Guidelines Breast
Version 2024.1D

FORSCHEN
LEHREN
HEILEN

Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

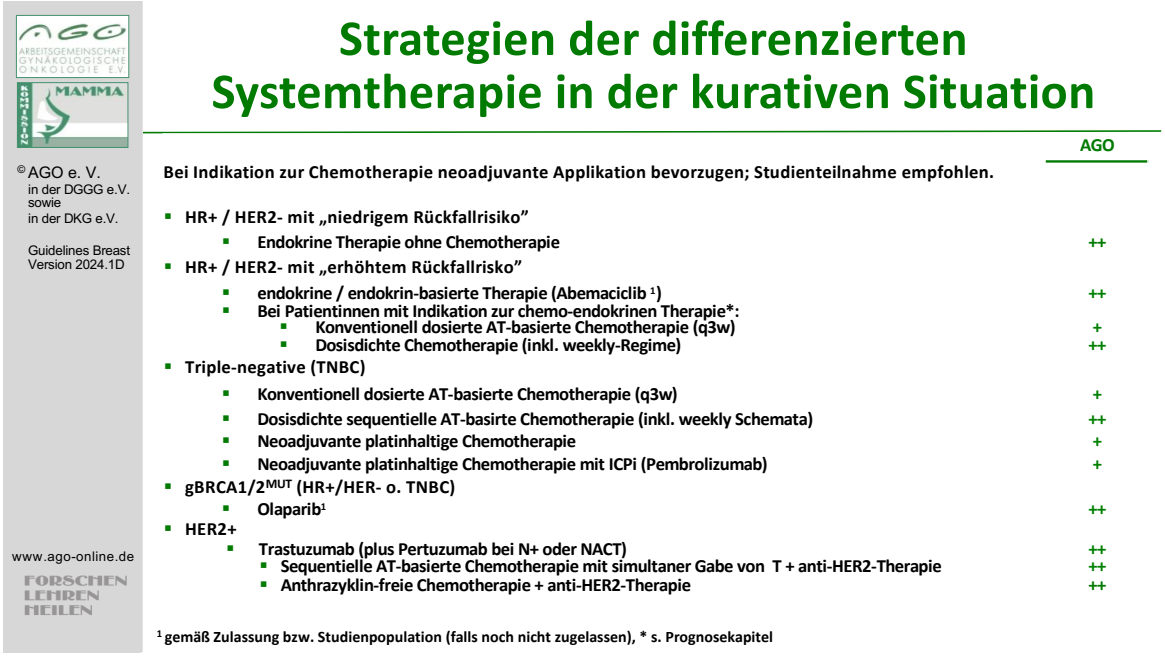
Neoadjuvante
(primäre) systemische Therapie

Neoadjuvante systemische Therapie

Guidelines Breast
Version 2024.1D

- **Versionen 2002–2023:**
  Bauerfeind / Blohmer / Costa / Dall / Fasching / Fehm / Fersis / Friedrich / Göhring / Harbeck / Heinrich / Huober / Jackisch / Kaufmann / Liedtke / Loibl / Lux / von Minckwitz / Müller / Mundhenke / Nitz / Schneeweiss / Schütz / Solomayer / Stickeler / Untch/ Thill / Thomssen
- **Version 2024:**
  Jackisch /Stickeler

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



Strategien der differenzierten Systemtherapie in der kurativen Situation

	AGO
Bei Indikation zur Chemotherapie neoadjuvante Applikation bevorzugen; Studienteilnahme empfohlen.	
▪ **HR+ / HER2- mit „niedrigem Rückfallrisiko"**	
▪ **Endokrine Therapie ohne Chemotherapie**	++
▪ **HR+ / HER2- mit „erhöhtem Rückfallrisko"**	
▪ **endokrine / endokrin-basierte Therapie (Abemaciclib [1])**	++
▪ **Bei Patientinnen mit Indikation zur chemo-endokrinen Therapie*:**	
▪ **Konventionell dosierte AT-basierte Chemotherapie (q3w)**	+
▪ **Dosisdichte Chemotherapie (inkl. weekly-Regime)**	++
▪ **Triple-negative (TNBC)**	
▪ **Konventionell dosierte AT-basierte Chemotherapie (q3w)**	+
▪ **Dosisdichte sequentielle AT-basirte Chemotherapie (inkl. weekly Schemata)**	++
▪ **Neoadjuvante platinhaltige Chemotherapie**	+
▪ **Neoadjuvante platinhaltige Chemotherapie mit ICPi (Pembrolizumab)**	+
▪ **gBRCA1/2^{MUT} (HR+/HER- o. TNBC)**	
▪ **Olaparib[1]**	++
▪ **HER2+**	
▪ **Trastuzumab (plus Pertuzumab bei N+ oder NACT)**	++
▪ **Sequentielle AT-basierte Chemotherapie mit simultaner Gabe von T + anti-HER2-Therapie**	++
▪ **Anthrazyklin-freie Chemotherapie + anti-HER2-Therapie**	++

[1] **gemäß Zulassung bzw. Studienpopulation (falls noch nicht zugelassen), * s. Prognosekapitel**

<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.

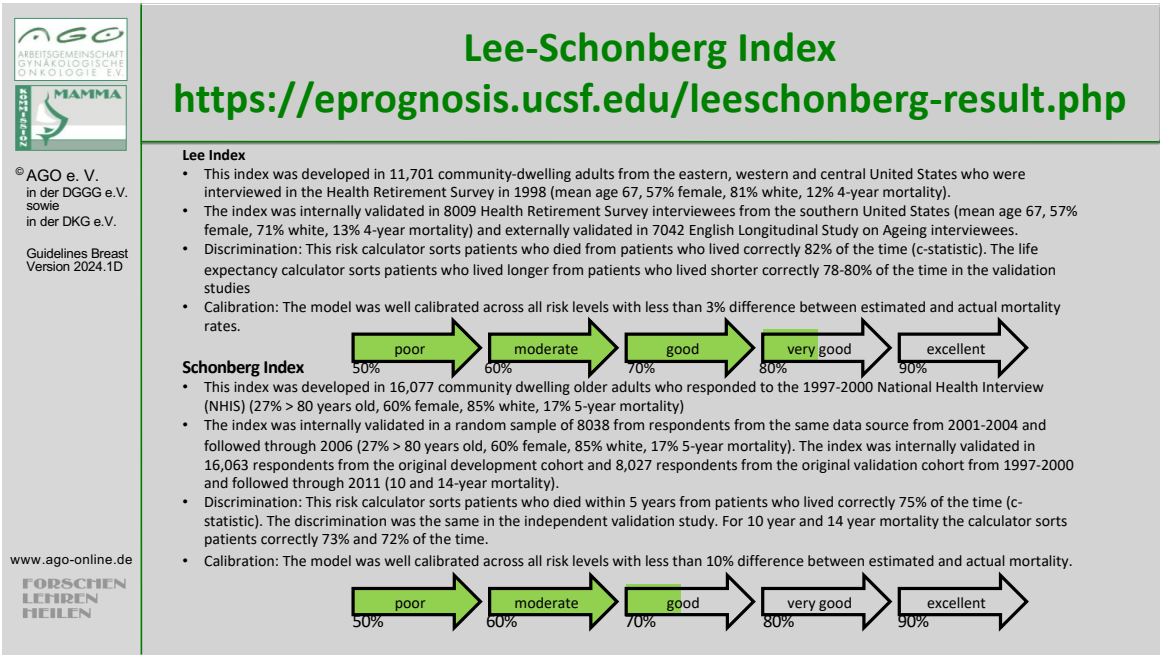
Olaparib

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

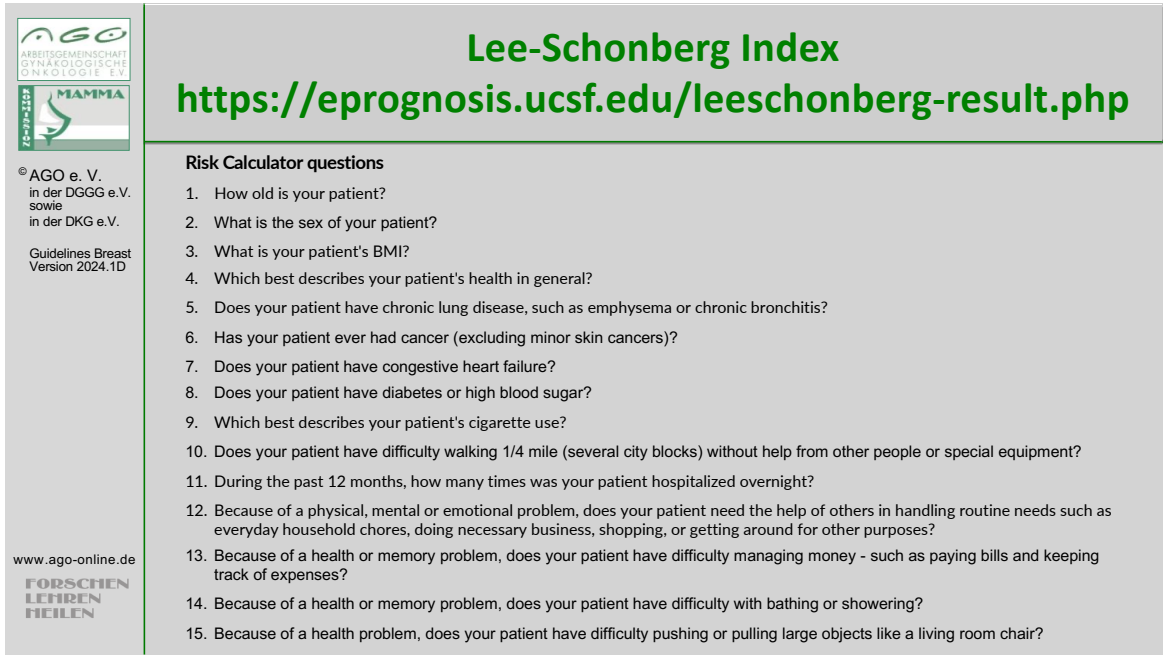
cancer. Ann Oncol 2022;33(12):1250-1268

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



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.
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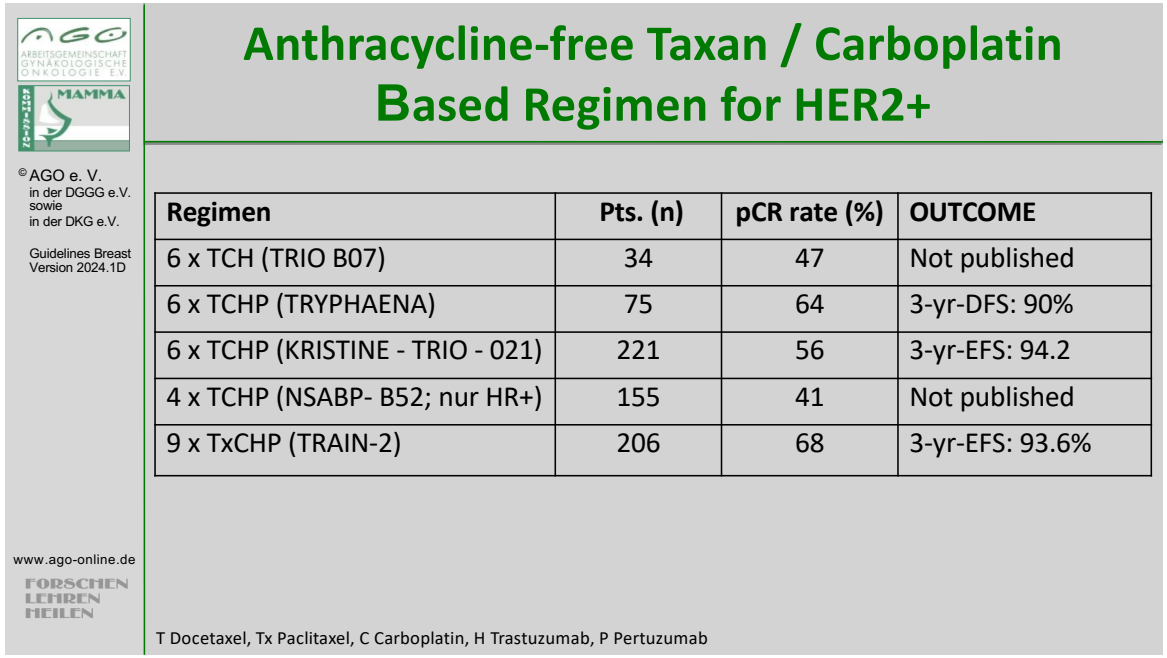
3. Lee SJ, Boscardin WJ, Kirby KA, Covinsky KE. Individualizing life expectancy estimates for older adults using the Gompertz Law of Human Mortality. Plos One. 2014;9(9):3108540.



