Guidelines Breast
Version 2023.1E

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Adjuvant Cytotoxic and Targeted Therapy

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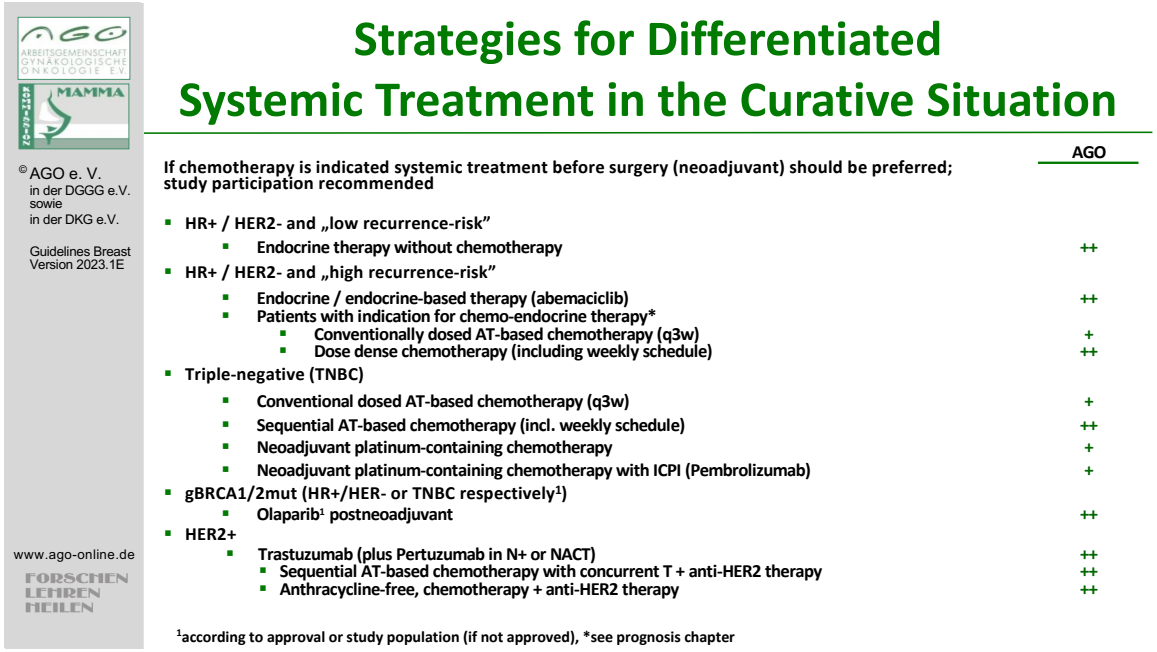
Version 2023.1E

- **Versions 2002 – 2022:**
  Albert / Dall / Fasching / Fehm / Harbeck / Jackisch /Janni / Kümmel / Loibl / Lux / von Minckwitz / Möbus / Müller / Nitz / Rody / Schmidt / Schneeweiss / Simon / Schütz / Solomayer / Stickeler / Thill / Thomssen / Untch

- **Version 2023:**
  Gluz / Thill

Systematic review of published evidence
PUBMED 1999-2022
ASCO 1999-2022
SABCS 1999-2022
ECCO/ESMO 1999-2022



<u>Systematic review of published evidence</u>
PUBMED 1999-2023
ASCO 1999-2023
SABCS 1999-2023
ECCO/ESMO 1999-2023

<u>Trastuzumab in combination with chemotherapy</u>

1. Gianni L, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet 2010: 375; 377
2. Untch M, et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. J Clin Oncol 2011: 29; 3351
3. Gianni L, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet Oncol 2014: 15; 640
4. Jackisch C, et al. HannaH phase III randomised study: Association of total pathological complete response with event-free survival in

HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. Eur J Cancer. 2016 Jul;62:62-

Pertuzumab + Trastuzumab in combination with chemotherapy

1. Gianni L, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012: 13; 25-32
2. Schneeweiss A, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Annals Oncol 2013: 24; 2278-84
3. Nagayama A, et al. Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis. J Natl Cancer Inst 2014; 106(9): in print
4. Gianni L et al. Five-year analysis of the phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P). J Clin Oncol 33, 2015 (suppl; abstr 505)
5. Loibl S, et al. Dual HER2-blockade with pertuzumab and trastuzumab in HER2-positive early breast cancer: a subanalysis of data from the randomized phase III GeparSepto trial. Ann Oncol. 2017;28:497-504
6. Schneeweiss A et al. Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: Evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer. Eur J Cancer 89:27-35, 2017
7. Hurvitz SA, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2017. pii: S1470-2045(17)30716-7 [Epub ahead of print]
8. Swain SM, et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. Ann Oncol 2017. doi: 10.1093/annonc/mdx773. [Epub ahead of print]
9. Von Minckwitz G, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017 13;377(2):122-131.

Her2+ Antrazyklin-freie Chemotherapie:

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

TNBC neoadjuvant chemotherapy with ICP

1. Mittendorf EA, Zhang H, Barrios Chet al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020 Oct 10;396(10257):1090-1100. doi: 10.1016/S0140-6736(20)31953-X.
2. Schmid P, Cortes J, Pusztai L et al. ; KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810-821. doi: 10.1056/NEJMoa1910549.
3. Schmid P, Cortes J, Dent R et al. KEYNOTE-522: Phase 3 study of pembrolizumab + chemotherapy vs placebo + chemotherapy as neoadjuvant treatment, followed by pembrolizumab vs placebo as adjuvant treatment for early triple-negative breast cancer (TNBC). ESMO 2021 Abstract #VP7_2021

Abemaciclib:

1. Harbeck N, Rastogi P, Martin M et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol. 2021 Dec;32(12):1571-1581. doi: 10.1016/j.annonc.2021.09.015. Epub 2021 Oct 14. PMID: 34656740.
2. Johnston SRD, Toi M, O'Shaughnessy J et al.; monarchE Committee Members.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.

