Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

FORSCHEN
LEHREN
HEILEN

Neoadjuvant
(Primary) Systemic Therapy

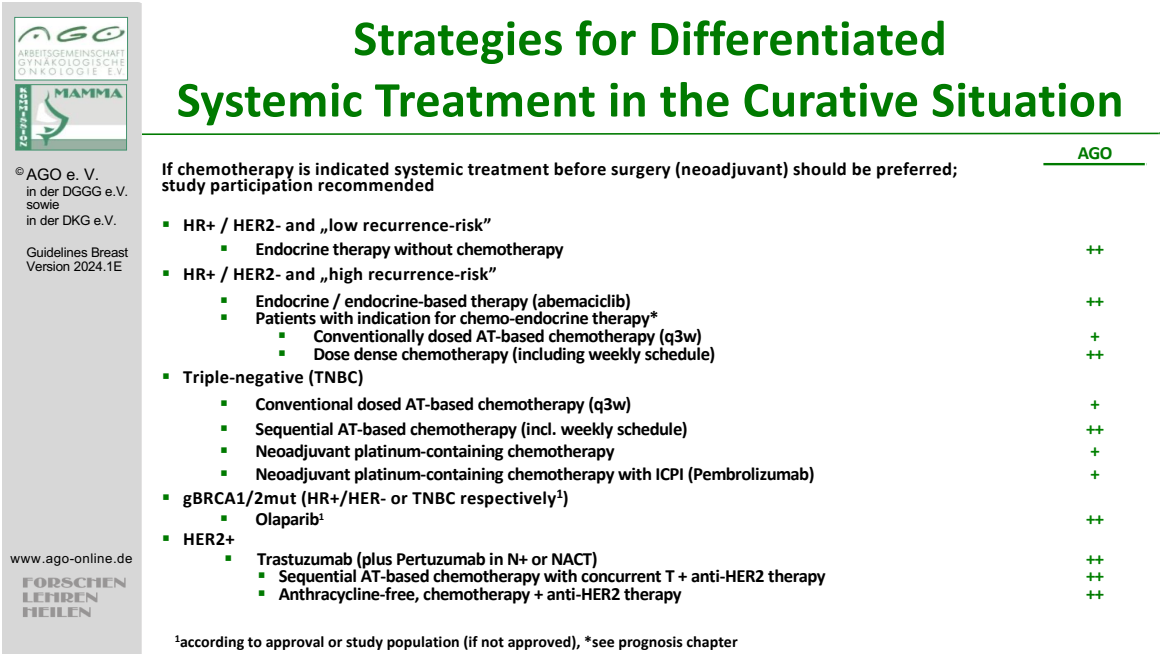
Guidelines Breast
Version 2024.1E

Neoadjuvant Systemic Therapy

- **Versions 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



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

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
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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

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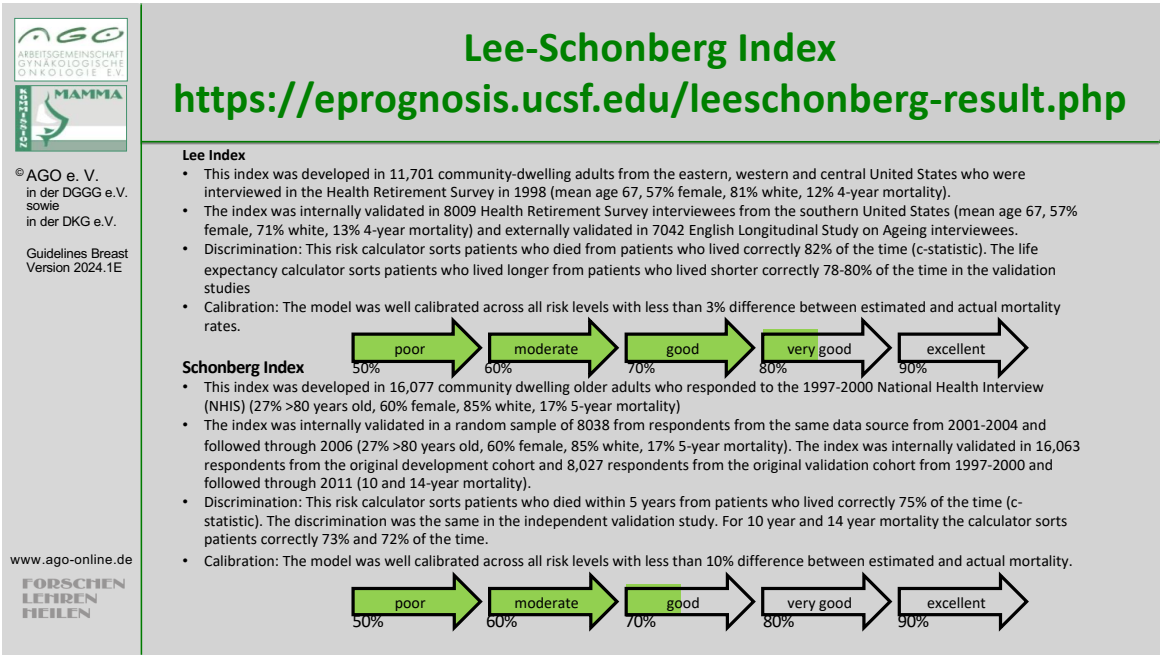
4. III randomized controlled trial SABCS 2022, GS5-01