Regimen	Pts. (n)	pCR rate (%)	OUTCOME
6 x TCH (TRIO B07)	34	47	Not published
6 x TCHP (TRYPHAENA)	75	64	3-yr-DFS: 90%
6 x TCHP (KRISTINE - TRIO - 021)	221	56	3-yr-EFS: 94.2
4 x TCHP (NSABP- B52; nur HR+)	155	41	Not published
9 x TxCHP (TRAIN-2)	206	68	3-yr-EFS: 93.6%

1. Hurvitz SA, Miller JM, Dichmann R et al. Final analysis of a phase II 3 arm randomized trial of neoadjuvant tratuzumab or lapatinib or th combination of trastuzumab and lapaitinib, followed by six cycels of docetaxel and carboplatin with trastuzumab and/or lapatinib in patients with Her2+ breast cancer (TRIO-US B07). Cancer Res 2013, 73(24 suppl). S1-02.
2. Schneeweiss A, Chia S, Hickish T 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 randomied phae II Cardiac safety study (TRYPHAENA) Ann Oncol. 2013 Sep;24(9):2278-84. doi:10.1093/annonc/mdt182.
3. Hurvitz SA, Martin M, Symmans WF et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with Her2-positive breast cancer (KRISTINE): a randomized, open-label, multicentre, phase 3 trial. Lancet oncol, 2018 Jan;19(1):115-126. doi:10.1016/S1470-2045(17)30716-7.
4. Rimawi MF, Cecchini RS, Rastogi P et al. A phase II trial evaluating pCR in patients with HR+ Her-positive breast cancer treated with neoadjuvant docetaxel, carboplatin, trastuzumab, pertuzumab (TCHP) +/- estrogen deprivation: NRG Oncology/NSABP B-52 Cancer Res 2017;77(4 suppl):S3-06.
5. Van der Voort A, van Ramshorst MS,, van Werkhoven ED et al. Three-Year Follow-up of Neoadjuvant Chemotherapy With or Without Anthracyclines in the Presence of Dual ERBB2 Blockade in Patients With ERBB2-Positive Breast Cancer: A Secondary Analysis of the TRAIN-2 Randomized, Phase 3 Trial. JAMA Oncol 2021 Jul 1;7(7):978-984. doi: 10.1001/jamaoncol.2021.1371.

Neoadjuvante systemische Chemotherapie – Klinischer Benefit

	Oxford	
	LoE	GR
▪ Ermöglicht eine Prognoseverbesserung durch Individualisierung der neoadjuvanten und post-neoadjuvanten Behandlung (insb. bei HER2 pos und TNBC)	1b	A
▪ Überleben ist gleich nach neoadjuvanter (präoperativer, primärer) und adjuvanter systemischer Therapie (bei gleichem Regime und gleicher Zyklenzahl, wenn die postneoadjuvante Therapie nicht anhand des pathologischen Ansprechens stratifiziert wird)	1a	A
▪ Pathologische Komplettremission ist mit einem besseren Überleben assoziiert	1b	A
▪ Der RCB Score und die RCB Klasse sind subtypen-unabhängige Prognosefaktoren	2a	B
▪ Kann Operabilität bei primär inoperablen Tumoren erreichen	1b	A
▪ Verbessert die Optionen für eine brusterhaltende Operation	1b	A
▪ Senkt die Rate an axillären Lymphonodektomien	2b	B
▪ Erlaubt Individualisierung der Therapie nach dem Interims-Ansprechen	1b	B

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

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

Pathological complete response is associated with improved survival in all subgroups

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

Research and Treatment of Cancer trial 10902. J Clin Oncol 2001: 19; 4224
4. Rastogi P, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008: 26; 778
5. EBCTCG. Long-term outcomes for neoad
6. Cortazar P, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014: 384; 164
7. Berruti A, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: a meta-regression of 29 randomized prospective studies. J Clin Oncol 2014: 32; 3883
8. Yee D, et al. Pathological complete response predicts event-free and distant disease free survival in the I-SPY 2 Trial. SABCS 2017 (abs GS3-08)

RCB Score and RCB class as prognostic factors

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

Can achieve operability in primary inoperable tumors

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

Can achieve operability in primary inoperable tumors

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

Improved options for breast conserving surgery

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant

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

Reduces the rate of lymphadenectomies

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

Allows individualization of therapy according to mid-course treatment effect

1. Von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012: 30; 1796

Allows individualization of post-neoadjuvant treatment

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

Neoadjuvante systemische Chemotherapie – Indikationen

	Oxford		
	LoE	GR	AGO
▪ **Wenn die gleiche postoperative adjuvante Chemotherapie indiziert ist**	1b	A	++
▪ **Um eine risikoadaptierte postoperative Therapie durchzuführen (insbesondere bei HER2 pos und TNBC)**	1b	A	++
▪ **Inflammatorisches Mammakarzinom**	2b	B	++
▪ **Inoperables Mammakarzinom**	1c	A	++
▪ **Große operable Mammakarzinome, die primär eine Mastektomie und adjuvante Chemotherapie erfordern, mit dem Ziel der Brusterhaltung**	1b	B	++

Inflammatory breast cancer

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

Inoperable breast cancer

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

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

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

systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508
3. EBCTCG. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol 2018 Jan;19(1):27-39.

<u>If similar postoperative adjuvant chemotherapy is indicated</u>

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

Neoadjuvante Chemotherapie (NACT)
Prädiktive Faktoren für pCR I

Faktor	pCR* Wahrscheinlichkeit	Oxford LoE	Oxford GR	AGO
▪ Junges Alter	↑	1a	A	+
▪ Adipositas	↓	2a	B	+
▪ cT1 / cT2-Tumoren o. N0 o. G3	↑↑	1a	A	++
▪ Negativer ER- und PR-Status	↑↑	1a	A	++
▪ Triple negative (TNBC)	↑↑	1a	A	++
▪ Positiver HER2-Status	↑↑	1a	A	++
▪ Frühes klinisches Ansprechen	↑	1b	A	+
▪ Invasives lobuläres Karzinom	↓	1a	A	+
▪ Metaplastisches Karzinom	↓↓	4	C	+

* Hohe (↑) oder sehr hohe (↑↑) Wahrscheinlichkeit einer pCR, niedrigere (↓) oder sehr niedrige (↓↓) Wahrscheinlichkeit einer pCR
Siehe auch Kapitel „Prognostische und prädiktive Faktoren"

General evidence

1. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384: 164-72.
2. Gerber B, Loibl S, Eidtmann H, et al. Neoadjuvant bevacizumab and anthracycline-taxane-based chemotherapy in 678 triple-negative primary breast cancers; results from the geparquinto study (GBG 44). Ann Oncol 2013;24: 2978-84.
3. van Mackelenbergh MT, Denkert C, Nekljudova V, et al. Outcome after neoadjuvant chemotherapy in estrogen receptor-positive and progesterone receptor-negative breast cancer patients: a pooled analysis of individual patient data from ten prospectively randomized controlled neoadjuvant trials. Breast Cancer Res Treat 2017.
4. von Minckwitz G, Eidtmann H, Rezai M, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med 2012;366: 299-309.
5. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012;30: 1796-804.

Body mass index

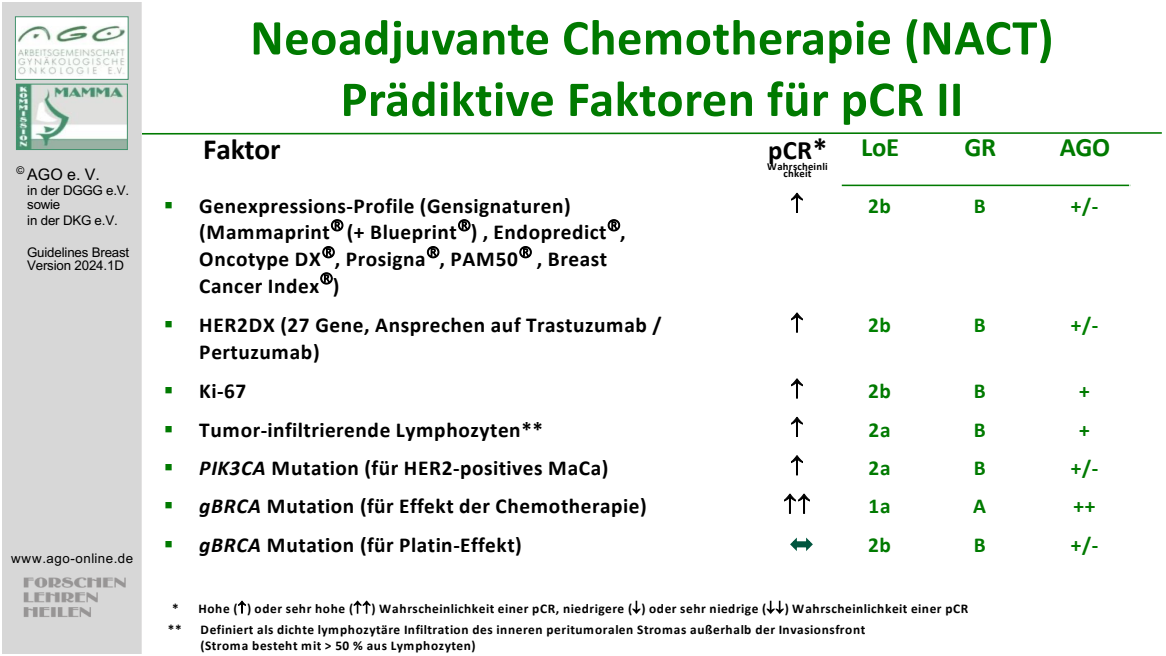
1. Wang H, Zhang S, Yee D, et al. Impact of body mass index on pathological complete response following neoadjuvant chemotherapy in operable breast cancer: a meta analysis. Breast Cancer 2021;28(3):616-629

Lobular cancer

1. Loibl S, Volz C, Mau C, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014;144: 153-62.

Metaplastic breast cancer

1. McMullen ER, Zoumberos NA, Kleer CG. Metaplastic Breast Carcinoma: Update on Histopathology and Molecular Alterations. Arch Pathol Lab Med. 2019 Dec;143(12):1492-1496.
2. Tzanninis IG, Kotteas EA, Ntanasis-Stathopoulos I et al. Management and Outcomes in Metaplastic Breast Cancer. Clin Breast Cancer. 2016 Dec;16(6):437-443.
3. Al-Hilli Z, Choong G, Keeney MG, et al. Metaplastic breast cancer has a poor response to neoadjuvant systemic therapy. *Breast Cancer Res Treat*. 2019;176(3):709–716.



Neoadjuvante Chemotherapie (NACT)
Prädiktive Faktoren für pCR II

Faktor	pCR* Wahrscheinlichkeit	LoE	GR	AGO
Genexpressions-Profile (Gensignaturen) (Mammaprint® (+ Blueprint®) , Endopredict®, Oncotype DX®, Prosigna®, PAM50® , Breast Cancer Index®)	↑	2b	B	+/-
HER2DX (27 Gene, Ansprechen auf Trastuzumab / Pertuzumab)	↑	2b	B	+/-
Ki-67	↑	2b	B	+
Tumor-infiltrierende Lymphozyten**	↑	2a	B	+
PIK3CA Mutation (für HER2-positives MaCa)	↑	2a	B	+/-
gBRCA Mutation (für Effekt der Chemotherapie)	↑↑	1a	A	++
gBRCA Mutation (für Platin-Effekt)	⬌	2b	B	+/-

* Hohe (↑) oder sehr hohe (↑↑) Wahrscheinlichkeit einer pCR, niedrigere (↓) oder sehr niedrige (↓↓) Wahrscheinlichkeit einer pCR

** Definiert als dichte lymphozytäre Infiltration des inneren peritumoralen Stromas außerhalb der Invasionsfront (Stroma besteht mit > 50 % aus Lymphozyten)

TIL

1. Denkert, C., Loibl, S., Noske, A., et al. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. 2010. J. Clin. Oncol. 28, 105–113. doi:10.1200/JCO.2009.23.7370.
2. Denkert C, von Minckwitz G, Brase JC, et al. Tumor-Infiltrating Lymphocytes and Response to Neoadjuvant Chemotherapy With or Without Carboplatin in Human Epidermal Growth Factor Receptor 2-Positive and Triple-Negative Primary Breast Cancers. J Clin Oncol. 2014 Dec 22. pii: JCO.2014.58.1967.
3. Ibrahim EM, Al-Foheidi ME, Al-Mansour MM, et al. The prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancer: a meta-analysis. Breast Cancer Res Treat. 2014 Dec;148(3):467-76
4. Loi S, Michiels S, Salgado R, et al. Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial. Ann Oncol. 2014 Aug;25(8):1544-50. Doi
5. Mao Y, Qu Q, Zhang Y, et al. The Value of Tumor Infiltrating Lymphocytes (TILs) for Predicting Response to Neoadjuvant Chemotherapy in Breast Cancer: A Systematic Review and Meta-Analysis. PLoS One. 2014 Dec 12;9(12)
6. Tung NM, Winer EP. Tumor-Infiltrating Lymphocytes and Response to Platinum in Triple-Negative Breast Cancer. J Clin Oncol. 2015 Jan 5. pii: JCO.2014.59.6031.