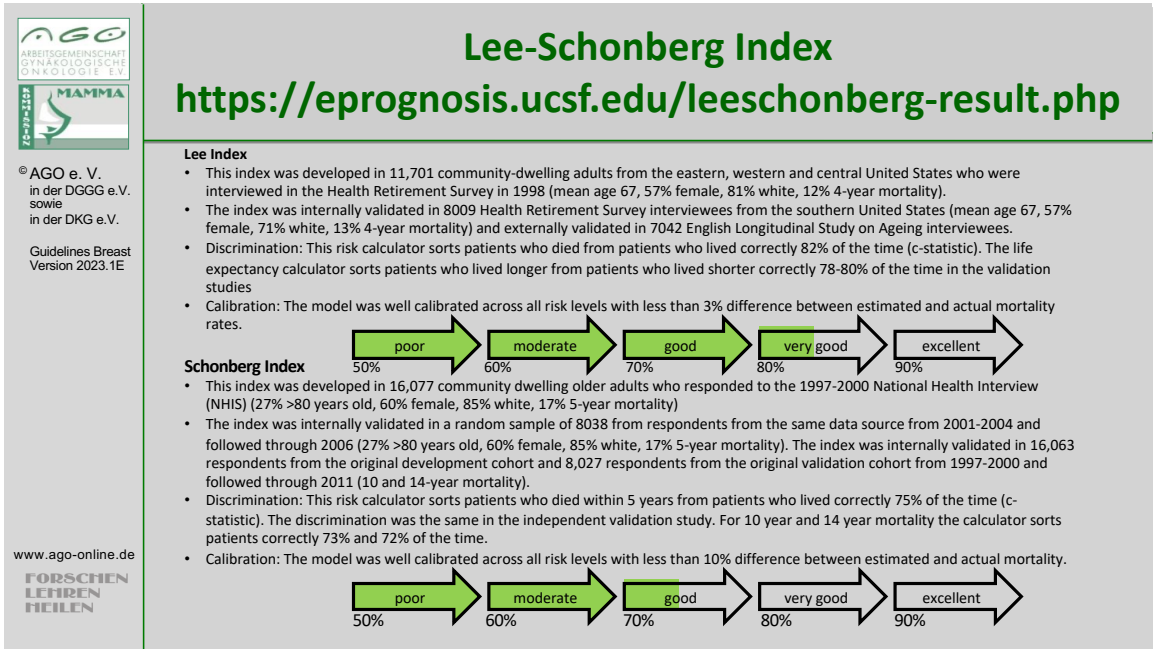
Olaparib

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

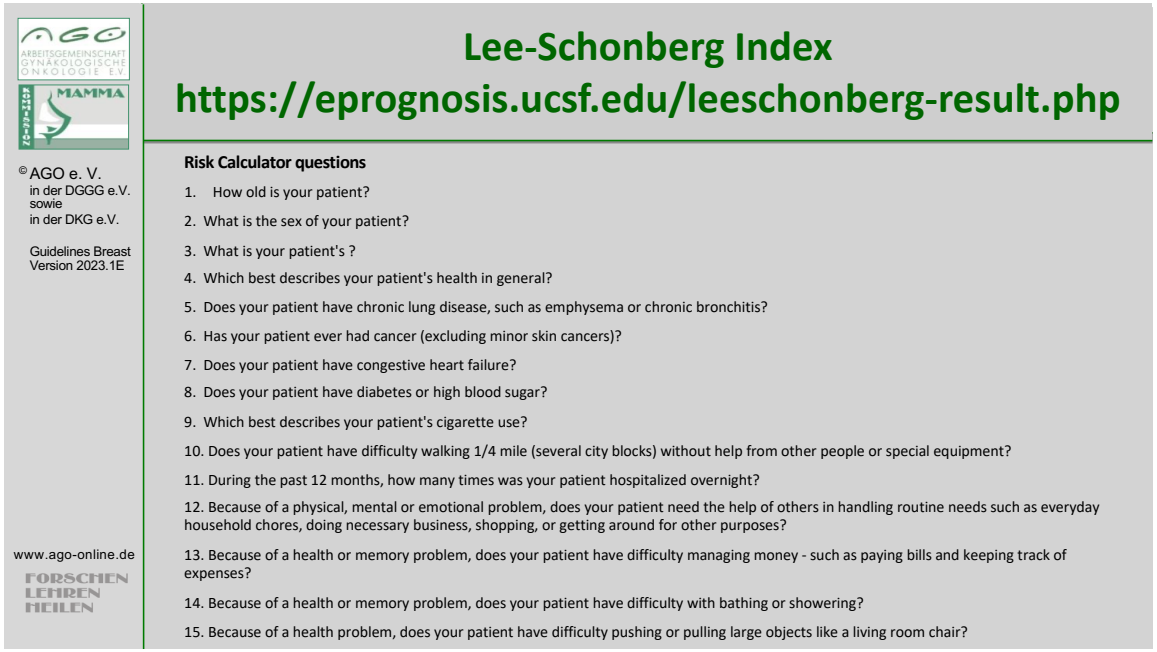
cancer. Ann Oncol 2022;33(12):1250-1268

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
4. III randomized controlled trial SABCS 2022, GS5-01



1. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA. 2006 Feb 15;295(7):801-808.
2. Schonberg MA, Davis RB, McCarthy EP, and Marcantonio ER. Index to predict 5-year mortality of community dwelling adults aged 65 an older using data from the National Health Interview Survey. J Gen Intern Med. 2009;24(10):1115-1022.
3. Lee SJ, Boscardin WJ, Kirby KA, Covinsky KE. Individualizing life expectancy estimates for older adults using the Gompertz Law of Human Mortality. Plos One. 2014;9(9):3108540.



1. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA. 2006 Feb 15;295(7):801-808.
2. Schonberg MA, Davis RB, McCarthy EP, and Marcantonio ER. Index to predict 5-year mortality of community dwelling adults aged 65 an older using data from the National Health Interview Survey. J Gen Intern Med. 2009;24(10):1115-1022.
3. Lee SJ, Boscardin WJ, Kirby KA, Covinsky KE. Individualizing life expectancy estimates for older adults using the Gompertz Law of Human Mortality. Plos One. 2014;9(9):3108540.

Adjuvant Chemotherapy: in Small, Node-Negative Tumors (T1)

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	Oxford		
	LoE	GR	AGO
Indication for chemotherapy in			
TNBC			
> 10 mm	2b	B	++
> 5–10 mm	2b	B	+
≤ 5 mm	2b	B	+/-
HER2+ in combination with trastuzumab			
> 10 mm	1a	A	++
6–10 mm	2b	B	+
≤ 5 mm	2b	B	+/-

TNBC

1. Gamucci T, Vaccaro A, Ciancola F et. al. Recurrence risk in small, node-negative, early breast cancer: a multicenter retrospective analysis. J Cancer Res Clin Oncol. 2013;139(5):853-60. doi: 10.1007/s00432-013-1388-2. Epub 2013 Feb 15.
2. Kolben T, Harbeck N, Wuerstlein R et al. Endocrine sensitivity is decisive for patient outcome in small node-negative breast cancers (BC) (pT1a,b) - results from the Munich Cancer Registry. Breast. 2015;24(1):24-31. doi: 10.1016/j.breast.2014.10.007. Epub 2014 Nov 8.
3. Nonneville A, Goncalves C, Zemmour M et al. Adjuvant chemotherapy in pT1ab node-negative triple-negative breast carcinomas: Results of a national multi-institutional retrospective study . European J Cancer. 2017; (84):34-43.
4. Oladeru OT, Singh AK, Ma SJ. Association of Adjuvant Chemotherapy With Overall Survival Among Women With Small, Node-Negative, Triple-Negative Breast Cancer. JAMA Netw Open. 2020 Sep 1;3(9):e2016247.
5. Steenbruggen TG, van Werkhoven E, van Ramshorst MS, et al.. Adjuvant chemotherapy in small node-negative triple-negative breast cancer. Eur J Cancer. 2020 Aug;135:66-74. doi: 10.1016/j.ejca.2020.04.033. Epub 2020 Jun 14. PMID: 32554215.

HER2

1. Denduluri N, Somerfield MR, Eisen A 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, Bradbury I, Campbell C 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, Gonçalves A, Zemmour C, 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.

HR+/HER2-

1. Sparano JA, Crager MR, Tang G et al. Development and Validation of a Tool Integrating the 21-Gene Recurrence Score and Clinical-Pathological Features to Individualize Prognosis and Prediction of Chemotherapy Benefit in Early Breast Cancer. Journal of Clinical Oncology 2021; 39: 557-564.
2. Shen K, Yao L, Zhu J et al. Impact of adjuvant chemotherapy on T1N0M0 breast cancer patients: a propensity score matching study based on SEER database and external cohort. BMC Cancer 2022; 22: 863.
3. Nguyen TTA, Postlewait LM, Zhang C et al. Utility of Oncotype DX score in clinical management for T1 estrogen receptor positive, HER2 negative, and lymph node negative breast cancer. Breast Cancer Res Treat 2022; 192: 509-516.