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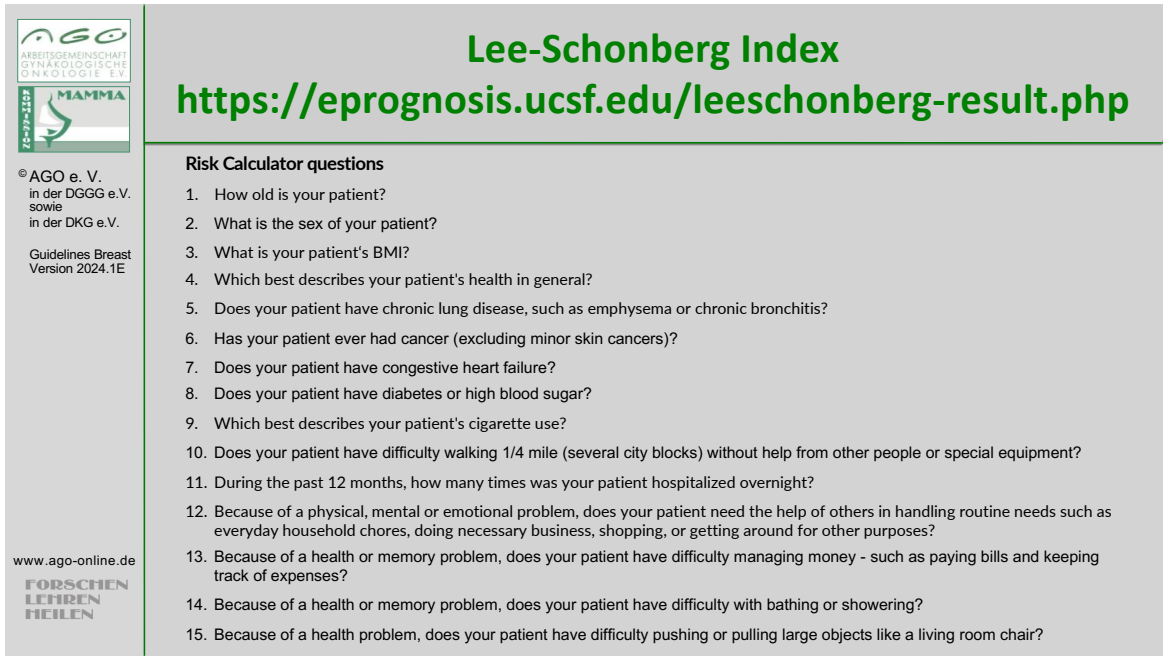

1. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA. 2006 Feb 15;295(7):801-808.
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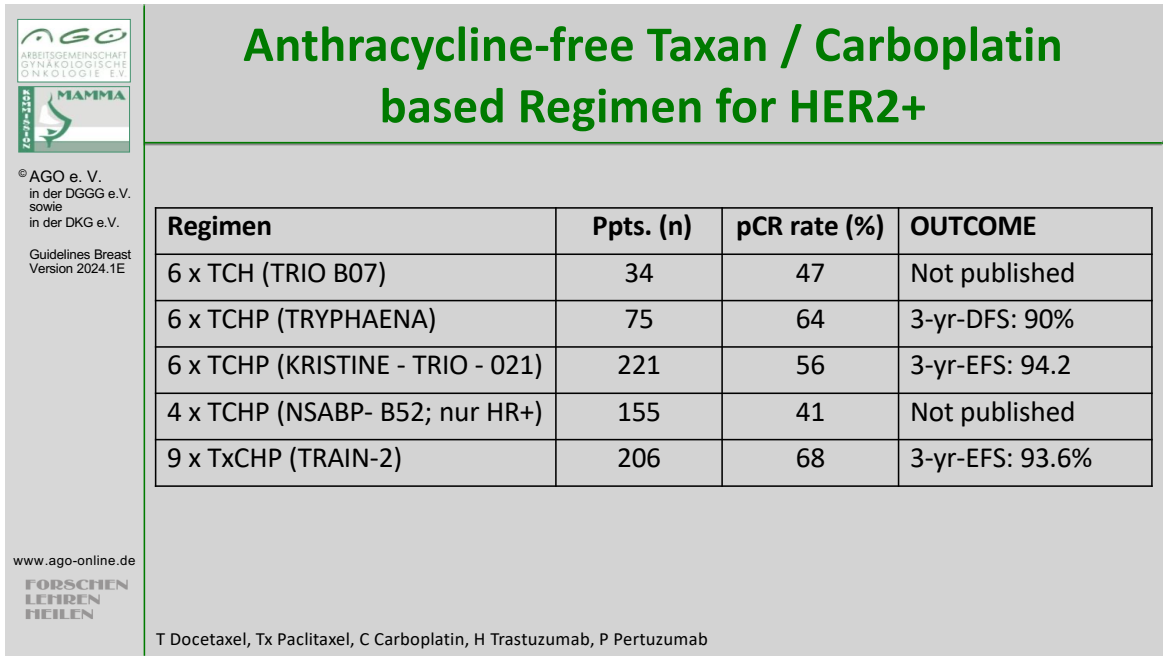
3. Lee SJ, Boscardin WJ, Kirby KA, Covinsky KE. Individualizing life expectancy estimates for older adults using the Gompertz Law of Human Mortality. Plos One. 2014;9(9):3108540.



Anthracycline-free Taxan / Carboplatin based Regimen for HER2+

Regimen	Ppts. (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%

T Docetaxel, Tx Paclitaxel, C Carboplatin, H Trastuzumab, P Pertuzumab

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 dbrivation: NRG Oncology/NSABP B-52 Cancer Res 2017;77(4 suppl):S3-06.
5. Van Ramshorst MS, van der Voort A, van Werkhoven ED et 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. JAMA Oncol 2021 Jul 1;7(7):978-984.

Guidelines Breast
Version 2024.1E

Neoadjuvant Systemic Chemotherapy
Clinical Benefit

	Oxford	
	LoE	GR
▪ Leads to improvement of prognosis by individualization of neoadjuvant and post-neoadjuvant therapy (data most consistent for HER2pos and TNBC)	1b	A
▪ Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and number of cycles), if the postneoadjuvant therapy is not stratified according to pathologic response	1a	A
▪ Pathological complete response is associated with improved survival	1b	A
▪ The RCB Score and the class of RCB are subtype independent prognostic factors	2a	B
▪ Can achieve operability in primary inoperable tumors	1b	A
▪ Improved options for breast conserving surgery	1b	A
▪ Decreases rate of axillary lymphadenectomies lymphonodectomies	2b	B
▪ Allows individualization of therapy according to mid-course treatment effect	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)

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
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RCB Score and RCB class as prognostic factors

1. Yau C, Osdoit M, van der Noordaa Metz al. Residual cancer burden after neoadjuvant chemotherapy and long term survival outcoem in breast cancer: a multicentre pooled analysis of 5161 patients.
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Neoadjuvant Systemic Chemotherapy - Indications

	Oxford		
	LoE	GR	AGO
▪ **If similar postoperative adjuvant chemotherapy is indicated**	1b	A	++
▪ **To allow a risk adapted postoperative therapy (data most consistent for HER2 pos and TNBC)**	1b	A	++
▪ **Inflammatory breast cancer**	2b	B	++
▪ **Inoperable breast cancer**	1c	A	++
▪ **Large operable breast cancer requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation**	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