7. Denkert C, von Minckwitz G, Darb—Esfahani S et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvanttherapy. Lancet Oncol 2018;19(1):40-50.

PIK3CA

1. Loibl S, von Minckwitz G, Schneeweiss A, et al. PIK3CA mutations are associated with lower rates of pathologic complete response to anti-human epidermal growth factor receptor 2 (her2) therapy in primary HER2-overexpressing breast cancer. J Clin Oncol. 2014 Oct
2. Nuciforo PG, Aura C, Holmes E, et al: Benefit to neoadjuvant anti–Human Epidermal Growth Factor Receptor 2 (HER2)-targeted therapies in HER2-positive primary breast cancer is independent of Phosphatase and tensin homolog deleted from chromosome 10 (PTEN) status. Ann Oncol. 2015 Jul;26(7):1494-500.
3. Pogue-Geile KL, Song N, Jeong JH, et al: Intrinsic Subtypes, PIK3CA Mutation, and the Degree of Benefit From Adjuvant Trastuzumab in the NSABP B-31 Trial. Clin Oncol. 2015 Jan 5. pii: JCO.2014.56.2439
4. Sueta A, Yamamoto Y, Yamamoto-Ibusuki M, et al. An Integrative Analysis of PIK3CA Mutation, PTEN, and INPP4B Expression in Terms of Trastuzumab Efficacy in HER2-Positive Breast Cancer. PLoS One. 2014 Dec 26;9(12):e116054.
5. Loibl S, Majewski I, Guarneri V, et al. PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol. 2016 Aug;27(8):1519-25.
6. Loibl S, Majewski I, Guarneri V, et al. PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol. 2019; 30(7):1180.
7. Fan H, Li C, Xiang Q, et al. PIK3CA mutations and their response to neoadjuvant treatment in early breast cancer: A systematic review and meta-analysis. Thorac Cancer. 2018 May;9(5):571-579.
8. Zardavas D, Te Marvelde L, Milne RL, et al. Tumor PIK3CA Genotype and Prognosis in Early-Stage Breast Cancer: A Pooled Analysis of Individual Patient Data. J Clin Oncol. 2018 Apr 1;36(10):981-990.

gBRCA bei TNBC

1. Loibl S, Weber KE, Timms KM et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. Ann Oncol. 2018 Dec 1;29(12):2341-2347.

PAM50 neoadjuvant:

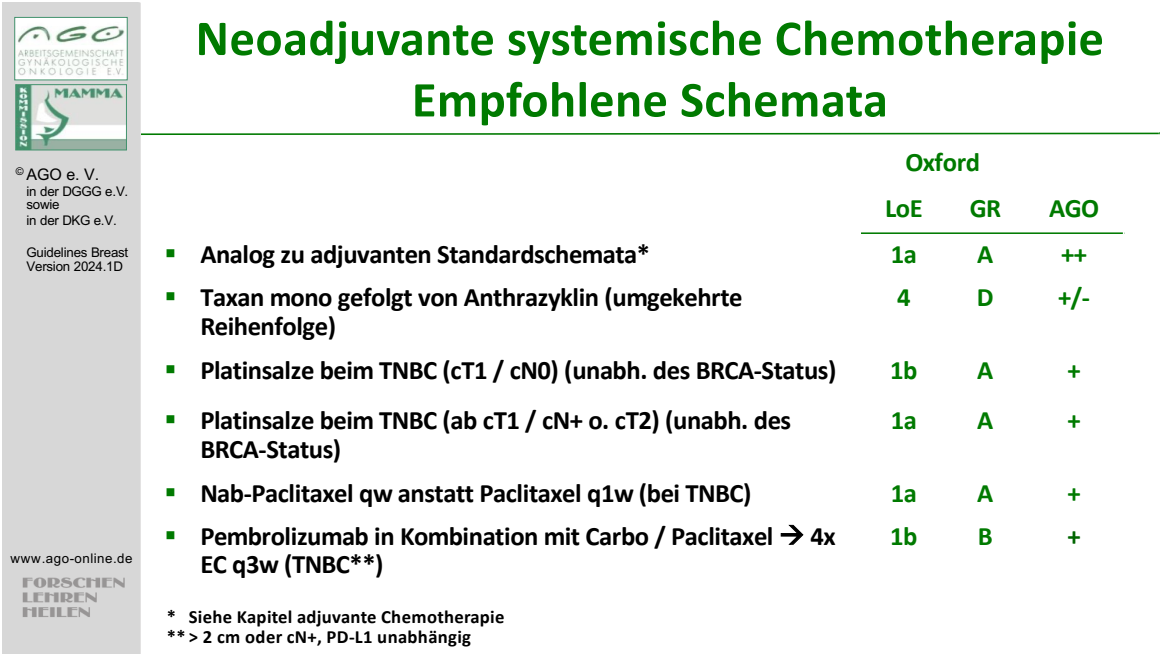
1. Ohara AM, Naoi Y, Shimazu K, et al. PAM50 for prediction of response to neoadjuvant chemotherapy for ER-positive breast cancer. Breast Cancer Res Treat. 2019 Feb;173(3):533-543.
2. Pascual T, Fernandez-Martinez A, Tanioka M, et al. Independent Validation of the PAM50-Based Chemo-Endocrine Score (CES) in Hormone Receptor-Positive HER2-Positive Breast Cancer Treated with Neoadjuvant Anti-HER2-Based Therapy. Clin Cancer Res. 2021 Jun 1;27(11):3116-3125.
3. Díaz-Redondo T, Lavado-Valenzuela R, Jimenez B, et al. Different Pathological Complete Response Rates According to PAM50 Subtype in HER2+ Breast Cancer Patients Treated With NeoadjuvantPertuzumab/Trastuzumab vs. Trastuzumab Plus Standard Chemotherapy: An Analysis of Real-World Data. Front Oncol. 2019 Nov 5;9:1178.
4. Gluz O, Kolberg-Liedtke C, Prat A, et al. Efficacy of deescalated chemotherapy according to PAM50 subtypes, immune and proliferation genes in triple-negative early breast cancer: Primary translational analysis of the WSG-ADAPT-TN trial. Int J Cancer. 2020 Jan 1;146(1):262-271.

Blueprint:

1. Beitsch P, Whitworth P, Baron P, et al. Pertuzumab/Trastuzumab/CT Versus Trastuzumab/CT Therapy for HER2+ Breast Cancer: Results from the Prospective Neoadjuvant Breast Registry Symphony Trial (NBRST). Ann Surg Oncol. 2017 Sep;24(9):2539-2546.
2. Whitworth P, Stork-Sloots L, de Snoo FA, et al. Chemosensitivity predicted by BluePrint 80-gene functional subtype and MammaPrint in the Prospective Neoadjuvant Breast Registry Symphony Trial (NBRST). Ann Surg Oncol. 2014 Oct;21(10):3261-7.
3. Whitworth P, Beitsch PD, Pellicane JV et al. ; NBRST Investigators Group.Age-Independent Preoperative Chemosensitivity and 5-Year Outcome Determined by Combined 70- and 80-Gene Signature in a Prospective Trial in Early-Stage Breast Cancer. Ann Surg Oncol. 2022 Apr 4;29(7):4141-52.
4. Pellicane JV, Beitsch PD, Rock DT, et al. ; NBRST Investigators Group.Combined 70- and 80-gene signatures identify tumors with genomically luminal biology responsive to neoadjuvant endocrine therapy and are prognostic of 5-year outcome in early-stage breast cancer. Surg Oncol. 2022 Dec;45:101885.
5. Liefaard MC, van der Voort A, van Ramshorst MS, et al. BluePrint molecular subtypes predict response to neoadjuvant pertuzumab

in HER2-positive breast cancer. Breast Cancer Res. 2023 Jun 19;25(1):71.
6. Göker E, Hendriks MP, van Tilburg M et al.; of the NBREaST II Investigators Group. Treatment response and 5-year distant metastasis-free survival outcome in breastcancer patients after the use of MammaPrint and BluePrint to guide preoperative systemic treatment decisions. Eur J Cancer. 2022 May;167:92-102.

HER2DX:
1. Guarneri V, Bras-Maristany F, Dieci MV, et al. HER2DX genomic test in HER2-positive/hormone receptor-positive breast cancertreated with neoadjuvant trastuzumab and pertuzumab: A correlative analysis from the PerELISA trial. EBioMedicine. 2022 Nov;85:104320.
2. Prat A, Guarneri V, Paré L, et al. A multivariable prognostic score to guide systemic therapy in early-stage HER2-positive breast cancer: a retrospective study with an external evaluation. Lancet Oncol. 2020 Nov;21(11):1455-1464.
3. Villacampa G, Tung NM, Pernas S, et al. Association of HER2DX with pathological complete response and survival outcomes in HER2-positive breast cancer. Ann Oncol. 2023 Sep;34(9):783-795.



Neoadjuvante systemische Chemotherapie
Empfohlene Schemata

	Oxford		
	LoE	GR	AGO
▪ Analog zu adjuvanten Standardschemata*	1a	A	++
▪ Taxan mono gefolgt von Anthrazyklin (umgekehrte Reihenfolge)	4	D	+/-
▪ Platinsalze beim TNBC (cT1 / cN0) (unabh. des BRCA-Status)	1b	A	+
▪ Platinsalze beim TNBC (ab cT1 / cN+ o. cT2) (unabh. des BRCA-Status)	1a	A	+
▪ Nab-Paclitaxel qw anstatt Paclitaxel q1w (bei TNBC)	1a	A	+
▪ Pembrolizumab in Kombination mit Carbo / Paclitaxel → 4x EC q3w (TNBC**)	1b	B	+

* Siehe Kapitel adjuvante Chemotherapie
** > 2 cm oder cN+, PD-L1 unabhängig

Use of adjuvant standard regimens for NACT

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol. 2018;19(1):27-39. doi: 10.1016/S1470-2045(17)30777-5.

Taxane followed by anthracycline sequence

1. Bines J, et al. Anthracyclines and taxanes in the neo/adjuvant treatment of breast cancer: does the sequence matter? Ann Oncol 2014: 25; 1079
2. Earl HM, et al. Effects of the addition of gemcitabine, and paclitaxel-first sequencing, in neoadjuvant sequential epirubicin, cyclophosphamide, and paclitaxel for women with high-risk early breast cancer (Neo-tAnGo): an open-label, 2×2 factorial randomised phase 3 trial. Lancet Oncol 2014: 15; 201
3. Wang D, Feng J, Xu B. A meta-analysis of platinum-based neoadjuvant chemotherapy versus standard neoadjuvant chemotherapy for triple-negative breast cancer. Future Oncol. 2019: 15(23); 2779-2790

Platinum in TNBC (irrespective of BRCA status)

1. 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
2. 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
3. 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
4. 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
5. 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
6. Byrski T, et al. Pathologic complete response to neoadjuvant cisplatin in BRCA1-positive breast cancer patients. Breast Cancer Res Treat 2014: 147; 401
7. 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, 2014
8. Loibl S, 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;19(4):497-509.
9. Loibl S et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. Ann Oncol 2018;29(12):2341-2347
10. Li ZY, Zhang Z, Cao XZ, et al. Platinum-based neoadjuvant chemotherapy for triple-negative breast cancer: a systematic review and meta-analysis. J Int Med Res. 2020 Oct;48(10):300060520964340.
11. Iwase M, Ando M, Aogi K, et al. Long-term survival analysis of addition of carboplatin to neoadjuvant chemotherapy in HER2-negative breast cancer. Breast Cancer Res Treat. 2020 Apr;180(3):687-694.
12. Bian L, Yu P, Wen J, et al. Survival benefit of platinum-based regimen in early stage triple negative breastcancer: A meta-analysis of randomized controlled trials. NPJ Breast Cancer. 2021 Dec 21;7(1):157.
13. Saleh RR, Nadler MB, Desnoyers A, et al. Platinum-based chemotherapy in early-stage triple negative breast cancer: A meta-analysis. Cancer Treat Rev. 2021 Nov;100:102283.