Adjuvant Chemotherapy without Trastuzumab: Overview

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

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

1. Moylan EJ, Connell LC, O'Reilly S et al. Are dose-dense and triplet chemotherapy regimens optimal adjuvant therapy in the majority of women with node-positive early breast cancer? J Clin Oncol. 2014;32(6):605-6.
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 alAnthracyclines 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

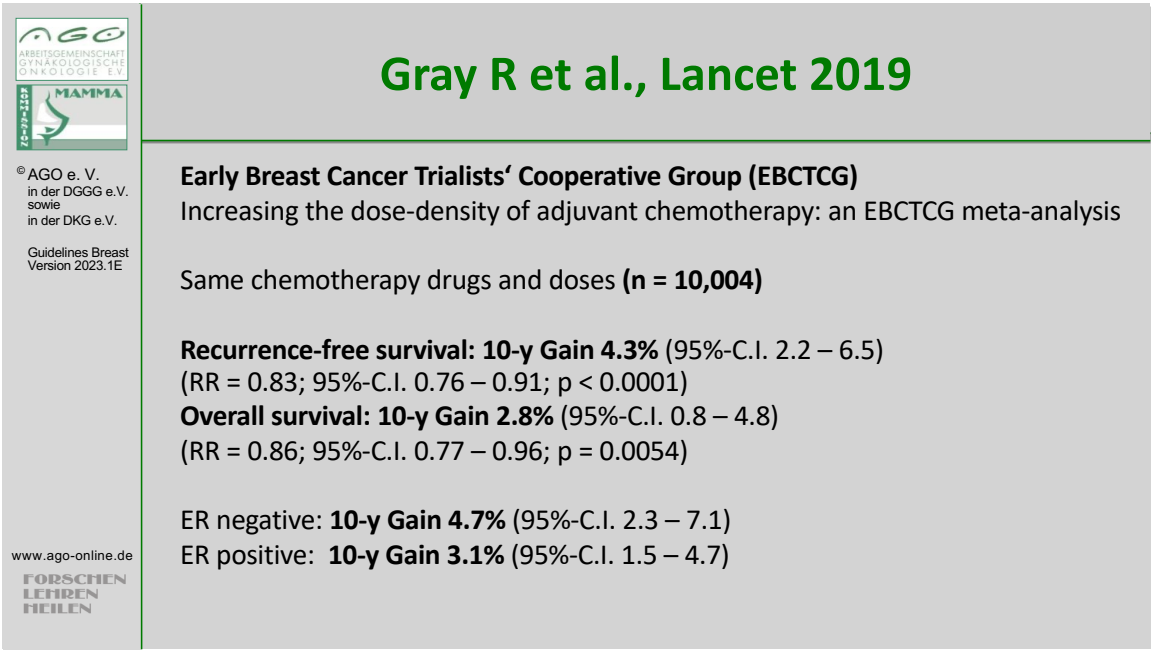
1. Amoroso V, Pedersini R, Sharratt P et al. Should adjuvant weekly Paclitaxel be considered less efficacious than anthracyclines plus cyclophosphamide for lower-risk patients with early-stage breast cancer? J Clin Oncol. 2015 Jan 20;33(3):290.
2. Shulman LN, Berry DA, Cirrincione CT et al. Comparison 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



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;393(10179):1440-1452. doi: 10.1016/S0140-6736(18)33137-4. Epub 2019 Feb 8

Recommended Dose-dense and / or Dose-escalated, Sequential Adjuvant Chemotherapy

	Oxford		
	LoE	GR	AGO
Dose-dense regimen			
▪ 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	+
Dose-dense and dose-escalated regimen (N ≥ 4+)			
▪ E_{150} → Pac_{225} → C2000 q2w	1b	A	++

Statement: Dose-dense regimen

NabPac bei allergischer Reaktion auf Paclitaxel:

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

Statement: Dose-dense regimen

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

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

Statement: Dose-dense regimen

AC /EC q2w x 4 Pac q2w x 4

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

Statement: Dose-dense regimen

EC q2w / Pac q1w

EC q3w / Pac q1w

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

EBCTCG Metaanalyse

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

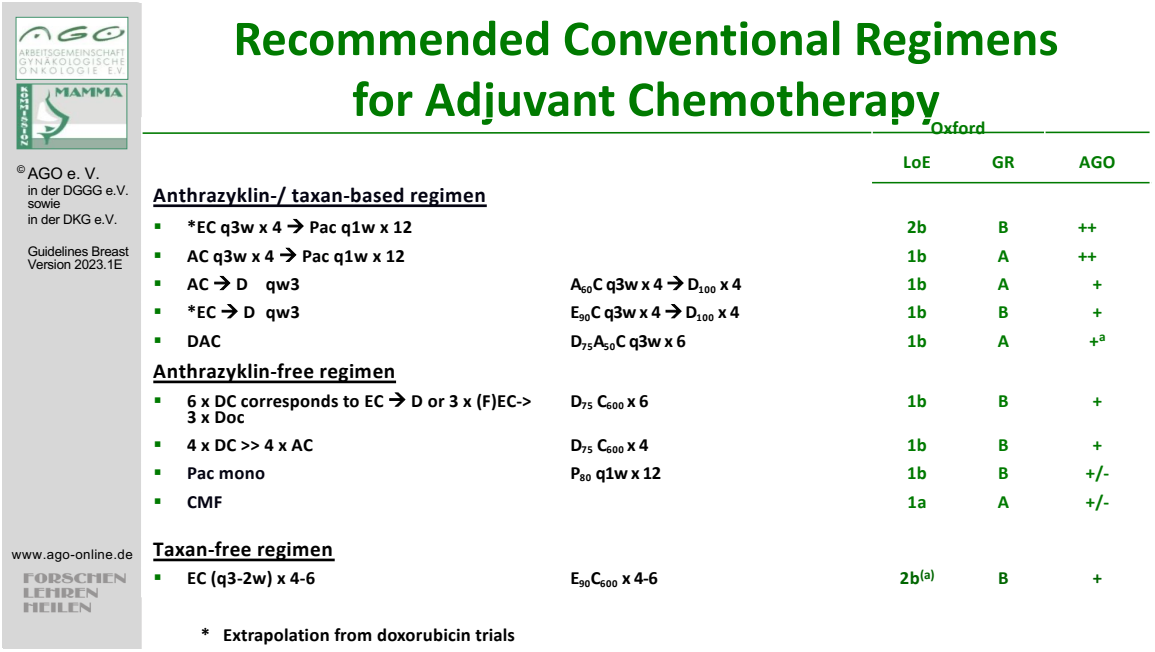
Statement: Dose-dense and dose-escalated regimen (N ≥ 4+)

E-Pac-C q2w

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

Negative Trial

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



Recommended Conventional Regimens for Adjuvant Chemotherapy

		Oxford LoE	GR	AGO
Anthrazyklin-/ taxan-based regimen				
▪ *EC q3w x 4 → Pac q1w x 12		2b	B	++
▪ AC q3w x 4 → Pac q1w x 12		1b	A	++
▪ AC → D qw3	$A_{60}C$ q3w x 4 → D_{100} x 4	1b	A	+
▪ *EC → D qw3	$E_{90}C$ q3w x 4 → D_{100} x 4	1b	B	+
▪ DAC	$D_{75}A_{50}C$ q3w x 6	1b	A	+[a]
Anthrazyklin-free regimen				
▪ 6 x DC corresponds to EC → D or 3 x (F)EC-> 3 x Doc	D_{75} C_{600} x 6	1b	B	+
▪ 4 x DC >> 4 x AC	D_{75} C_{600} x 4	1b	B	+
▪ Pac mono	P_{80} q1w x 12	1b	B	+/-
▪ CMF		1a	A	+/-
Taxan-free regimen				
▪ EC (q3-2w) x 4-6	$E_{90}C_{600}$ x 4-6	2b[(a)]	B	+