Neoadjuvant Systemic Chemotherapy (NACT)
Predictive Factors for pCR I

Factor	pCR* Probability	Oxford LoE	Oxford GR	AGO
▪ Young age	↑	1a	A	+
▪ Obesity	↓	2a	B	+
▪ cT1 / cT2 tumors o. N0 o. G3	↑↑	1a	A	++
▪ Negative hormone receptor status	↑↑	1a	A	++
▪ Triple negative breast cancer	↑↑	1a	A	++
▪ Positive HER2-status	↑↑	1a	A	++
▪ Early clinical response	↑	1b	A	+
▪ Lobular tumor type	↓	1a	A	+
▪ Metaplastic tumor type	↓↓	4	C	+

* High (↑) or very high (↑↑) probability to reach pCR, low (↓) or very low(↓↓) probability to reach pCR; See aso chapter „Prognostic and predictive factors“

General evidence

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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.
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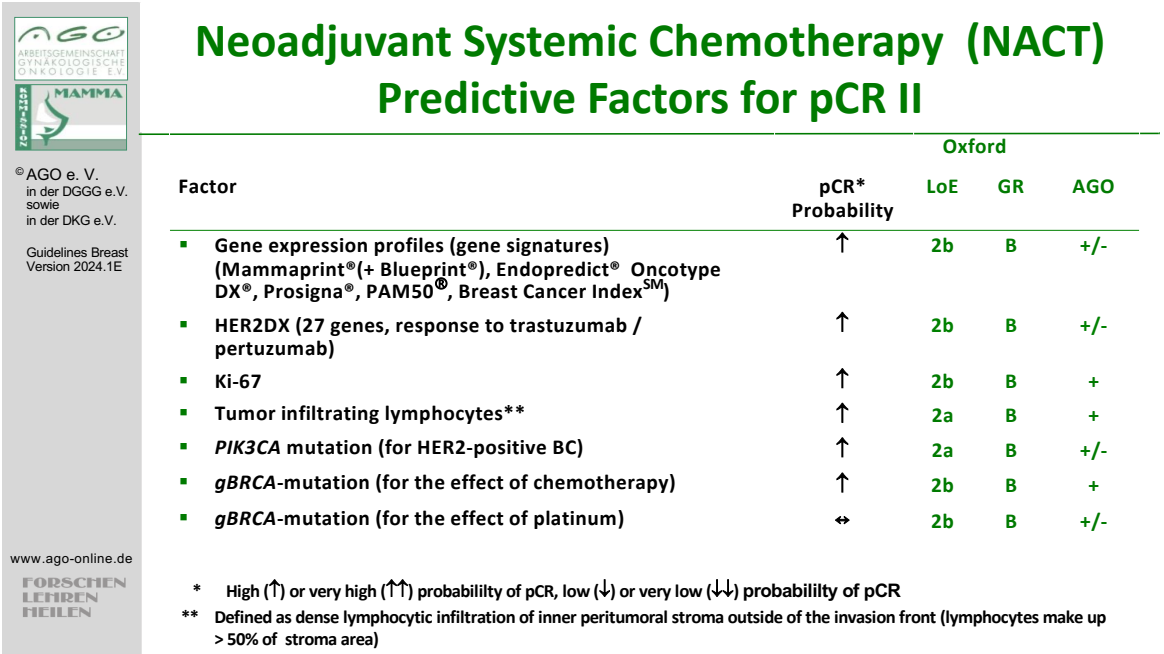

Neoadjuvant Systemic Chemotherapy (NACT)
Predictive Factors for pCR II

Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford AGO
▪ Gene expression profiles (gene signatures) (Mammaprint®(+ Blueprint®), Endopredict® Oncotype DX®, Prosigna®, PAM50®, Breast Cancer Index^{SM})	↑	2b	B	+/-
▪ HER2DX (27 genes, response to trastuzumab / pertuzumab)	↑	2b	B	+/-
▪ Ki-67	↑	2b	B	+
▪ Tumor infiltrating lymphocytes**	↑	2a	B	+
▪ *PIK3CA* mutation (for HER2-positive BC)	↑	2a	B	+/-
▪ *gBRCA*-mutation (for the effect of chemotherapy)	↑	2b	B	+
▪ *gBRCA*-mutation (for the effect of platinum)	↔	2b	B	+/-

* High (↑) or very high (↑↑) probabililty of pCR, low (↓) or very low (↓↓) probabililty of pCR

** Defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (lymphocytes make up > 50% of stroma area)

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.
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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
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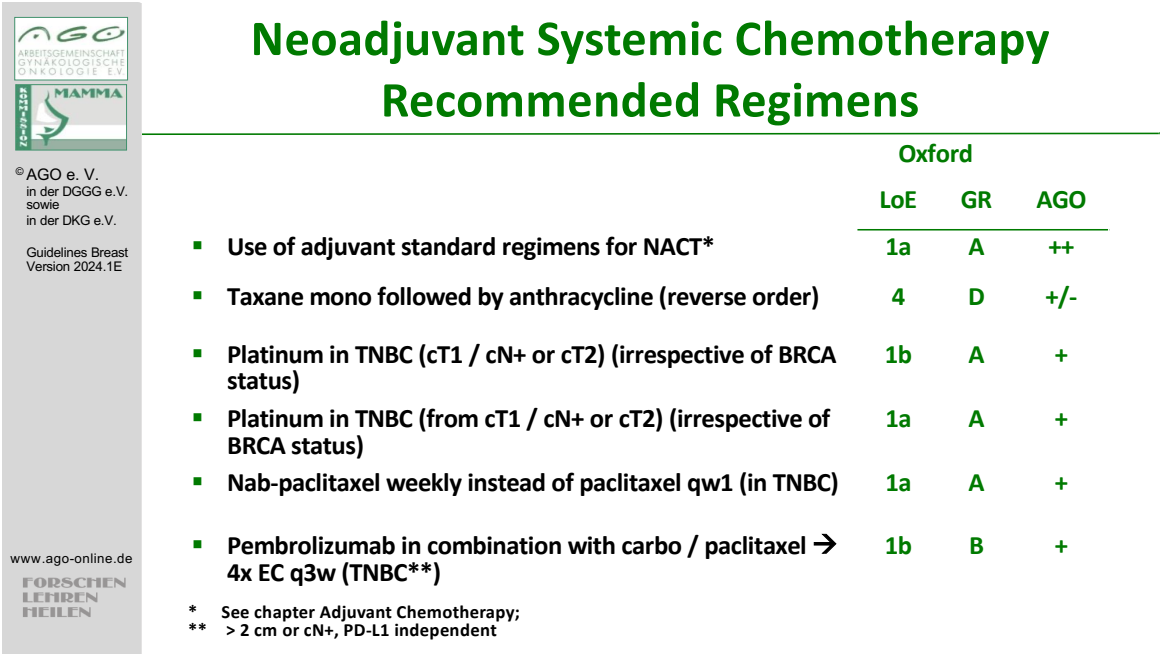

Neoadjuvant Systemic Chemotherapy
Recommended Regimens

	Oxford		
	LoE	GR	AGO
▪ Use of adjuvant standard regimens for NACT*	1a	A	++
▪ Taxane mono followed by anthracycline (reverse order)	4	D	+/-
▪ Platinum in TNBC (cT1 / cN+ or cT2) (irrespective of BRCA status)	1b	A	+
▪ Platinum in TNBC (from cT1 / cN+ or cT2) (irrespective of BRCA status)	1a	A	+
▪ Nab-paclitaxel weekly instead of paclitaxel qw1 (in TNBC)	1a	A	+
▪ Pembrolizumab in combination with carbo / paclitaxel → 4x EC q3w (TNBC**)	1b	B	+

* See chapter Adjuvant Chemotherapy;
** > 2 cm or cN+, PD-L1 independent

Use of adjuvant standard regimens for NACT

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Recommended Regimen in Triple Negative Breast Cancer

	Oxford		
	LoE	GR	AGO
Non-platinum-containing regimen			
ddEC x 4 → $pacli_{80}$ q1w x 12	1b	B	++
$NabPac_{125}$ q1w x 12 → $E_{90}C$ q(2)3w x 4	1b	B	+/-
Platinum-containing regimen			
$NabPac_{125}$ / $carbo_{AUC\,2}$ 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 or paclitaxel/$carbo_{AUC1,5}$ q1w x18	2b	B	+
$NabPac_{1oo}$ / $carbo_{AUC\,6}$ q4w x 4	2b	C	+
Checkpoint inhibitors			
$Pembro_{200}$ 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	+

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Docetaxel/Carboplatin

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ICPi plus Neoadjuvant Chemotherapy for Patients with Triple Negative Breast Cancer

Guidelines Breast
Version 2024.1E

	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%	33,9% vs. 35.4%
pCR PD-L1 negative	44% vs. 18%	48% vs. 34%	45% vs. 30%	32% vs. 32%
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%