14. 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.
15. Li J, Chen L, Tan W, et al. Platinum is essential in neoadjuvant treatment of triple-negative breast cancer: a network meta-analysis. Cancer Biol Med. 2022 Feb 16:j.issn.2095-3941.2021.0529. doi: 10.20892/j.issn.2095-3941.2021.0529. Online ahead of print
16. Feng W, He Y, Xu J, et al. A meta-analysis of the effect and safety of platinum-based neoadjuvant chemotherapy in treatment of resectable triple-negative breast cancer. Anticancer Drugs. 2022 Jan 1;33(1):e52-e60.

Nab-Paclitaxel weekly instead of Paclitaxel weekly

1. M Untch et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto—GBG 69): a randomised, phase 3 trial. Lancet Oncol. 2016 Mar;17(3):345-56
2. Gianni L, et al. Comparing Neoadjuvant Nab-paclitaxel vs Paclitaxel Both Followed by Anthracycline Regimens in Women With ERBB2/HER2-Negative Breast Cancer-The Evaluating Treatment With Neoadjuvant Abraxane (ETNA) Trial: A Randomized Phase 3 Clinical Trial. JAMA Oncol 2017; 4: 302-08
3. Futamura M, et al.Preoperative neoadjuvant chemotherapy using nanoparticle albumin-bound paclitaxel followed by epirubicin and cyclophosphamide for operable breast cancer: a multicenter phase II trial.Breast Cancer. 2017 Jan 3. doi:
4. Zong Y, et al. Nanoparticle albumin-bound paclitaxel as neoadjuvant chemotherapy of breast cancer: a systematic review and meta-analysis. Oncotarget 8(10):17360-17372, 2017
5. Schneeweiss A, et al. Survival analysis of the prospectively randomized phase III GeparSepto trial comparing neoadjuvant chemotherapy with weekly nab-paclitaxel with solvent-based paclitaxel followed by anthracycline/cyclophosphamide for patients with early breast cancer – GBG69. SABCS 2017 (abs GS3-05)
6. Li Y, et al. Is nab paclitaxel better thean conventional taxanes as neoadjuvant therapy for breast cancer? A meta-analysis. J Int Med Res. 2020 Aug;48(8):300060520943473..

ICPi in combination with chemotherapy

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 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
4. Schmid P, Cortes J, Dent R, et al.; KEYNOTE-522 Investigators.Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer. N Engl J Med. 2022 Feb 10;386(6):556-567.

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Guidelines Breast
Version 2024.1D

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FORSCHEN
LEHREN
HEILEN

Empfohlene Schemata beim triple-negativen Mammakarzinom

	Oxford		
	LoE	GR	AGO
Nicht-platinhaltige Regime			
ddEC x 4 → $Pacli_{80}$ q1w x 12	1b	B	++
$NabPac_{125}$ q1w x 12 → $E_{90}C$ q2(3)w x 4	1b	B	+/-
Platinhaltige Regime			
$NabPac_{125}$ / $Carbo_{AUC\ 2}$ q1w x 8 → ddEC x 4	1b	B	+
$Pacli_{80}$ q1w x 12 / $Carbo_{AUC\ 6}$ q3w x 4 → ddAC / ddEC x 4	1b	B	+
Docetaxel / $Carbo_{AUC6}$ q3w x 6 oder Paclitaxel/$Carbo_{AUC\ 1,5}$ q1w x 18	2b	B	+
$NabPac_{1oo}$ / $Carbo_{AUC\ 6}$ q4w x 4	2b	C	+
Checkpoint-Inhibitoren			
$Pembro_{200}$ q3w + Pac_{80} / $Carbo_{AUC\ 1,5}$ q1w x 12 → $E_{90}C$ q3w x 4	1b	B	+
$Pembro_{200}$ q3w + Pac_{80} q1w x 12 / $Carbo_{AUC\ 5}$ q3w → $E_{90}C$ q3w x 4	1b	B	+

Non-platin containing chemotherapy

1. 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. doi: 10.1056/NEJMoa0707056.PMID: 18420499
2. Loibl S, Weber KE, Timms KM, et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. Ann Oncol. 2018 Dec 1;29(12):2341-2347. doi: 10.1093/annonc/mdy460.PMID: 30335131

ICPi 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. doi: 10.1056/NEJMoa1910549.
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
3. Schmid P, Cortes J, Dent R, et al.; KEYNOTE-522 Investigators.Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer. N Engl J Med. 2022 Feb 10;386(6):556-567.

Statement Platin

1. Loibl S, 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;19(4):497-509.
2. Loibl S, Sikov W, Huober J, et al. Event-free survival (EFS), overall survival (OS), and safety of adding veliparib (V) plus carboplatin (Cb) or carboplatin alone to neoadjuvant chemotherapy in triple-negative breast cancer (TNBC) after ≥4 years of follow-up: BrighTNess, a randomized phase III trial. Annals of Oncology (2021) 32 (suppl_5): S407-S446. 10.1016/annonc/annonc687
3. Thomssen C, Schüler K, Bauer M et al.. Efficacy of neoadjuvant systemic carboplatin therapy in triple-negative breast cancer San Antonio Breast Cancer Symposium 2021, Abstr.# P2-12-05
4. Mason SR, Willson ML, Egger SJ et al. Platinum-based chemotherapy for early triple-negative breast cancer. Cochrane Database Syst Rev. 2023 Sep 8; 9(9):CD014805.

Docetaxel/Carboplatin

1. Sharma P, Kimler BF, O'Dea A et al. Randomized Phase II Trial of Anthracycline-free and Anthracycline-containing Neoadjuvant Carboplatin Chemotherapy Regimens in Stage I-III Triple-negative Breast Cancer (NeoSTOP). Clin Cancer Res. 2021 Feb 15;27(4):975-982.

NabPaclitraxel/Carboplatin

1. Thomssen C, Schüler K, Bauer M et al.. Efficacy of neoadjuvant systemic carboplatin therapy in triple-negative breast cancer San Antonio Breast Cancer Symposium 2021, Abstr.# P2-12-05
2. Gluz O, Kolberg-Liedtke C, Prat A,et al. Efficacy of deescalated chemotherapy according to PAM50 subtypes, immune and proliferation genes in triple-negative early breast cancer: Primary translational analysis of the WSG-ADAPT-TN trial. Int J Cancer. 2020 Jan 1;146(1):262-271. doi: 10.1002/ijc.32488. Epub 2019 Jun 19.PMID: 31162838
3. 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. doi: 10.1093/jnci/djx258.PMID: 29228315

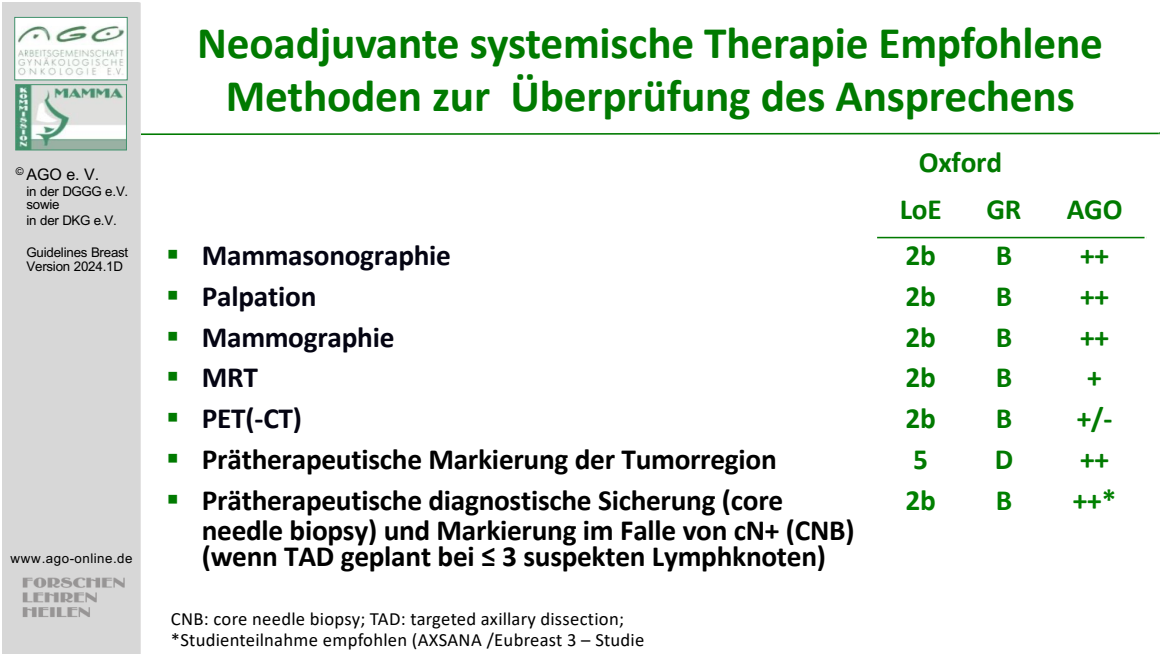
ICPi plus Neoadjuvant Chemotherapy for Patients with Triple Negative Breast Cancer

Guidelines Breast
Version 2024.1D

	GeparNuevo	IMpassion031	Keynote 522	neoTRIP
Phase	II	III	III	II
N	174	333	602 (pCR) 1174 (EFS)	280
Prim. endpoint	pCR	pCR	pCR + EFS	EFS
CPi	Durvalumab (24-26 weeks)	Atezolizumab (1 y)	Pembrolizumab (1 y)	Atezolizumab (24 weeks)
Chemo	$NabPac_{125}$ q1w x12 → EC q2w x4	$NabPac_{125}$q1w x12 → EC q2w x4	Pac q1w x12 + carbo q3w AUC 5 or q1w AUC 1,5 → AC/EC q3w x4	$NabPac_{125}$ + carbo AUC 2 q1w d1 and d8
Inclusion criteria	cT1b-cT4a-d	cT2-cT4, cN0-cN3	cT1cN1-2 or cT2 N0-2	cT1cN1; cT2cN1; cT3cN0
PD-L1 positive	87%	46%	83%	56%
pCR ITT	53.4% vs. 44.2% Δ 10.8% (n.s.)	57.6% vs. 41.2% Δ 16.5% (p < 0.01)	64.8% vs. 51.2% Δ 13.6% (p < 0.00055)	48.6% vs. 44.4% Δ 4.2% (n.s.)
pCR PD-L1 positive	58% vs. 50%	69% vs. 49%	69% vs. 55%	59.5% vs. 51.9%
pCR PD-L1 negative	44% vs. 18%	48% vs. 34%	45% vs. 30%	33,9% vs. 35.4%
Follow up/EFS/iDFS (months)/HR EFS/iDFS	43.7 months iDFS: 0.48 (p = 0.0389)	24 months EFS: 85% vs. 80% 0.76 (n.s.)	63.1 months EFS: 81.3% vs. 72.3% 0.63 (p = 0.00031)	54 months EFS: 70.6% vs. 74.9% 1.076 (p = 0.76)
EFS/iDFS adjusted to pCR/non-pCR	pCR 95.5% vs. 86.1% npCR 76.3% vs. 69.7%	---	pCR 92.2% vs. 88.2% npCR 62.6% vs. 52.3%	pCR vs. non pCR 90.3% vs. 55.7%

1. Loibl S, Untch M, Burchardi N et al. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol. 2019;30(8):1279-1288. doi: 10.1093/annonc/mdz158.
2. Loibl S, Schneeweiss A, Huober J, et al. Neoadjuvant Durvalumab improves survival in early triple negative breast cancer independent of pathological response. Ann Oncol. 2022 Nov;33(11):1149-1158. doi: 10.1016/j.annonc.2022.07.1940. Epub 2022 Aug 9.PMID: 35961599
3. 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.
4. Barrios CH, Harbeck N, Zhang HA, et al: Final analysis of the placebo-controlled randomized phase 3 IMpassion031 trial evaluating neoadjuvant atezolizumab plus chemotherapy followed by open-label adjuvant atezolizumab in patients with early-stage triple-negative breast cancer. ESMO Breast Cancer Annual Congress 2023. Abstract LBA1. Presented May 12, 2023.
5. 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.
6. 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