* Extrapolation from doxorubicin trials

Statement: Anthracycline/ taxane based regimen

*EC □ Pw E90C q3w x 4 □ P80 qw1 x 12

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

Statement: Anthracycline/ taxane based regimen

AC □ Pw A60Cq3w x 4 □ P80qw1 x 12

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

Statement: Anthracycline/ taxane based regimen

AC □ 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, 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

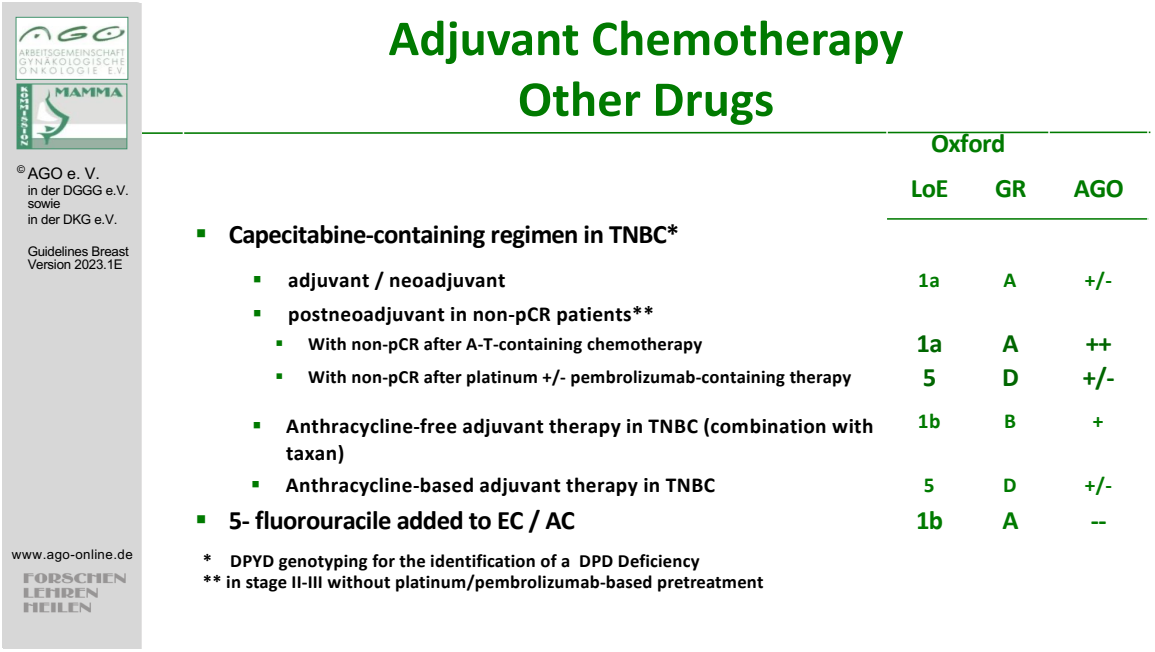
CMF 600/40/600 mg q3w x 6

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.



Statement: Capecitabine containing regimen in TNBC

1. O'Shaughnessy J, Koeppen H, Xiao Y 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, Yin W, Zhou L 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, Kellokumpu-Lehtinen PL, Huovinen R 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.
5. 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.

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.
2. Li, Y.; Zhou, Y.; Mao, F.; et al. Adjuvant addition of capecitabine to early-stage triple-negative breast cancer patients receiving standard chemotherapy: A meta-analysis. *Breast Cancer Res. Treat.* 2019, *179*, 533–542.

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

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):2147-59.

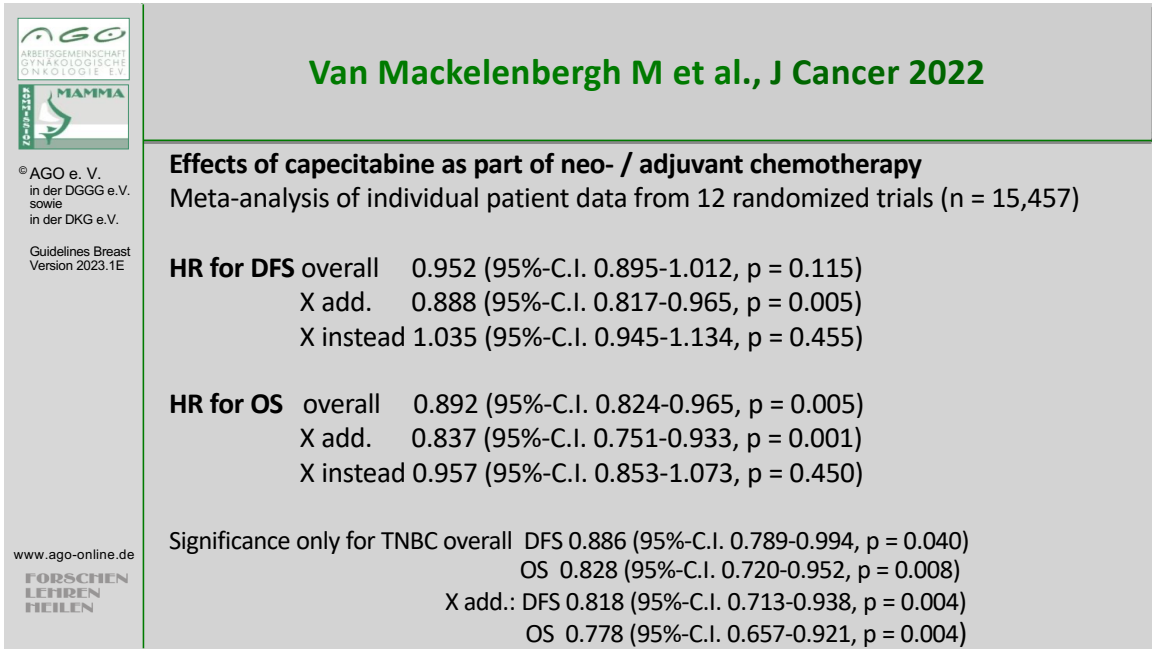
Statement: 5- Fluorouracile added to EC/AC=>Pac

1. 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.

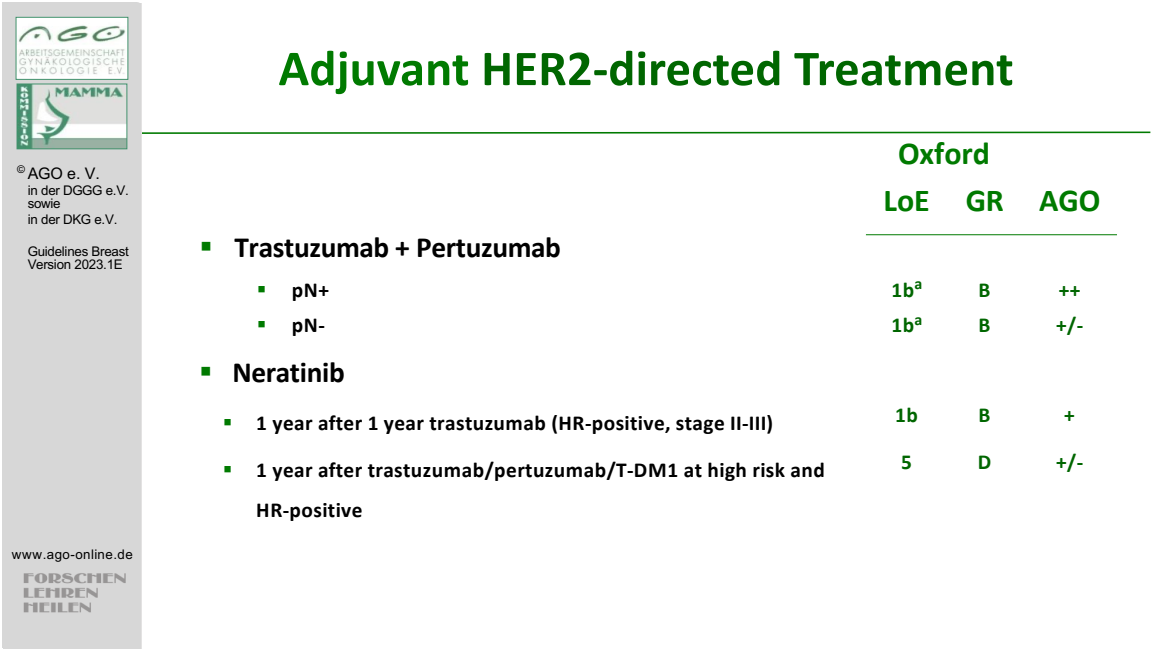
Statement: Platinum containing regimen in TNBC

