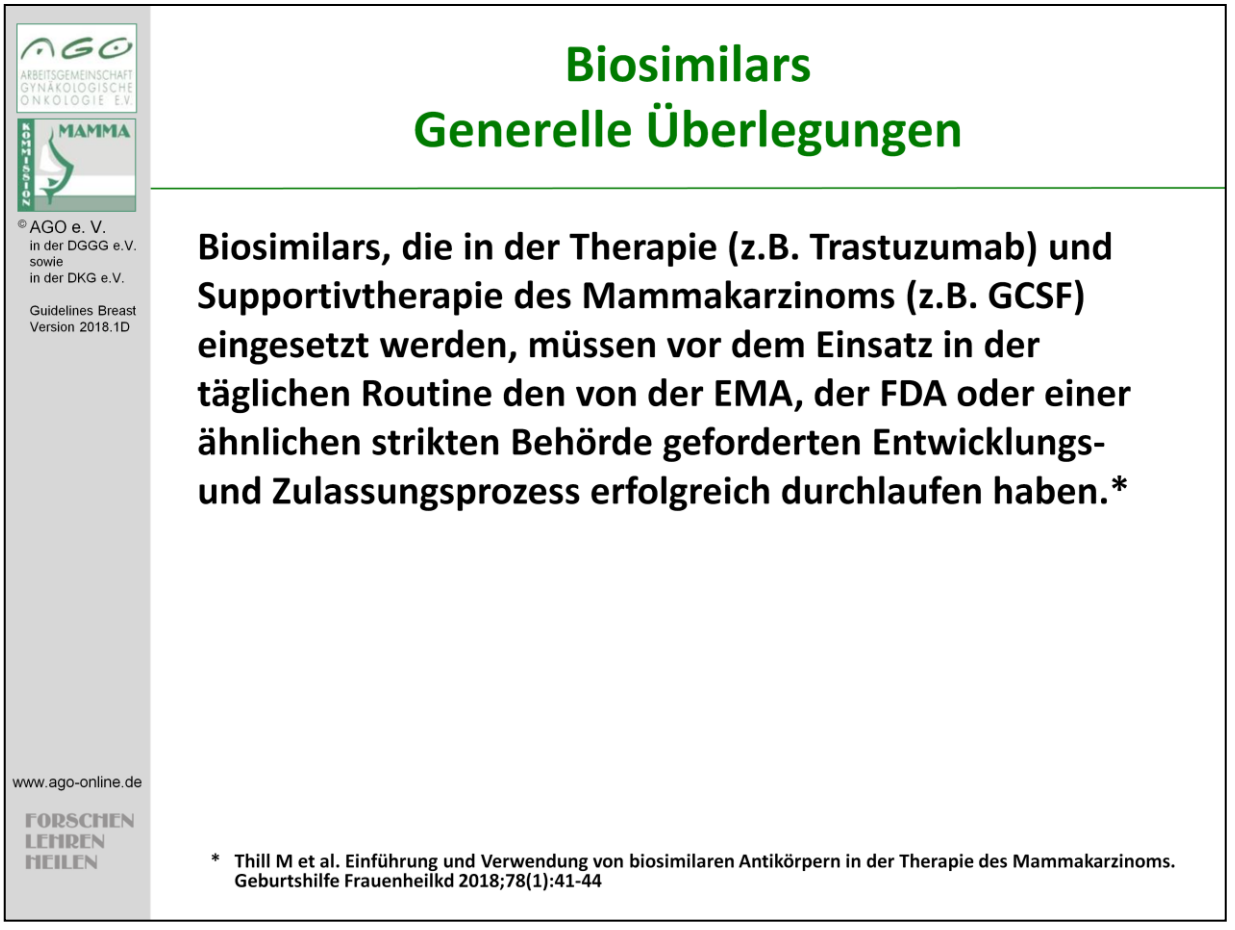
1. Cameron D et al. Adjuvant bevacizumab-containing therapy in triple-negative breast cancer (BEATRICE): primary results of a randomised, phase 3 trial. Lancet Oncol.

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

Statement: Neratinib after adjuvant trastuzumab

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



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