7. Schmid P, Cortes J, Dent R, et al.; KEYNOTE-522 Investigators.Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer. N Engl J Med. 2022 Feb 10;386(6):556-567.
8. Schmid P, Cortés J, Dent RA, et al. Pembrolizumab or placebo plus chemotherapy followed by pembrolizumab or placebo for early-stage TNBC: Updated EFS results from the phase III KEYNOTE-522 study. *Ann Onc*. 2023;34(S2):S1256-S1257. doi:10.1016/j.annonc.2023.10.008.
9. Gianni L. Huang CS, Egle I, et al. Pathologic complete response (pCR) to neoadjuvant treatment with or without atezolizumab in triple negative, early high-risk and locally advanced breast cancer. NeoTRIPaPDL1 Michelangelo randomized study: Ann Oncol. 2022 May;33(5):534-543. doi: 10.1016/j.annonc.2022.02.004. Epub 2022 Feb 17.PMID: 35182721
10. Gianni L. Huang CS, Egle I, et al. Event-free survival (EFS) analysis of neoadjuvant taxane/carboplatin with or without atezolizumab followed by an adjuvant anthracycline regimen in high-risk triple negative breast cancer (TNBC): NeoTRIP Michelangelo randomized study Ann Oncol. 2023 October; VOLUME 34, SUPPLEMENT 2, S1258-S1259,



Neoadjuvante systemische Therapie Empfohlene Methoden zur Überprüfung des Ansprechens

	Oxford		
	LoE	GR	AGO
▪ **Mammasonographie**	2b	B	++
▪ **Palpation**	2b	B	++
▪ **Mammographie**	2b	B	++
▪ **MRT**	2b	B	+
▪ **PET(-CT)**	2b	B	+/-
▪ **Prätherapeutische Markierung der Tumorregion**	5	D	++
▪ **Prätherapeutische diagnostische Sicherung (core needle biopsy) und Markierung im Falle von cN+ (CNB) (wenn TAD geplant bei ≤ 3 suspekten Lymphknoten)**	2b	B	++*

CNB: core needle biopsy; TAD: targeted axillary dissection;
*Studienteilnahme empfohlen (AXSANA /Eubreast 3 – Studie

Breast ultrasound

1. Rauch GM, et al. Multimodality Imaging for Evaluating Response to Neoadjuvant Chemotherapy in Breast Cancer. AJR Am J Roentgenol. 2016 Nov 3:1-10
2. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508
3. Von Minckwitz G, et al. Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. J Natl Cancer Inst 2008: 100; 542
4. Von Minckwitz G, et al. Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. J Natl Cancer Inst 2008: 100; 552
5. Schwentner L,et al. Using ultrasound and palpation for predicting axillary lymph node status following neoadjuvant chemotherapy - Results from the multi-center SENTINA trial. Breast. 2017 Feb;31:202-207.

Palpation

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

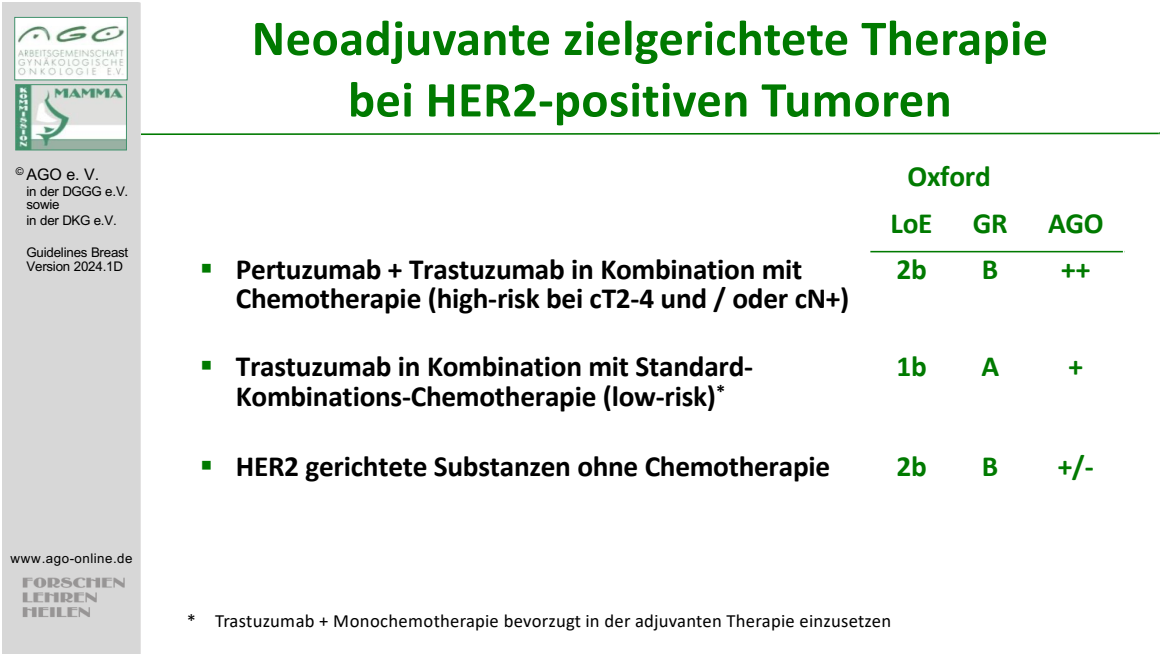
Mammography
1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

MRI
1. Javid S, et al. Can breast MRI predict axillary lymph node metastasis in women undergoing neoadjuvant chemotherapy. Ann Surg Oncol 2010: 17; 1841
2. Morrow M, et al. MRI for breast cancer screening, diagnosis, and treatment. Lancet 2011: 378; 1804
3. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508
4. Bolan PJ, et al. MR spectroscopy of breast cancer for assessing early treatment response: Results from the ACRIN 6657 MRS trial. J Magn Reson Imaging. 2016 Dec 16. doi: 10.1002/jmri.25560. [Epub ahead of print]

PET(-CT)
1. Dose-Schwarz J, et al. Assessment of residual tumour by FDG-PET: conventional imaging and clinical examination following primary chemotherapy of large and locally advanced breast cancer. Br J Cancer 2010: 102; 35
2. Coudert B, et al. Use of [(18)F]-FDG PET to predict response to neoadjuvant trastuzumab and docetaxel in patients with HER2-positive breast cancer, and addition of bevacizumab to neoadjuvant trastuzumab and docetaxel in [(18)F]-FDG PET-predicted non-responders (AVATAXHER): an open-label, randomised phase 2 trial. Lancet Oncol 2014: 15; 1493
3. Groheux D,et al. ¹⁸FDG-PET/CT for predicting the outcome in ER+/HER2- breast cancer patients: comparison of clinicopathological parameters and PET image-derived indices including tumor texture analysis. Breast Cancer Res. 2017 Jan 5;19(1):3

Clip pN+
1. Caudle AS, Yang WT, Krishnamurthy S et al.: Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection. J Clin Oncol. 2016;34(10):1072-8.
2. Hartmann et al. Wire localization of clip-marked axillary lymph nodes in breast cancer patients treated with primary systemic therapy. Eur J Surg Oncol. 2018 ;44:1307-1311

3. Siso C et al. Intraoperative Ultrasound-Guided Excision of Axillary Clip in Patients with Node-Positive Breast Cancer Treated with Neoadjuvant Therapy (ILINA Trial). Ann Surg Oncol 2018; 25:784–791
4. Simons JM, et al. Diagnostic Accuracy of Different Surgical Procedures for Axillary Staging After Neoadjuvant Systemic Therapy in Node-positive Breast Cancer: A Systematic Review and Metaanalysis. Ann Surg Oncol 2018 Oct 11. doi: 10.1097/SLA.0000000000003075. [Epub ahead of print]
5. Banys-Pachulowski et al. Axillary ultrasound for prediction of responsein the context of surgical strategies to axillary diessection in primary breast cancer: a systematic review of the current literature. Archives of Gynecology and Obstetrics 2020 Feb;301(2):341-353.doi:10.1007/s00404-019-05428-x.
6. Kuemmel S et al. A Prospective, Multicenter Registry Study to Evaluate the Clinical Feasibility of Targeted Axillary Dissection (TAD) in Node-Positive Breast Cancer Patients. Ann Surg. 2020 Nov 4. doi: 10.1097/SLA.0000000000004572. Epub ahead of print. PMID: 33156057.



Review

1. Jackisch C et al. Risk-based decision-making in the treatment of HER2-positive early breast cancer: Recommendations based on the current state of knowledge. Cancer Treat Rev. 2021 Sep;99:102229.
2. Pernas S, Tolaney SM. Management of Early-Stage Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer. JCO Oncol Pract. 2021 Jun;17(6):320-330.

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. Clark A, et al. Neoadjuvant T-DM1/pertuzumab and paclitaxel/trastuzumab/pertuzumab for HER2^{+} breast cancer in the adaptively randomized I-SPY2 trial. Nat Commun. 2021 Nov 5;12(1):6428.
3. Hatschek T et al. Neoadjuvant Trastuzumab, Pertuzumab, and Docetaxel vs Trastuzumab Emtansine in Patients With ERBB2-Positive Breast Cancer: A Phase 2 Randomized Clinical Trial. JAMA Oncol. 2021 Sep 1;7(9):1360-1367.
4. Kim JY et al. Real World Evidence of Neoadjuvant Docetaxel/Carboplatin/Trastuzumab/Pertuzumab (TCHP) in Patients with HER2-Positive Early or Locally Advanced Breast Cancer: A Single-Institutional Clinical Experience. Cancer Res Treat. 2022 Jan 10.
5. 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
6. 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
7. Gianni L et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016 Jun;17(6):791-800.
8. 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
9. 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
10. 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]
11. 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]
12. 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.
13. Loibl et al: VP6-2022: Adjuvant pertuzumab and trastuzumab in patients with early HER-2 positive breast cancer in APHINITY: 8.4 years' follow-up; ESMO Virtual Plenary DOI: https://doi.org/10.1016/j.annonc.2022.06.009

Trastuzumab in combination with chemotherapy

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

groups. J Clin Oncol 2011: 29; 3351
3. Gianni L, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet Oncol 2014: 15; 640
4. De Azambuja E, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. Lancet Oncol 2014: 15; 1137
5. 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
6. Tolaney SM, Tarantino P, Graham N et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer: final 10-year analysis of the open-label, single-arm, phase 2 APT trial. Lancet Oncol 2023Mar;24(3):273-285. doi: 10.1016/S1470-2045(23)00051-7.PMID: 36858723

Anti-HER2 agents without chemotherapy

1. Gianni L et al. Effects of neoadjuvant trastuzumab, pertuzumab and palbociclib on Ki67 in HER2 and ER-positive breast cancer. NPJ Breast Cancer. 2022 Jan 10;8(1):1.
2. Pérez-García JM et al; PHERGain steering committee and trial investigators. Chemotherapy de-escalation using an 18F-FDG-PET-based pathological response-adapted strategy in patients with HER2-positive early breast cancer (PHERGain): a multicentre, randomised, open-label, non-comparative, phase 2 trial. Lancet Oncol. 2021 Jun;22(6):858-871.
3. 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. 2018 Jan;19(1):115-126.
4. Nitz UA et al. De-escalation strategies in HER2-positive early breast cancer (EBC): final analysis of the WSG-ADAPT HER2+/HR- phase II trial: efficacy, safety, and predictive markers for 12 weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab ± weekly paclitaxel. Ann Oncol. 2017 Nov 1;28(11):2768-2772.
5. Rimawi M, et al. Multicenter phase II study of neoadjuvant lapatinib and trastuzumab with hormonal therapy and without chemotherapy in patients with human epidermal growth factor receptor 2-overexpressing breast cancer: TBCRC 006. J Clin Oncol 2013: 31; 1726.