1. Joensuu H, Gligorov J. Adjuvant treatments for triple-negative breast cancers. Ann Oncol. 2012;23 Suppl 6:vi40-5.
2. Alba E, Chacon JI, Lluch A 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; 487–493.
3. Von Minckwitz G, Schneeweiss A, Loibl S 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; 747-56.
4. Ando M, Yamauchi H, Aogi K 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; 401-09.
5. Petrelli F, Coinu A, Borgonova K 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; 223-32.
6. Sikov WM, Berry DA, Perou CM 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; 13-21.
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.
9. Yu KD, Ye FG, He M, et al.Effect of Adjuvant Paclitaxel and Carboplatin on Survival in Women With Triple-Negative Breast Cancer: A Phase 3 Randomized Clinical Trial. JAMA Oncol. 2020 Sep 1;6(9):1390-1396. doi: 10.1001/jamaoncol.2020.2965. PMID: 32789480; PMCID: PMC7426881.
10. 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.
11. 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.



1. 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.



Adjuvant HER2-directed Treatment

	Oxford LoE	Oxford GR	Oxford AGO
Trastuzumab + Pertuzumab			
pN+	1b[a]	B	++
pN-	1b[a]	B	+/-
Neratinib			
1 year after 1 year trastuzumab (HR-positive, stage II-III)	1b	B	+
1 year after trastuzumab/pertuzumab/T-DM1 at high risk and HR-positive	5	D	+/-

Statement Trastuzumab + Pertuzumab (pN+/-)

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;377(2):122-131.
2. Piccart M , Procter M, Fumagalli D et al. Interim overall survival analysis of APHINITY (BIG 4-11): A randomized multicenter, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab versus chemotherapy plus trastuzumab plus placebo as adjuvant therapy in patients with operable HER2-positive early breast cancer. SABCS 2019; abstr. GS 01-04
3. Yu L, Fu F, Li J, Huang M, Zeng B, Lin Y, Mei Q, Lv J, Wang C. Dual HER2 Blockade versus a Single Agent in Trastuzumab-Containing Regimens for HER2-Positive Early Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Oncol 2020 https://doi.org/10.1155/2020/5169278 (accecced 12302020)
4. Loibl, S., et al. (2022). "VP6-2022: Adjuvant pertuzumab and trastuzumab in patients with early HER-2 positive breast cancer in APHINITY: 8.4 years' follow-up." Annals of Oncology **33**(9): 986-987.

Neratinib

1. Chan A, Moy B, Mansi J, Ejlertsen B, Holmes FA, Chia S, Iwata H, Gnant M, Loibl S, Barrios CH, Somali I, Smichkoska S, Martinez N, Alonso MG, Link JS, Mayer IA, Cold S, Murillo SM, Senecal F, Inoue K, Ruiz-Borrego M, Hui R, Denduluri N, Patt D, Rugo HS, Johnston SRD, Bryce R, Zhang B, Xu F, Wong A, Martin M; ExteNET Study Group. Final Efficacy Results of Neratinib in HER2-positive Hormone

Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial. Clin Breast Cancer. 2021 Feb;21(1):80-91.e7. doi: 10.1016/j.clbc.2020.09.014. Epub 2020 Oct 6. PMID: 33183970.

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

1. Piccart-Gebhart MJ, Procter M, Leyland-Jones B 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, Procter M, Gelber RD 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, Gelber RD, Piccart-Gebhart, MJ 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, Piccart-Gebhart MJ, Gelber RD, 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, Romond EH , Suman VJ 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, Hegg R, Stroyakovskiy D 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.

Adjuvant Treatment with Trastuzumab / Pertuzumab

	Oxford		
	LoE	GR	AGO
Start of treatment			
▪ **Simultaneously with taxanes**	1a	A	++
▪ **Sequentially up to 3 months after chemotherapy**	1b	B	+
Duration			
▪ **For 1 year**	1a	A	++
▪ **For 0.5 years (Trastuzumab)**	1a	A	+
▪ **For 2 years**	1b	A	-

Statement: Start of treatment simultaneously with taxanes

1. Smith I, Procter M, Gelber RD 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, Gelber RD, Piccart-Gebhart, MJ 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, Piccart-Gebhart MJ, Gelber RD, 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, Romond EH , Suman VJ 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, Bono P, Kataja V 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;27(34):5685-92.
6. Yin W, Jiang Y, Shen Z 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 EA, Suman VJ, Davidson NE et al. Sequential Versus Concurrent Trastuzumab in Adjuvant Chemotherapy for Breast Cancer. J Clin

Oncol 2011;29:4491-4497
8. Slamon D, Eiermann W, Robert N et al.; Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273-83.

Statement s.c.

1. Gligorov J, Ataseven B, Verrill M 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, Verma S, Fallowfield L 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.
3. Jackisch C, Stroyakovskiy D, Pivot X et al. Subcutaneous vs Intravenous Trastuzumab for Patients With ERBB2-Positive Early Breast Cancer: Final Analysis of the HannaH Phase 3 Randomized Clinical Trial. JAMA Oncol. 2019;5(5):e190339. doi: 10.1001/jamaoncol.2019.0339.
4. Federica Tan AR, *et al*. SABCS 2019 (Abstract PD4-07),
5. Phrancesca O'Shaughnessy J *et al.* ESMO 2020, Abstract-Nr. 165MO

Statement: Duration

Duration Trastuzumab 1 year

Duration Trastuzumab 2 year

Duration Trastuzumab 0.5 years

1. Goldhirsch A, Gelber RD, Piccart-Gebhart, MJ 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, Piccart-Gebhart MJ, Gelber RD, 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. Joensuu H, Fraser J, Wildiers H et al. Effect of Adjuvant Trastuzumab for a Duration of 9 Weeks vs 1 Year With Concomitant

Chemotherapy for Early Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: The SOLD Randomized Clinical Trial. JAMA Oncol. 2018;4(9):1199–1206.
4. 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;29(12):2328-2333.
5. Pivot X, Romieu G, Debled Met al. 6 months versus 12 months of adjuvant trastuzumab in early breast cancer (PHARE): final analysis of a multicentre, open-label, phase 3 randomised trial. Lancet. 2019;393(10191):2591-2598. doi: 10.1016/S0140-6736(19)30653-1.
6. Earl HM, Hiller L, Vallier AL et al. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. Lancet. 2019;393(10191):2599-2612. doi: 10.1016/S0140-6736(19)30650-6.