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FORSCHEN
LEHREN
HEILEN

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Neoadjuvant Systemic Therapy
Recommended Methods of Monitoring of Response

	Oxford		
	LoE	GR	AGO
▪ **Breast ultrasound**	2b	B	++
▪ **Palpation**	2b	B	++
▪ **Mammography**	2b	B	++
▪ **MRI**	2b	B	+
▪ **PET(-CT)**	2b	B	+/-
▪ **Pretherapeutical marking of tumor region**	5	D	++
▪ **Pretherapeutical diagnostic core needle biopsy and marking in case of of cN+ (CNB) (in case TAD is planned for ≤ 3 suspect lymph nodes)**	2b	B	++*

(CNB: core needle biopsy; TAD: targeted axillary dissection;
*study participation recommended (AXSANA /Eubreast 3 Trial)

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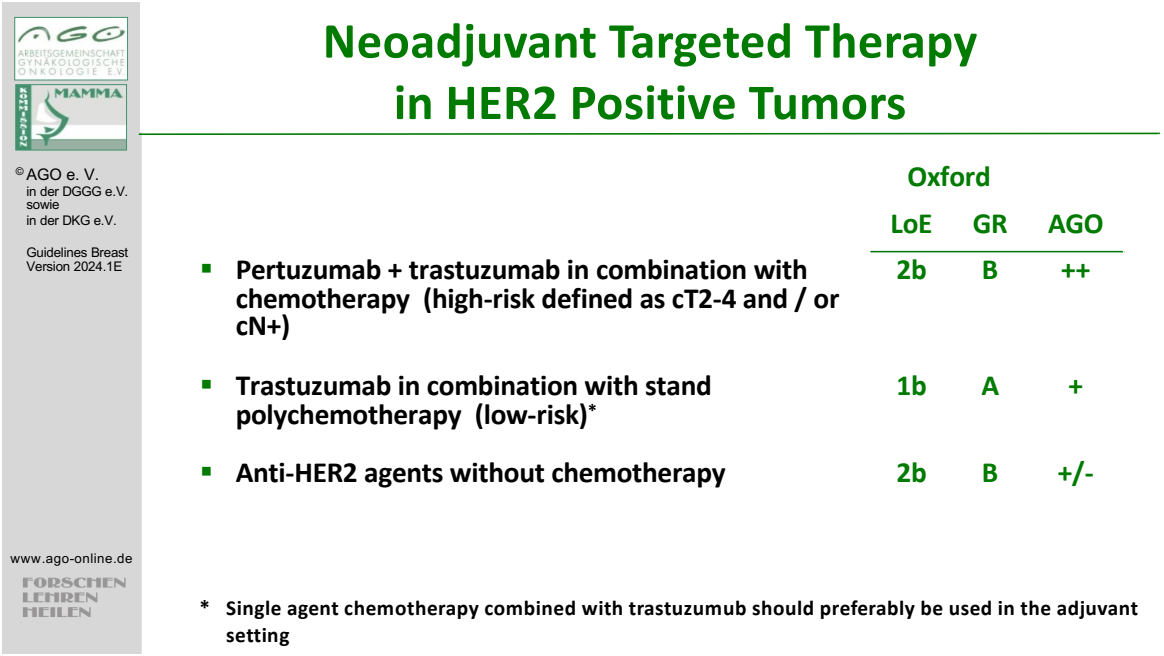

Neoadjuvant Targeted Therapy in HER2 Positive Tumors

	Oxford		
	LoE	GR	AGO
▪ **Pertuzumab + trastuzumab in combination with chemotherapy (high-risk defined as cT2-4 and / or cN+)**	2b	B	++
▪ **Trastuzumab in combination with stand polychemotherapy (low-risk)***	1b	A	+
▪ **Anti-HER2 agents without chemotherapy**	2b	B	+/-

* **Single agent chemotherapy combined with trastuzumub should preferably be used in the adjuvant setting**

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Pertuzumab + Trastuzumab in combination with chemotherapy

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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
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Neoadjuvant Chemotherapy
Treatment Strategies Based on Clinical Response