6. Gianni L et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016 Jun;17(6):791-800.
7. 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.
8. Ismael G, et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial. Lancet Oncol 2012: 13; 869
9. Tarantino P et al. Adjuvant Trastuzumab Emtansine Versus Paclitaxel plus Trastuzumab for Stage I HER2+ Breast Cancer: 5-year results and correlative analyses from ATEMPT (TBCRC033). March 2023, Cancer Research 83(5_Supplement):PD18-01-PD18-01 DOI:10.1158/1538-7445.SABCS22-PD18-01

Anti-HER2 and Immunechekpoint inhibitors

1. Huober et al. Atezolizumab With Neoadjuvant Anti-Human Epidermal Growth Factor Receptor 2 Therapy and Chemotherapy in Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer: Primary Results of the Randomized Phase III IMpassion050 Trial; J Clin Oncol 2022 Pages JCO2102772

Neoadjuvante Chemotherapie – Vorgehen je nach Ansprechen

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

Completion of neoadjuvant chemotherapy

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

In case of no change:

Completion of NACT, followed by surgery

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

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

Continuation of NST with non-cross-resistant regimen

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

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

DAC2x -> NX x 4

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

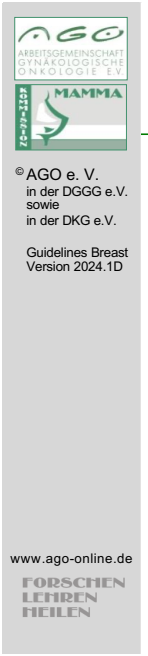
In case of progressive disease:

Stop of NACT and immediate surgery or radiotherapy

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

Additional adjuvant chemotherapy with non-cross-resistant regimen

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



Axilläre operative Interventionen bei NACT (cN0)

cN-Status (vor NACT)	pN-Status (vor NACT)	ycN-Status (nach NACT)	Axilläre operative Intervention (nach NACT)	AGO	ypN-Status (nach NACT und Operation)	Operative Konsequenz aus Histobefund	Oxford LoE	Oxford GR	AGO
cN0*	Keine OP vor NACT	ycN0	SLNE	++	ypN0 (sn)	Keine	2b	B	++
					ypN0 (i+) (sn)	ALND	2b	C	+/-
					ypN1mi (sn)	ALND	2b	C	+
					ypN1 (sn)	ALND	2b	C	++

* Studienbeteiligung an EUBREAST-01 empfohlen

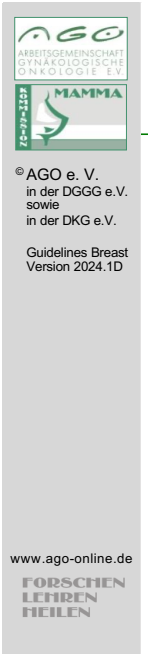
1. Giuliano AE, Ballman KV, McCall L et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: The acosog z0011 (alliance) randomized clinical trial. JAMA 2017, 318, 918-926
2. Reimer TS, Nekljudova V, Loibl, S et al. Restricted axillary staging in clinically and sonographically node-negative early invasive breast cancer (c/i t1-2) in the context of breast concerving therapy: First results following commencement of the intergroup-sentinel-mamma (insema) trial. Geburtsh Frauenheilk 2017, 77, 149-157
3. Gion M, Pérez-García JM, Llombart-Cussac A et al. Surrogate endpoints for early-stage breast cancer: a review of the state of the art, controversies, and future prospects. Ther Adv Med Oncol 2021, 13:17588359211059587.
4. Chiec L, Shah AN. Risk-based Approaches for Optimizing Treatment in HER2-Positive Early Stage Breast Cancer. Semin Oncol 2020, 47:249-258.
5. Cortazar P, Geyer CE Jr. Pathological complete response in neoadjuvant treatment of breast cancer. Ann Surg Oncol 2015, 22, 1441-1446.
6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: Meta-analysis of individual patient data from ten randomised trials. Lancet Oncol 2018, 19, 27-39.
7. Cirier J, Body G, Jourdan ML et al. Impact of pathological complete response to neoadjuvant chemotherapy in invasive breast cancer according to molecular subtype. Gynecologie, obstetrique, fertilite & senologie 2017, 45, 535-544.
8. Gustavo Werutsky G, Untch M, Hanusch C, Fasching PA, Blohmer JU, Seiler S, Denkert C, Tesch H, Jackisch C, Gerber B et al.

Locoregional recurrence risk after neoadjuvant chemotherapy: A pooled analysis of nine prospective neoadjuvant breast cancer trials. Eur J Cancer 2020, 130, 92-101.
9. Kuehn T, Bauerfeind I, Fehm T et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (sentina): A prospective, multicentre cohort study. Lancet Oncol 2013, 14, 609-618.
10. Boughey JC, Suman VJ, Mittendorf EA et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: The acosog z1071 (alliance) clinical trial. Jama 2013, 310, 1455-1461.
11. Carter S, Neuman H, Mamounas EP et al. Debating the optimal approach to nodal management after pathologic complete response to neoadjuvant chemotherapy in patients with breast cancer. American Society of Clinical Oncology educational book. American Society of Clinical Oncology. Annual Meeting 2019, 39, 42-48.
12. Simons JM, van Nijnatten TJA, van der Pol CC et al. Diagnostic accuracy of different surgical procedures for axillary staging after neoadjuvant systemic therapy in node-positive breast cancer: A systematic review and meta-analysis. Ann Surg 2019, 269, 432-442.
13. Tee, S.R.; Devane, L.A.; Evoy, D.; et al. E.W. Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. Br J Surg 2018, 105, 1541-1552.
14. Schneeweiss A, Mobus V, Tesch H et al. Intense dose-dense epirubicin, paclitaxel, cyclophosphamide versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer) for neoadjuvant treatment of high-risk early breast cancer (geparocto-gbg 84): A randomised phase iii trial. Eur J Cancer 2019, 106, 181-192.
15. Barron AU, Hoskin TL, Day CN et al. Association of low nodal positivity rate among patients with erbb2-positive or triple-negative breast cancer and breast pathologic complete response to neoadjuvant chemotherapy. JAMA surgery 2018.
16. Samiei, S.; Simons, J.M.; Engelen, S.M.E.; et al. Axillary pathologic complete response after neoadjuvant systemic therapy by breast cancer subtype in patients with initially clinically node-positive disease: A systematic review and meta-analysis. JAMA surgery 2021, e210891.
17. Tadros, A.B.; Yang, W.T.; Krishnamurthy, S.; et al. Identification of patients with documented pathologic complete response in the breast after neoadjuvant chemotherapy for omission of axillary surgery. JAMA surgery 2017, 152, 665-670.
18. Samiei, S.; van Nijnatten, T.J.A.; de Munck, L.; et al. Correlation between pathologic complete response in the breast and absence of axillary lymph node metastases after neoadjuvant systemic therapy. Ann Surg 2018.
19. Kuemmel, S.; Heil, J.; Rueland, A.; et al. A prospective, multicenter registry study to evaluate the clinical feasibility of targeted axillary dissection (tad) in node-positive breast cancer patients. Ann Surg 2020.
20. Banys-Paluchowski M, Gasparri ML, de Boniface J et al. Surgical management of the axilla in clinically node-positive breast cancer patients converting to clinical node negativity through neoadjuvant chemotherapy: Current status, knowledge gaps, and rationale

for the eubreast-03 axsana study. Cancers 2021, 13.
21. Hartmann, S.; Kühn, T.; de Boniface, J.; et al. Carbon tattooing for targeted lymph node biopsy after primary systemic therapy in breast cancer: Prospective multicentre tattoo trial. Br J Surg 2021.
22. Barrio, A.V.; Montagna, G.; Mamtani, A.; et al. Nodal recurrence in patients with node-positive breast cancer treated with sentinel node biopsy alone after neoadjuvant chemotherapy-a rare event. JAMA oncology 2021.
23. Wong S.M.; Almana N.; Choi J.; et al. Prognostic Significance of Residual Axillary Nodal Micrometastases and Isolated Tumor Cells After Neoadjuvant Chemotherapy for Breast Cancer. Ann Surg Oncol 2019, 26:3502-3509.
24. Canavese G.; Tinterri C.; Carli F.; et al. Correlation between outcome and extent of residual disease in the sentinel node after neoadjuvant chemotherapy in clinically fine-needle proven node-positive breast cancer patients. Eur J Surg Oncol 2021, 47:1920-1927.
25. Moo, T.A.; Jochelson, M.S.; Zabor, E.C.; et al. Is clinical exam of the axilla sufficient to select node-positive patients who downstage after nac for slnb? A comparison of the accuracy of clinical exam versus mri. Ann Surg Oncol 2019, 26:4238-4243.
26. Boughey, J.C.; Ballman, K.V.; Hunt, K.K.; et al. Axillary ultrasound after neoadjuvant chemotherapy and its impact on sentinel lymph node surgery: Results from the american college of surgeons oncology group z1071 trial (alliance). J Clin Oncol 2015, 33, 3386-3393.
27. Schwentner, L.; Helms, G.; Nekljudova, V.; et al. Using ultrasound and palpation for predicting axillary lymph node status following neoadjuvant chemotherapy - results from the multi-center sentina trial. Breast 2017, 31, 202-207.
28. Le-Petross, H.T.; McCall, L.M.; Hunt, K.K.; et al. Axillary ultrasound identifies residual nodal disease after chemotherapy: Results from the american college of surgeons oncology group z1071 trial (alliance). AJR Am J Roentgenol 2018, 210, 669-676.
29. Kim, W.H.; Kim, H.J.; Park, H.Y.; et al. Axillary pathologic complete response to neoadjuvant chemotherapy in clinically node-positive breast cancer patients: A predictive model integrating the imaging characteristics of ultrasound restaging with known clinicopathologic characteristics. Ultrasound in medicine & biology 2019, 45, 702-709.
30. Liedtke, C.; Gorlich, D.; Bauerfeind, I.; et al. Validation of a nomogram predicting non-sentinel lymph node metastases among patients with breast cancer after primary systemic therapy - a transsentina substudy. Breast Care (Basel) 2018, 13, 440-446.
31. Moo, T.A.; Jochelson, M.S.; Zabor, E.C.; et al. Is clinical exam of the axilla sufficient to select node-positive patients who downstage after nac for slnb? A comparison of the accuracy of clinical exam versus mri. Ann Surg Oncol 2019, 26, 4238-4243.
32. Kantor, O.; Sipsy, L.M.; Yao, K.; et al. A predictive model for axillary node pathologic complete response after neoadjuvant chemotherapy for breast cancer. Ann Surg Oncol 2018, 25, 1304-1311.

Statement: SLNE after NACT

1. El Hage Chehade H, Headon H, El Tokhy O et al. Is sentinel lymph node biopsy a viable alternative to complete axillary dissection following neoadjuvant chemotherapy in women with node-positive breast cancer at diagnosis? An updated meta-analysis involving 3,398 patients. Am J Surg. 2016 Nov;212(5):969-981.



Axilläre operative Interventionen bei NACT (cN+)

cN-Status (vor NACT)	pN-Status (vor NACT)	ycN-Status (nach NACT)	Axilläre operative Intervention (nach NACT)	AGO	ypN-Status (nach NACT und Operation)	Operative Konsequenz aus Histobefund	Oxford LoE	Oxford GR	AGO
cN+*	pN+CNB	ycN0	ALND	+	ypN0 / ypN+	Keine	2b	B	++
			TAD	+	ypN0	Keine	2b	B	+
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ inkl. ypN1mi	ALND	2b	B	+
			SLNE	+/-	ypN0	Keine	2b	B	+/-
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ inkl. ypN1mi	ALND	2b	B	+
			TLNE	+/-	ypN0	keine	2b	B	+/-
					ypN0 (i+)	ALND	3b	B	+/-
					ypN+ inkl. ypN1mi	ALND	3b	B	+
		ycN+**	ALND	++	ypN0 / ypN+	Keine	2b	B	++

*** Studienbeteiligung an AXSANA empfohlen; **Cave: In 30,3% falsch-positive Befunde, ggf. CNB**

1. Giuliano AE, Ballman KV, McCall L et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: The acosog z0011 (alliance) randomized clinical trial. JAMA 2017, 318, 918-926
2. Reimer TS, Nekljudova V, Loibl, S et al. Restricted axillary staging in clinically and sonographically node-negative early invasive breast cancer (c/i t1-2) in the context of breast concerving therapy: First results following commencement of the intergroup-sentinel-mamma (insema) trial. Geburtsh Frauenheilk 2017, 77, 149-157
3. Gion M, Pérez-García JM, Llombart-Cussac A et al. Surrogate endpoints for early-stage breast cancer: a review of the state of the art, controversies, and future prospects. Ther Adv Med Oncol 2021, 13:17588359211059587.
4. Chiec L, Shah AN. Risk-based Approaches for Optimizing Treatment in HER2-Positive Early Stage Breast Cancer. Semin Oncol 2020, 47:249-258.
5. Cortazar P, Geyer CE Jr. Pathological complete response in neoadjuvant treatment of breast cancer. Ann Surg Oncol 2015, 22, 1441-1446.
6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: Meta-analysis of individual patient data from ten randomised trials. Lancet Oncol 2018, 19, 27-39.
7. Cirier J, Body G, Jourdan ML et al. Impact of pathological complete response to neoadjuvant chemotherapy in invasive breast cancer according to molecular subtype. Gynecologie, obstetrique, fertilite & senologie 2017, 45, 535-544.
8. Gustavo Werutsky G, Untch M, Hanusch C, Fasching PA, Blohmer JU, Seiler S, Denkert C, Tesch H, Jackisch C, Gerber B et al.