Metaanalyses analyzing optimal duration:
1. Chen L, Zhou W, Hu X et al. Short-duration versus 1-year adjuvant trastuzumab in early HER2 positive breast cancer: A meta-analysis of randomized controlled trials. Cancer Treat Rev. 2019;75:12-19. doi: 10.1016/j.ctrv.2019.02.003.
2. 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. 2019;173(2):247-254. doi: 10.1007/s10549-018-5001-x.
3. Niraula S, Gyawali B. Optimal duration of adjuvant trastuzumab in treatment of early breast cancer: a meta-analysis of randomized controlled trials. Breast Cancer Res Treat. 2019;173(1):103-109. doi: 10.1007/s10549-018-4967-8..
4. Goldvaser H, Korzets Y, Shepshelovich D et al. Deescalating Adjuvant Trastuzumab in HER2-Positive Early-Stage Breast Cancer: A Systemic Review and Meta-Analysis. JNCI Cancer Spectr. 2019;3(2):pkz033. doi: 10.1093/jncics/pkz033.

Adjuvant Treatment with Trastuzumab +/- Pertuzumab: Chemotherapy regimen

	Oxford		
	LoE	GR	AGO
Trastuzumab simultaneously with			
▪ paclitaxel / docetaxel after AC / EC	1a	A	++
▪ P q1w 12 x in pT < 2 cm, pN0	2b	B	+
▪ docetaxel and carboplatin	1b	A	+
Trastuzumab + Pertuzumab simultaneously with			
▪ paclitaxel q1w (or docetaxel q3w) after EC / AC	1b	B	++
▪ docetaxel+ carboplatin	1b	B	++
▪ taxanes dose-dense	2b	B	+
Radiotherapy concurrently with Trastuzumab / Pertuzumab	1a	A	++

Statement: with paclitaxel/docetaxel after AC/EC

1. Perez EA, Suman VJ, Davidson NE et al. Sequential Versus Concurrent Trastuzumab in Adjuvant Chemotherapy for Breast Cancer. J Clin Oncol 2011;29:4491-4497
2. Cameron D, Piccart-Gebhart MJ, Gelber RD, 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. Papakonstantinou A, Matikas A, Bengtsson NO et al. Efficacy and Safety of Tailored and Dose-Dense Adjuvant Chemotherapy and Trastuzumab for Resected HER2-Positive Breast Cancer: Results From the Phase 3 PANTHER Trial. Cancer 2019 doi: 10.1002/cncr.32653. [Epub ahead of print]

Statement: P q1w12 in pT < 2 cm pN0

1. Tolaney SM, Barry WT, Dang CT 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, Guo H, Pernas S et al. Seven-Year Follow-Up Analysis of Adjuvant Paclitaxel and Trastuzumab Trial for Node-Negative, Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer. J Clin Oncol. 2019;37(22):1868-1875. doi: 10.1200/JCO.19.00066.

Statement: with docetaxel and carboplatin

1. Valero V, Forbes J, Pegram MD 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, Piccart-Gebhart MJ, Perez EA 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, 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;377(2):122-131.

Statement: Trastuzumab + Pertuzumab simultaneously with Docetaxel and Carboplatin q3w

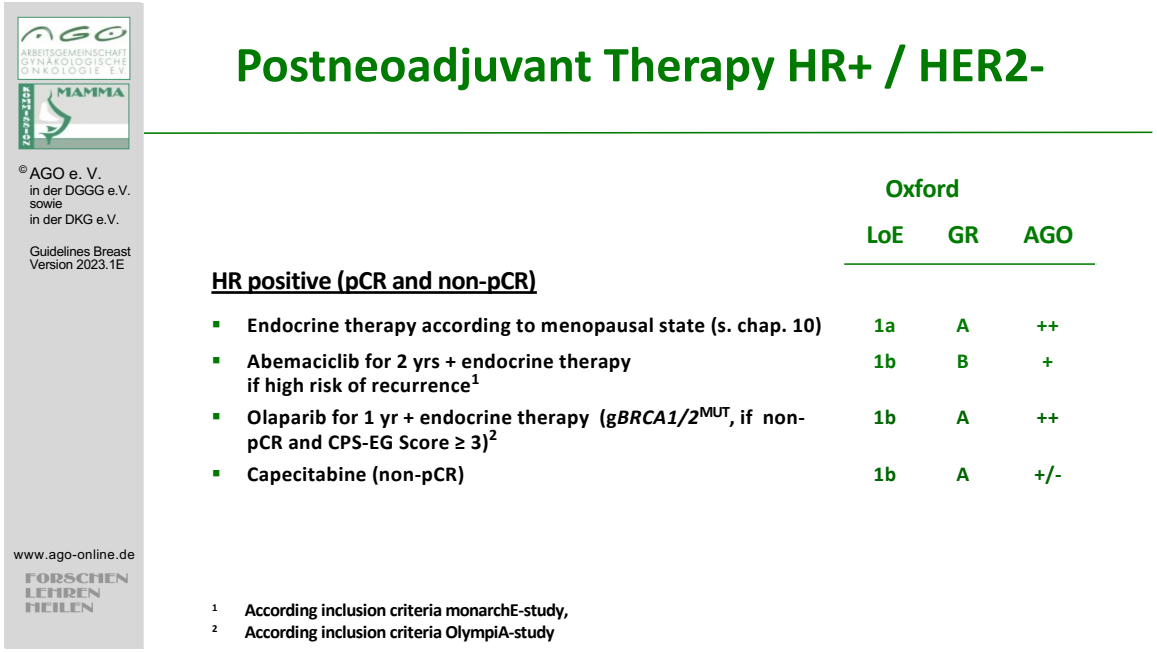
1. von Minckwitz G, Procter M, de Azambuja E et al; APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017;377(2):122-131.
2. Schneeweiss A, Chia S, Hickish T et al. Long-term efficacy analysis of the randomised, phase 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, 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;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



Postneoadjuvant Therapy HR+ / HER2-

	Oxford		
	LoE	GR	AGO
HR positive (pCR and non-pCR)			
▪ Endocrine therapy according to menopausal state (s. chap. 10)	1a	A	++
▪ Abemaciclib for 2 yrs + endocrine therapy if high risk of recurrence[1]	1b	B	+
▪ Olaparib for 1 yr + endocrine therapy (g*BRCA1/2*^{MUT}, if non-pCR and CPS-EG Score ≥ 3)[2]	1b	A	++
▪ Capecitabine (non-pCR)	1b	A	+/-

[1] According inclusion criteria monarchE-study,
[2] According inclusion criteria OlympiA-study

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

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005 May 14-20;365(9472):1687-717.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015 Oct 3;386(10001):1341-1352.

Statement CDK4/6 inhibitors

1. Harbeck N, Rastogi P, Martin M, et al.; monarchE Committee Members. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol. 2021 Dec;32(12):1571-1581.
2. Martin M, Hegg R, Sung-Bae K, et al., Abemaciclib combined with adjuvant endocrine therapy in patients with high risk early breast cancer who received neoadjuvant chemotherapy (NAC). J Clin Oncol 2021;39(15 suppl): abstract 517
3. Gnant M, Dueck AC, Frantal S, et al.; PALLAS groups and investigators. Adjuvant Palbociclib for Early Breast Cancer: The PALLAS Trial Results (ABCSG-42/AFT-05/BIG-14-03). J Clin Oncol. 2021 Dec 7:JCO2102554.
4. 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.
5. Loibl S, Marmé F, Martin M, et al. Palbociclib for Residual High-Risk Invasive HR-Positive and HER2-Negative Early Breast Cancer-

The Penelope-B Trial. J Clin Oncol. 2021 May 10;39(14):1518-1530.
6. O'Shaughnessy JA , Johnston S, Harbeck N et al. Primary outcome analysis of invasive disease-free survival for monarchE: abemaciclib combined with adjuvant endocrine therapy for high risk early breast cancer. SABCS 2020:GS1-01.
7. 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.