	Oxford		
	LoE	GR	AGO
In case of early response			
▪ Completion of neoadjuvant chemotherapy	1b	A	++
In case of no change:			
▪ Completion of neoadjuvant chemotherapy (NACT) followed by surgery	2b	C	++
▪ Continuation of NACT with non cross-resistant regimen	2b	B	+
▪ AC or EC x 4 → D x 4 or Pw x 12	2b	B	+
▪ DAC x 2 → NX x 4	1b	B	+
In case of disease progression			
▪ Re-evaluation of tumorbiological factors	5	D	+/-
▪ Stop NACT and proceed to surgery or radiotherapy	4	D	++
▪ Additional adjuvant chemotherapy with non cross-resistant regimen	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
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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
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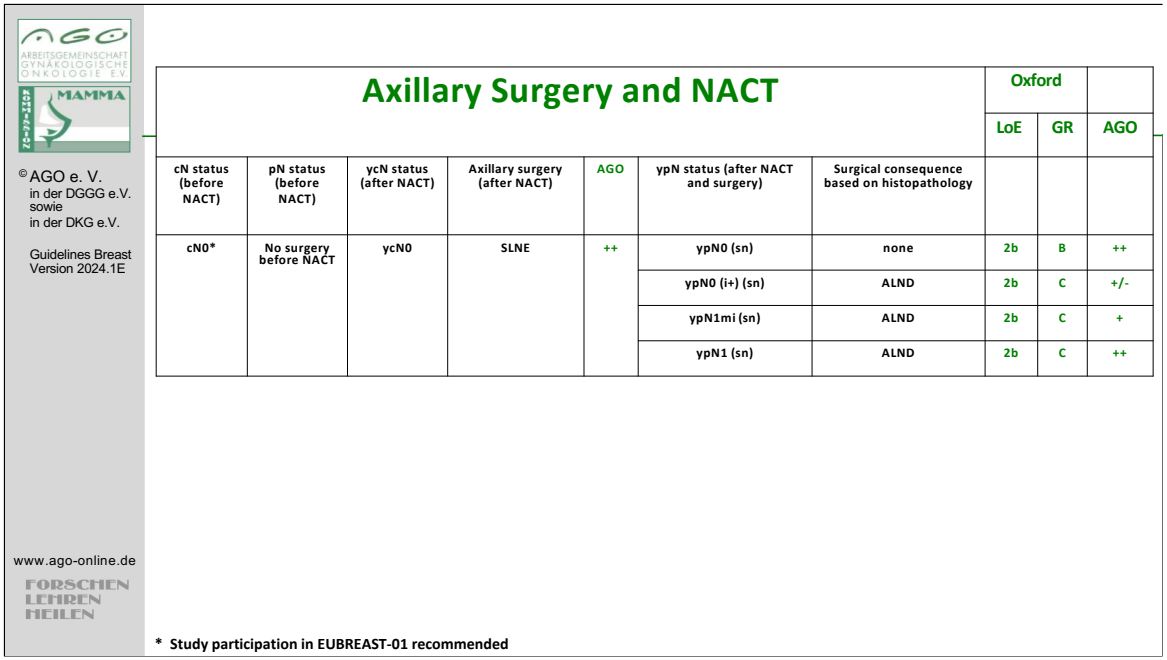

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Axillary Surgery and NACT

cN status (before NACT)	pN status (before NACT)	ycN status (after NACT)	Axillary surgery (after NACT)	AGO	ypN status (after NACT and surgery)	Surgical consequence based on histopathology	Oxford LoE	Oxford GR	AGO
cN0*	No surgery before NACT	ycN0	SLNE	++	ypN0 (sn)	none	2b	B	++
					ypN0 (i+) (sn)	ALND	2b	C	+/-
					ypN1mi (sn)	ALND	2b	C	+
					ypN1 (sn)	ALND	2b	C	++

* Study participation in EUBREAST-01 recommended

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
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Locoregional recurrence risk after neoadjuvant chemotherapy: A pooled analysis of nine prospective neoadjuvant breast cancer trials. Eur J Cancer 2020, 130, 92-101.
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Statement: SLNE after NACT