Locoregional recurrence risk after neoadjuvant chemotherapy: A pooled analysis of nine prospective neoadjuvant breast cancer trials. Eur J Cancer 2020, 130, 92-101.
9. Kuehn T, Bauerfeind I, Fehm T et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (sentina): A prospective, multicentre cohort study. Lancet Oncol 2013, 14, 609-618.
10. Boughey JC, Suman VJ, Mittendorf EA et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: The acosog z1071 (alliance) clinical trial. Jama 2013, 310, 1455-1461.
11. Carter S, Neuman H, Mamounas EP et al. Debating the optimal approach to nodal management after pathologic complete response to neoadjuvant chemotherapy in patients with breast cancer. American Society of Clinical Oncology educational book. American Society of Clinical Oncology. Annual Meeting 2019, 39, 42-48.
12. Simons JM, van Nijnatten TJA, van der Pol CC et al. Diagnostic accuracy of different surgical procedures for axillary staging after neoadjuvant systemic therapy in node-positive breast cancer: A systematic review and meta-analysis. Ann Surg 2019, 269, 432-442.
13. Tee, S.R.; Devane, L.A.; Evoy, D.; et al. E.W. Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. Br J Surg 2018, 105, 1541-1552.
14. Schneeweiss A, Mobus V, Tesch H et al. Intense dose-dense epirubicin, paclitaxel, cyclophosphamide versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer) for neoadjuvant treatment of high-risk early breast cancer (geparocto-gbg 84): A randomised phase iii trial. Eur J Cancer 2019, 106, 181-192.
15. Barron AU, Hoskin TL, Day CN et al. Association of low nodal positivity rate among patients with erbb2-positive or triple-negative breast cancer and breast pathologic complete response to neoadjuvant chemotherapy. JAMA surgery 2018.
16. Samiei, S.; Simons, J.M.; Engelen, S.M.E.; et al. Axillary pathologic complete response after neoadjuvant systemic therapy by breast cancer subtype in patients with initially clinically node-positive disease: A systematic review and meta-analysis. JAMA surgery 2021, e210891.
17. Tadros, A.B.; Yang, W.T.; Krishnamurthy, S.; et al. Identification of patients with documented pathologic complete response in the breast after neoadjuvant chemotherapy for omission of axillary surgery. JAMA surgery 2017, 152, 665-670.
18. Samiei, S.; van Nijnatten, T.J.A.; de Munck, L.; et al. Correlation between pathologic complete response in the breast and absence of axillary lymph node metastases after neoadjuvant systemic therapy. Ann Surg 2018.
19. Kuemmel, S.; Heil, J.; Rueland, A.; et al. A prospective, multicenter registry study to evaluate the clinical feasibility of targeted axillary dissection (tad) in node-positive breast cancer patients. Ann Surg 2020.
20. Banys-Paluchowski M, Gasparri ML, de Boniface J et al. Surgical management of the axilla in clinically node-positive breast cancer patients converting to clinical node negativity through neoadjuvant chemotherapy: Current status, knowledge gaps, and rationale

for the eubreast-03 axsana study. Cancers 2021, 13.
21. Hartmann, S.; Kühn, T.; de Boniface, J.; et al. Carbon tattooing for targeted lymph node biopsy after primary systemic therapy in breast cancer: Prospective multicentre tattoo trial. Br J Surg 2021.
22. Barrio, A.V.; Montagna, G.; Mamtani, A.; et al. Nodal recurrence in patients with node-positive breast cancer treated with sentinel node biopsy alone after neoadjuvant chemotherapy-a rare event. JAMA oncology 2021.
23. Wong S.M.; Almana N.; Choi J.; et al. Prognostic Significance of Residual Axillary Nodal Micrometastases and Isolated Tumor Cells After Neoadjuvant Chemotherapy for Breast Cancer. Ann Surg Oncol 2019, 26:3502-3509.
24. Canavese G.; Tinterri C.; Carli F.; et al. Correlation between outcome and extent of residual disease in the sentinel node after neoadjuvant chemotherapy in clinically fine-needle proven node-positive breast cancer patients. Eur J Surg Oncol 2021, 47:1920-1927.
25. Boughey, J.C.; Ballman, K.V.; Hunt, K.K.; et al. Axillary ultrasound after neoadjuvant chemotherapy and its impact on sentinel lymph node surgery: Results from the american college of surgeons oncology group z1071 trial (alliance). J Clin Oncol 2015, 33, 3386-3393.
26. Schwentner, L.; Helms, G.; Nekljudova, V.; et al. Using ultrasound and palpation for predicting axillary lymph node status following neoadjuvant chemotherapy - results from the multi-center sentina trial. Breast 2017, 31, 202-207.
27. Le-Petross, H.T.; McCall, L.M.; Hunt, K.K.; et al. Axillary ultrasound identifies residual nodal disease after chemotherapy: Results from the american college of surgeons oncology group z1071 trial (alliance). AJR Am J Roentgenol 2018, 210, 669-676.
28. Kim, W.H.; Kim, H.J.; Park, H.Y.; et al. Axillary pathologic complete response to neoadjuvant chemotherapy in clinically node-positive breast cancer patients: A predictive model integrating the imaging characteristics of ultrasound restaging with known clinicopathologic characteristics. Ultrasound in medicine & biology 2019, 45, 702-709.
29. Liedtke, C.; Gorlich, D.; Bauerfeind, I.; et al. Validation of a nomogram predicting non-sentinel lymph node metastases among patients with breast cancer after primary systemic therapy - a transsentina substudy. Breast Care (Basel) 2018, 13, 440-446.
30. Moo, T.A.; Jochelson, M.S.; Zabor, E.C.; et al. Is clinical exam of the axilla sufficient to select node-positive patients who downstage after nac for slnb? A comparison of the accuracy of clinical exam versus mri. Ann Surg Oncol 2019, 26, 4238-4243.
31. Kantor, O.; Sipsy, L.M.; Yao, K.; et al. A predictive model for axillary node pathologic complete response after neoadjuvant chemotherapy for breast cancer. Ann Surg Oncol 2018, 25, 1304-1311.

<u>Statement: SLNE after NACT</u>

1. El Hage Chehade H, Headon H, El Tokhy O et al. Is sentinel lymph node biopsy a viable alternative to complete axillary dissection following neoadjuvant chemotherapy in women with node-positive breast cancer at diagnosis? An updated meta-analysis involving

3,398 patients. Am J Surg. 2016 Nov;212(5):969-981.

Statement: False-positives in ALND after ycN+

1. Hartmann S, Kühn T, Hauptmann M et al., Axillary staging after neoadjuvant chemotherapy for initially node-positive breast carcinoma in Germany. Geburtsh Frauenheilk 2022, online

Statement: TLNE alone:

1. Swarnkar PK, Tayeh S, Michell MJ et al., The Evolving Role of Marked Lymph Node Biopsy (MLNB) and Targeted Axillary Dissection (TAD) after Neoadjuvant Chemotherapy (NACT) for Node-Positive Breast Cancer: Systematic Review and Pooled Analysis. Cancers (Basel) 2021; 13(7):1539

Neoadjuvante systemische Therapie
Lokoregionäre Operation (Mamma)

	Oxford		
	LoE	GR	AGO
▪ **Prätherapeutische Vorstellung im Tumorboard (z. B. zur Festlegung des OP-Verfahrens)**	1a	B	++
▪ **Frühzeitige Markierung des Tumors mit exakter topographischer Dokumentation**	5	D	++
▪ **Resektion des Tumors / repräsentative Exzision des posttherapeutischen, markierten Tumorareals**	2b	C	++
▪ **Exzision in neuen Tumorgrenzen**	2b	C	++
▪ **Freie Resektionsränder**	2a	B	++

Pretherapeutic definition of the definitive surgical procedure

1. EBCTCG. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol Lancet Oncol. 2018 Jan;19(1):27-39.
2. Bossuyt V, Symmans WF. Standardizing of Pathology in Patients Receiving Neoadjuvant Chemotherapy. Ann Surg Oncol. 2016 Oct;23(10):3153-61.
3. Zdenkowski N et al. A survey of Australian and New Zealand clinical practice with neoadjuvant systemic therapy for breast cancer. Intern Med J. 2016 Jun;46(6):677-83.

Mark previous tumor region

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

Surgery

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

Microscopically clear margins

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

Tumor resection according to imaging result

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

Neoadjuvante systemische Therapie
Indikationen für Mastektomie

	Oxford		
	LoE	GR	AGO
▪ **Positive Absetzungsränder trotz mehrfacher Nachresektion**	3b	C	++
▪ **Radiotherapie nicht durchführbar**	5	D	++
▪ **Bei einer klinisch kompletten Remission**			
▪ **Inflammatorisches Mammakarzinom (bei pCR)**	2b	C	+/-
▪ **Multizentrisches Mammakarzinom**	2b	C	+/-
▪ **cT4a-c Mammakarzinom**	2b	B	+/-

Positive margins after repeated excisions

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508
2. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011: 22; 515

Radiotherapy not feasible

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

In case of clinical complete response:
Inflammatory breast cancer in case of pCR

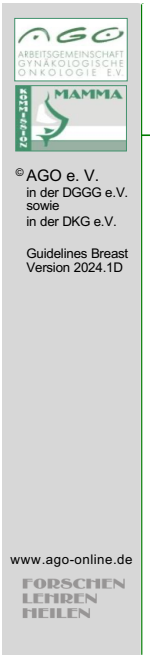
1. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011: 22; 515
2. Brzezinska M, Williams LJ, Thomas J et al.: Outcomes of patients with inflammatory breast cancer treated by breast-conserving surgery. Breast Cancer Res Treat 2016;160(3):387-91.

Multicentric lesions

1. Ataseven B, et al. Impact of Multifocal or Multicentric Disease on Surgery and Locoregional, Distant and Overall Survival of 6,134 Breast Cancer Patients Treated With Neoadjuvant Chemotherapy. Ann Surg Oncol 20215;;22(4):1118-1127.

cT4a-c breast cancer

1. Ataseven B, et al. Impact of Multifocal or Multicentric Disease on Surgery and Locoregional, Distant and Overall Survival of 6,134 Breast Cancer Patients Treated With Neoadjuvant Chemotherapy. Ann Surg Oncol 20215;;22(4):1118-1127.