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.

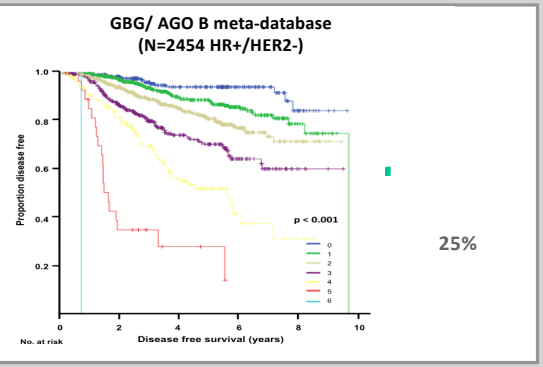
Statement Capecitabine (bei non-pCR; 8 Kurse)

1. Joensuu H, Kellokumpu-Lehtinen PL, Huovinen R et al. Adjuvant Capecitabine for Early Breast Cancer: 15-Year Overall Survival Results From a Randomized Trial. J Clin Oncol. 2022 Jan 12:JCO2102054.
2. Lluch A et al. Phase III Trial of adjuvant capecitabine after standard neo-/adjuvant chemotherapy in patients with early triple-negative breast cancer (GEICAM/2003-11_CIBOMA/2004-01). J Clin Oncol. 2020 Jan 20;38(3):203-213.
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.

How to calculate CPS+EG Score?

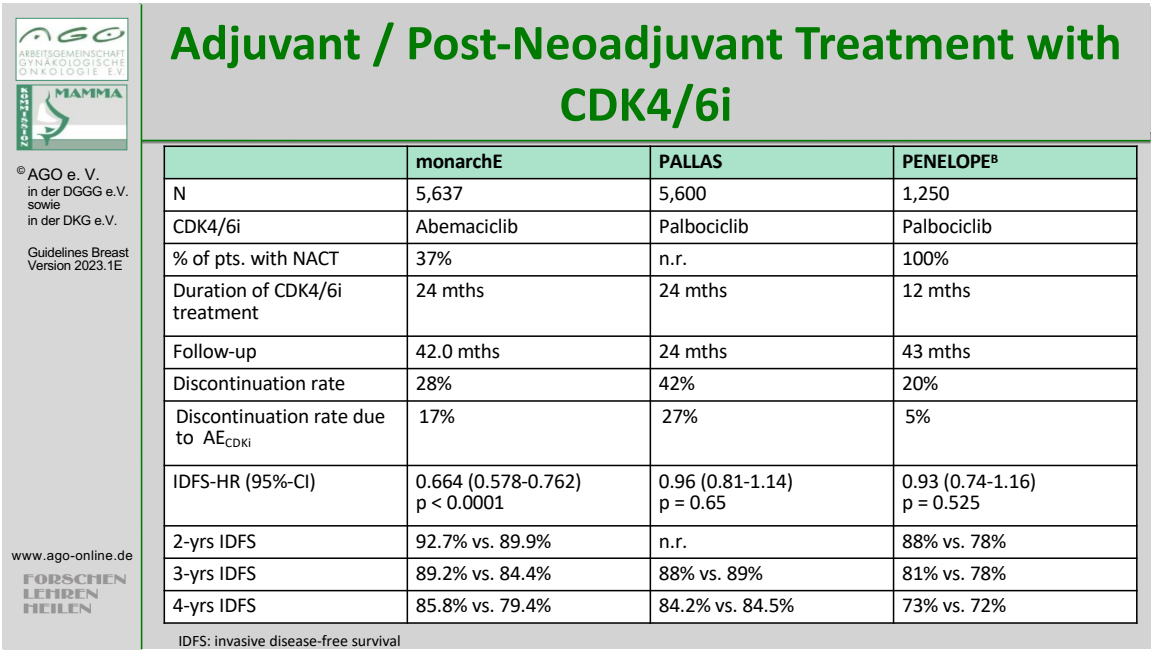
Point assignment for CPS+EG score

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/isN0
I	0	T1N0; T0N1mi, T1N1mi
IIA	1	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2 N2
IIIB	1	T4 N0-N2
Tumor Biologic Factors		
ER negative	1	
Nuclear grade 3	1	



25%

Mittendorf EA, J Clin Oncol 2011;
Marmé F, et al. Eur J Cancer 2016

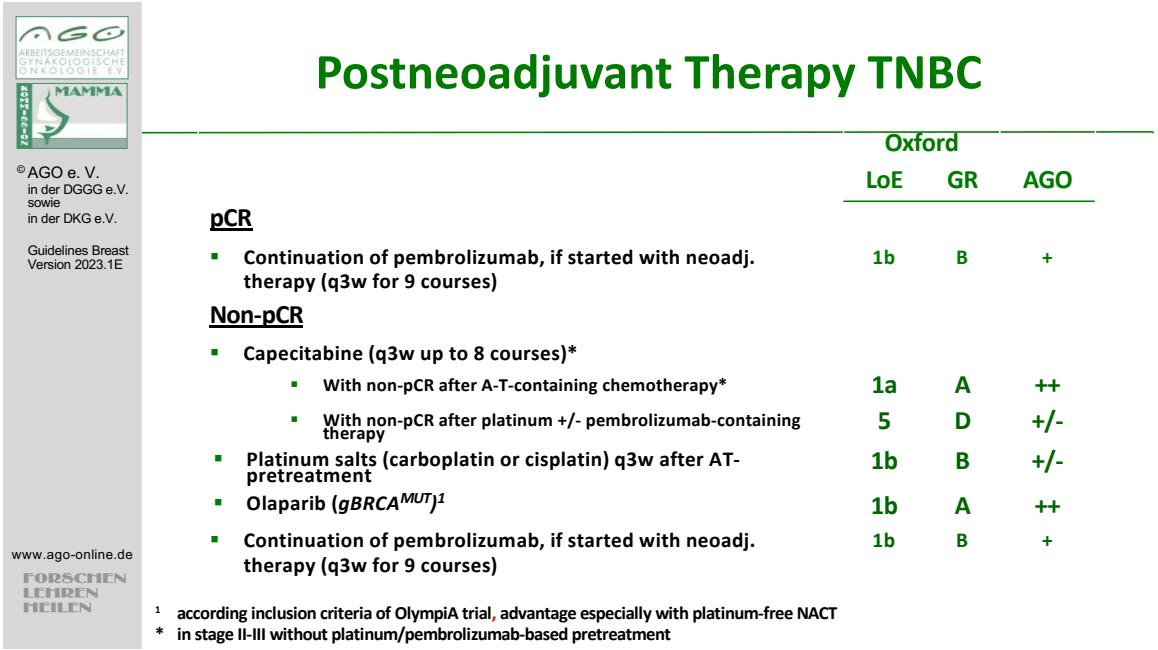


Adjuvant / Post-Neoadjuvant Treatment with CDK4/6i

	monarchE	PALLAS	PENELOPE[B]
N	5,637	5,600	1,250
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib
% of pts. with NACT	37%	n.r.	100%
Duration of CDK4/6i treatment	24 mths	24 mths	12 mths
Follow-up	42.0 mths	24 mths	43 mths
Discontinuation rate	28%	42%	20%
Discontinuation rate due to AE_{CDKi}	17%	27%	5%
IDFS-HR (95%-CI)	0.664 (0.578-0.762) p < 0.0001	0.96 (0.81-1.14) p = 0.65	0.93 (0.74-1.16) p = 0.525
2-yrs IDFS	92.7% vs. 89.9%	n.r.	88% vs. 78%
3-yrs IDFS	89.2% vs. 84.4%	88% vs. 89%	81% vs. 78%
4-yrs IDFS	85.8% vs. 79.4%	84.2% vs. 84.5%	73% vs. 72%