Neoadjuvante systemische Therapie Zeitablauf von Diagnosestellung, Operation und Radiotherapie

	Oxford		
	LoE	GR	AGO
Therapiebeginn der NACT ▪ **Therapieverzögerungen führen zu einer Prognoseverschlechterung**	2b	B	+
Zeitpunkt der Operation nach NACT ▪ **4-8 Wochen nach dem letzten Chemotherapiezyklus**	2a	B	++
Radiotherapie innerhalb von 2 Monaten nach der Operation	2b	B	++

Initiation of chemotherapy after histologic diagnosis

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

Time between surgery and last chemotherapy

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

Radiotherapy 2 mths after surgery BCS

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

Neoadjuvante endokrine Therapie (NET)
- Gute klinische Praxis -

Guidelines Breast
Version 2024.1D

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

1. Lerebours F, Cabel L, Pierga JY. Neoadjuvant Endocrine Therapy in Breast Cancer Management: State of the Art. Cancers (Basel). 2021 Feb 21;13(4):902.
2. Sella T, Weiss A, Mittendorf EA, et al. Neoadjuvant Endocrine Therapy in Clinical Practice: A Review. JAMA Oncol. 2021 Nov 1;7(11):1700-1708.
3. Harbeck N Rid-adapted adjuvant therapy of luminal early breast cancer in 2020. Curr Opin Obstet Gynecol. 2021 Feb 1;33(1):53-58.
4. Harbeck N, Gluz O, Kümmel S et al., Endocrine therapy alone in patients with intermediate or high-risk luminal early breast cancer (0-3 lymph nodes), Recurrence Score <26 and Ki67 response after preoperative endocrine therapy: Primary outcome results from the WSG-ADAPT HR+/HER2- trial. SABCS 2020 GS4-04.
5. Smith I et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy on postmemopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentric, parallel-group, randomized phase 3 trial . Lancet Oncol. 2020 Nov;21(11):1443-1454
6. Nitz U et al. The run-in phase of the prospective WSG-ADAPT HR+/Her2- trial demonstrates the feasibility of a study design combining static and dynamic biomarker assessments for individualized therapy in early breast cancer. Ther Adv Med Oncol. 2020 Nov23:12:1758835920973130
7. Madigan LI et al. Neoadjuvant endocrine therapy in locally advanced estrogen and progesterone receptor-positive breast cancer: determining the optimal endocrine agent and treatment duration in postmenopausal women-a literature review and proposed

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

NET bei Patienten mit endokrin-sensitivem Mammakarzinom

	Oxford LoE	Oxford GR	AGO
Postmenopausale Patienten			
Verbessert die Optionen für brusterhaltende Operationen	1b	A	+
Aromataseinhibitoren (mindestens 6 Monate)	1a*	B	+
Aromataseinhibitor + Lapatinib (HER2+ Mammakarzinom)	2b	B	+/-
Prämenopausale Patientinnen			
Tamoxifen	2b	C	+
Aromataseinhibitoren + LHRHa	1b	C	+/-
Simultane chemo-endokrine Therapie	1b	A	-
Ki-67 Analyse nach kurzer (2-4 W.) präoperativer endokriner Therapie (Tam/AI +/-GnRHa) (prognost./prädikt. Information)	1b	B	+
Prognostischer Score:	1b	B	+
PEPI: pTN-Stadium, ER-Expression und Ki-67 Expression nach neoadjuvanter endokriner Therapie			

* Keine Langzeitergebnisse zur neoadjuvanten endokrinen Therapie (vs. adjuvante endokrine Therapie)

Postmenopausal patients:
Aromatase inhibitors (for up to 6 months)

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

AI and fulvestrant

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

Concurrent chemo-endocrine therapy

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

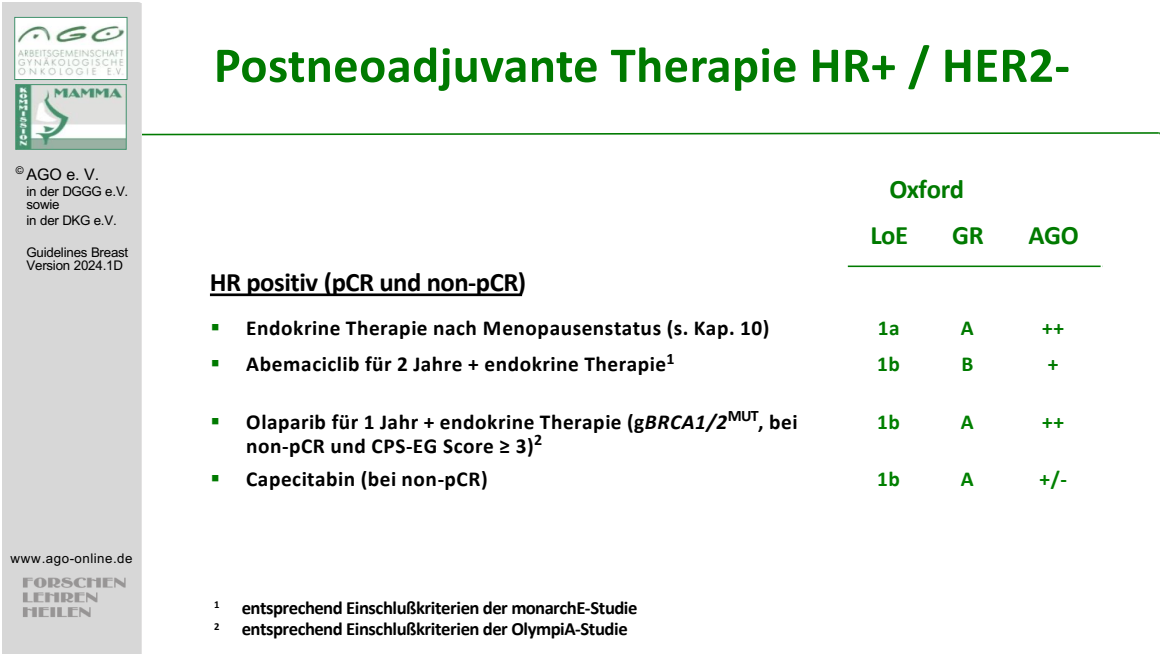
Preoperative ET and Ki67 measurement:

1. Lerebours F, Cabel L, Pierga JY. Neoadjuvant Endocrine Therapy in Breast Cancer Management: State of the Art. Cancers (Basel). 2021 Feb 21;13(4):902.
2. Sella T, Weiss A, Mittendorf EA, et al. Neoadjuvant Endocrine Therapy in Clinical Practice: A Review. JAMA Oncol. 2021 Nov 1;7(11):1700-1708.
3. Harbeck N Rid-adapted adjuvant therapy of luminal early breast cancer in 2020. Curr Opin Obstet Gynecol. 2021 Feb 1;33(1):53-58.
4. Smith I et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy on postmemopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentric, parallel-group, randomized phase 3 trial . Lancet Oncol. 2020 Nov;21(11):1443-1454
5. Nitz U et al. The run-in phase of the prospective WSG-ADAPT HR+/Her2- trial demonstrates the feasibility of a study design combining static and dynamic biomarker assessments for individualized therapy in early breast cancer. Ther Adv Med Oncol. 2020 Nov23:12:1758835920973130

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

<u>Prognostic scores following NST</u>

1. Ellis MJ et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. J Natl Cancer Inst. 2008;100(19):1380–8.
2. Marmé F, et al. Utility of the CPS+EG staging system in hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer treated with neoadjuvant chemotherapy. Eur J Cancer 53:65-74, 2015
3. Ellis MJ et al. Ki67 proliferation index as a tool for chemotherapy decisions during and after neoadjuvant aromatase inhibitor treatment of breast cancer: results from the American College of Surgeons Oncology Group Z1031 Trial (Alliance). J Clin Oncol. 2017;35(10):1061–9
4. Kurozumi S et al. Impact of combining the progesterone receptor and preoperative endocrine prognostic index (PEPI) as a prognostic factor after neoadjuvant endocrine therapy using aromatase inhibitors in postmenopausal ER positive and HER2 negative breast cancer. PLoS One. 2018;13(8):e0201846.



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.
8. 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.
9. 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.
10. Toi M, Boyle F, Im YH et al. Adjuvant Abemaciclib Combined with Endocrine Therapy: Efficacy Results in monarchE Cohort 1. Oncologist. 2023 Jan 18;28(1):e77-e81.
11. Hortobagyi GN, Stroyakovskiy D, Yardley DA et al. (GS03-03) Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2− early breast cancer: final invasive disease–free survival (iDFS) analysis from the NATALEE trial SABCS 2023 (GS03-03)

<u>Statement Olaparib gBRCAmt</u>

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

<u>Statement Capecitabine (bei non-pCR; 8 Kurse)</u>

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.

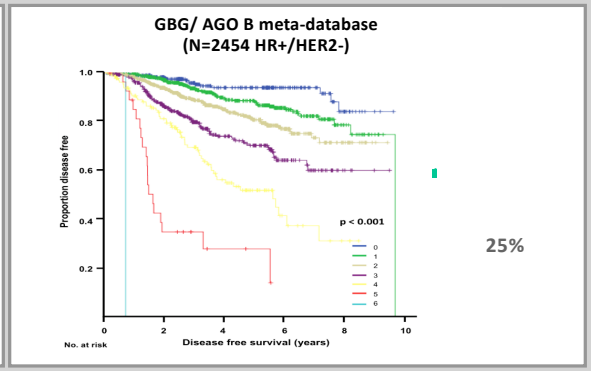
3. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med. 2017 Jun 1;376(22):2147-2159.

Guidelines Breast
Version 2024.1D

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

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	monarchE	PALLAS	PENELOPE[B]	NATALLEE
N	5,637	5,600	1,250	5101
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib	Ribociclib
% of pts. with NACT	37%	n.r.	100%	88%
Duration of CDK4/6i treatment	24 months	24 months	12 mths	36 months
Follow-up	42.0 months	24 months	43 months	33,3 months
Discontinuation rate	28%	42%	20%	35,5%
Discontinuation rate due to AE_{CDKi}	17%	27%	5%	19.5%
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	0.749(0,628-0.892) p = 0.0006
2-yrs IDFS	92.7% vs. 89.9%	n.r.	88% vs. 78%	93.5% vs. 92.0%
3-yrs IDFS	89.2% vs. 84.4%	88% vs. 89%	81% vs. 78%	90.7% vs. 87.6%
4-yrs IDFS	85.8% vs. 79.4%	84.2% vs. 84.5%	73% vs. 72%	

IDFS: invasive disease-free survival

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FORSCHEN
LEHREN
HEILEN

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
6. Hortobagyi GN, Stroyakovskiy D, Yardley DA et al. (GS03-03) Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2− early breast cancer: final invasive disease–free survival (iDFS) analysis from the NATALEE trial SABCS 2023 (GS03-03)

Postneoadjuvante Therapie triple-negativ

	Oxford LoE	Oxford GR	Oxford AGO
pCR			
▪ Fortführung Pembrolizumab, wenn neoadj. begonnen (q3w für 9 Kurse)	1b	B	+
Non-pCR			
▪ Capecitabin (q3w bis zu 8 Kurse)[1]			
▪ Bei non-pCR nach A-T-haltiger Chemotherapie[1]	1a	A	++
▪ Bei non-pCR nach Platin +/- Pembrolizumab-haltiger Therapie	5	D	+/-
▪ Platinderivate (Carboplatin oder Cisplatin) q3w nach AT-Vorbehandlung	1b	B	+/-
▪ Olaparib (*gBRCA^{MUT}*)[2]	1b	A	++
▪ Fortführung Pembrolizumab, wenn neoadj. begonnen (q3w für 9 Kurse)	1b	B	++

[1] Studienlage bei Stadium II-III ohne Platin/Pembrolizumab-basierte Vortherapie
[2] entsprechend Einschlußkriterien der OlympiA-Studie, Vorteil v.a. bei platin-freier NACT

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.

Statement Platinum salts adjuvant/postneoadjuvant:

1. 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.
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

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

Statement Olaparib gBRCAmut

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

Postneoadjuvante Therapie HER2-positiv

	Oxford LoE	Oxford GR	Oxford AGO
pCR			
▪ Low risk: Trastuzumab (bis 12 Mon. komplett)	2a	C	++
▪ High risk (cN+): Trastuzumab + Pertuzumab (bis 12 Mon. komplett)	2b	C	+
▪ Neratinib nach 1 Jahr* Trastuzumab (HR-positiv, Stadium II-III)*	2b	B	+/-
non-pCR			
▪ T-DM1	1b	B	++
▪ Trastuzumab + Pertuzumab bei cN+ (bis 12 Mon. komplett)	2b	C	+
▪ Zusätzlich nach 1 Jahr (erweiterte adj. Therapie)			
▪ Neratinib nach Trastuzumab (HR-positiv, Stadium II-III)*	2b	B	+
▪ Neratinib nach anderer anti-HER2-Therapie (HR-positiv, Stadium II-III)*	5	D	+/-

* kombiniert mit Standard endokriner Therapie

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
4. Loibl S, Mano MS, Untch M et al. Phase III study of adjuvant ado-trastuzumab emtansine vs. Trastuzumab for residual invasive HER2-positive early breast cancer after neoadjuvant chemotherapy and HER2-targeted therapy: KATHERINE final IDFS and updated OS analysis.

Statement rastuzumab + Pertuzumab in N+:

1. Gelber RD, Wang XV, Cole BF et al.; APHINITY Steering Committee and Investigators. Six-year absolute invasive disease-free survival benefit of adding adjuvant pertuzumab to trastuzumab and chemotherapy for patients with early HER2-positive breast cancer: A Subpopulation Treatment Effect Pattern Plot (STEPP) analysis of the APHINITY (BIG 4-11) Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. Eur J Cancer 2022;166:219-228.
2. Piccart M, Procter M, Fumagalli D et al.; APHINITY Steering Committee and Investigators. J Clin Oncol 2021;39(13):1448-1457.
3. Loibl S, Jassem J, Sonnenblick A, Viale G, Bines J, Piccart M. Adjuvant pertuzumab and trastuzumab in patients with early HER-2 positive breast cancer in APHINITY: 8.4 years' follow-up. ESMO Virtual Plenary, 15.07.2022, # VP6-2022, Annals of Oncology 33(9): 986-987.