IDFS: invasive disease-free survival

1. Mayer EL, Gnant MI, DeMichele A et al. PALLAS: A randomized phase III trial of adjuvant palbociclib with endocrine therapy versus endocrine therapy alone for HR+/HER2- early breast cancer. Ann Oncol (2020) 31 (suppl_4): S1142-S1215. 10.1016/annonc/annonc325
2. Loibl S, Marmé F, Martin M, et al. Palbociclib for Residual High-Risk Invasive HR-Positive and HER2-Negative Early Breast Cancer-The Penelope-B Trial. J Clin Oncol. 2021 May 10;39(14):1518-1530. doi: 10.1200/JCO.20.03639. Epub 2021 Apr 1.PMID: 33793299
3. Harbeck N, Rastogi P, Martin M, et al.; monarchE Committee Members. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol. 2021 Dec;32(12):1571-1581. doi: 10.1016/j.annonc.2021.09.015. Epub 2021 Oct 14.PMID: 34656740
4. Gnant M, Dueck AC, Frantal S, et al.; PALLAS groups and investigators. Adjuvant Palbociclib for Early Breast Cancer: The PALLAS Trial Results (ABCSG-42/AFT-05/BIG-14-03). J Clin Oncol. 2021 Dec 7:JCO2102554. doi: 10.1200/JCO.21.02554. Online ahead of print.PMID: 34874182
5. Johnston et al. SABCS 2022



Postneoadjuvant Therapy TNBC

	Oxford LoE	Oxford GR	AGO
pCR			
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	+
Non-pCR			
▪ Capecitabine (q3w up to 8 courses)*			
▪ With non-pCR after A-T-containing chemotherapy*	1a	A	++
▪ With non-pCR after platinum +/- pembrolizumab-containing therapy	5	D	+/-
▪ Platinum salts (carboplatin or cisplatin) q3w after AT-pretreatment	1b	B	+/-
▪ Olaparib (*gBRCA^{MUT}*)[1]	1b	A	++
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	+

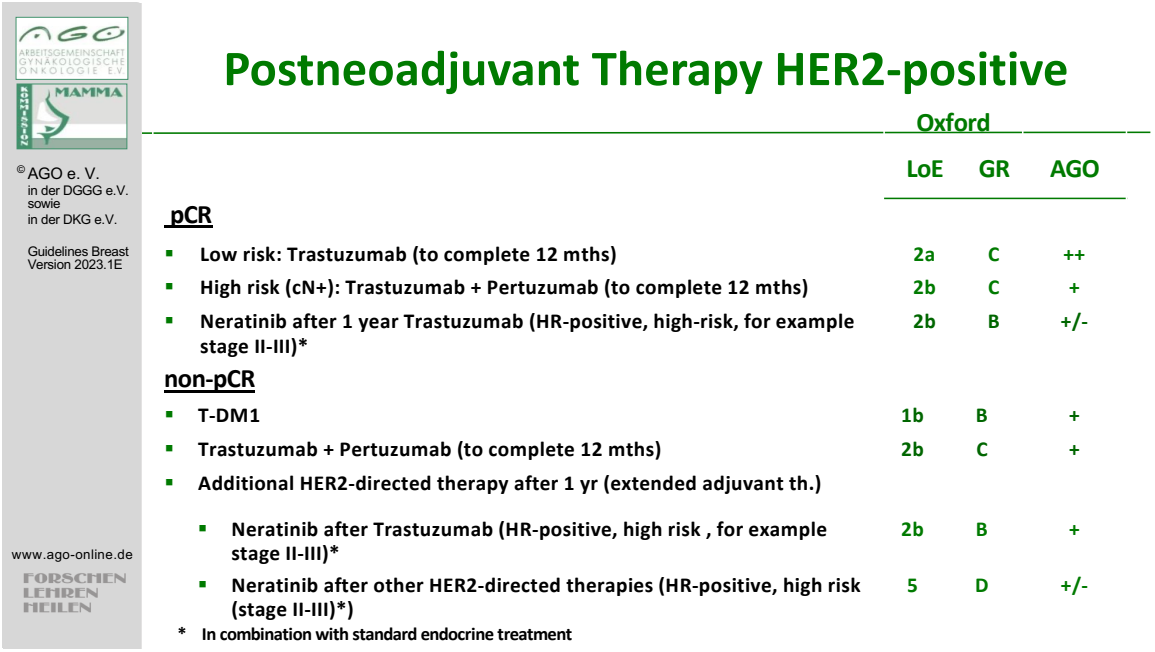
[1] according inclusion criteria of OlympiA trial, advantage especially with platinum-free NACT
* in stage II-III without platinum/pembrolizumab-based pretreatment

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

1. Joensuu H, Kellokumpu-Lehtinen PL, Huovinen R et al. Adjuvant Capecitabine for Early Breast Cancer: 15-Year Overall Survival Results From a Randomized Trial. J Clin Oncol. 2022 Jan 12:JCO2102054.
2. Lluch A et al. Phase III Trial of adjuvant capecitabine after standard neo-/adjuvant chemotherapy in patients with early triple-negative breast cancer (GEICAM/2003-11_CIBOMA/2004-01). J Clin Oncol. 2020 Jan 20;38(3):203-213.
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.
4. Schneider BP, Jiang G, Ballinger TJ et al. BRE12-158: A Postneoadjuvant, Randomized Phase II Trial of Personalized Therapy Versus Treatment of Physician's Choice for Patients With Residual Triple-Negative Breast Cancer. Journal of Clinical Oncology 2022; 40: 345-355.

Pembrolizumab in combination with chemotherapy

1. Schmid P, Cortes J, Pusztai L et al. ; KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810-821.
2. Schmid P, Cortes J, Dent R, et al. KEYNOTE-522: Phase III study of neoadjuvant pembrolizumab + chemotherapy vs. placebo + chemotherapy, followed by adjuvant pembrolizumab vs. placebo for early-stage TNBC. https://doi.org/10.1016/j.annonc.2021.06.014



Postneoadjuvant Therapy HER2-positive

	Oxford LoE	GR	AGO
pCR			
▪ Low risk: Trastuzumab (to complete 12 mths)	2a	C	++
▪ High risk (cN+): Trastuzumab + Pertuzumab (to complete 12 mths)	2b	C	+
▪ Neratinib after 1 year Trastuzumab (HR-positive, high-risk, for example stage II-III)*	2b	B	+/-
non-pCR			
▪ T-DM1	1b	B	+
▪ Trastuzumab + Pertuzumab (to complete 12 mths)	2b	C	+
▪ Additional HER2-directed therapy after 1 yr (extended adjuvant th.)			
▪ Neratinib after Trastuzumab (HR-positive, high risk , for example stage II-III)*	2b	B	+
▪ Neratinib after other HER2-directed therapies (HR-positive, high risk (stage II-III)*)	5	D	+/-

* In combination with standard endocrine treatment

Statement HER2 positiv (pCR):

1. Piccart M et al.; APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. J Clin Oncol. 2021 May 1;39(13):1448-1457.
2. Chan A, Moy B, Mansi J et al.: ExteNET Study Group. Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial. Clin Breast Cancer. 2020 Oct 6:S1526-8209(20)30258-5. doi: 10.1016/j.clbc.2020.09.014.
3. 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
4. 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.
5. 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.

Statement HER2 positiv (non-pCR) :

1. Chan A, Moy B, Mansi J, et al.; ExteNET Study Group. Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial. Clin Breast Cancer. 2021 Feb;21(1):80-91.e7.

2. 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.
3. 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