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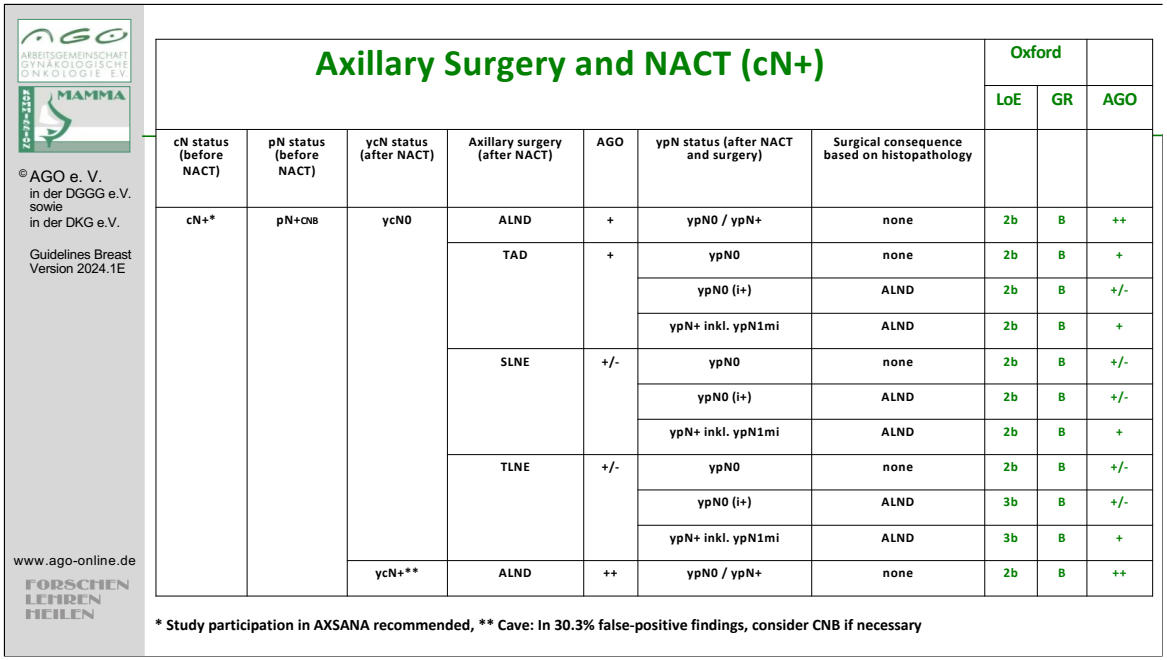

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Axillary Surgery and NACT (cN+)

cN status (before NACT)	pN status (before NACT)	ycN status (after NACT)	Axillary surgery (after NACT)	AGO	ypN status (after NACT and surgery)	Surgical consequence based on histopathology	Oxford LoE	Oxford GR	AGO
cN+*	pN+CNB	ycN0	ALND	+	ypN0 / ypN+	none	2b	B	++
			TAD	+	ypN0	none	2b	B	+
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ inkl. ypN1mi	ALND	2b	B	+
			SLNE	+/-	ypN0	none	2b	B	+/-
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ inkl. ypN1mi	ALND	2b	B	+
			TLNE	+/-	ypN0	none	2b	B	+/-
					ypN0 (i+)	ALND	3b	B	+/-
					ypN+ inkl. ypN1mi	ALND	3b	B	+
		ycN+**	ALND	++	ypN0 / ypN+	none	2b	B	++

* Study participation in AXSANA recommended, ** Cave: In 30.3% false-positive findings, consider CNB if necessary

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
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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

Neoadjuvant Systemic Therapy
Loco-regional Surgery (Breast)

	Oxford		
	LoE	GR	AGO
▪ **Pretherapeutic discussion in a multidisciplinary tumor board (e.g. to define the surgical procedure)**	1a	B	++
▪ **Early marking of tumor (incl. detailed topographic documentation)**	5	D	++
▪ **Surgical removal of tumor / representative excicion of posttherapeutic, marked tumorareal**	2b	C	++
▪ **Tumor resection in new margins**	2b	C	++
▪ **Microscopically clear margins**	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

Neoadjuvant Systemic Therapy
Indications for Mastectomy

	Oxford		
	LoE	GR	AGO
▪ **Positive margins after repeated excisions**	3b	C	++
▪ **Radiotherapy not feasible**	5	D	++
▪ **In case of clinical complete response**			
▪ **Inflammatory breast cancer (in case of pCR)**	2b	C	+/-
▪ **Multicentric lesions**	2b	C	+/-
▪ **cT4a-c breast cancer**	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.

Neoadjuvant Systemic Therapy
Timing of Diagnosis, Surgery and Radiotherapy

	Oxford		
	LoE	GR	AGO
Initiation of therapy **Delay of therapy associated with worse prognosis**	2b	B	+
Timing of surgery **4-8 weeks after last course of chemotherapy**	2a	B	++
Radiotherapy within 2 months after surgery	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.

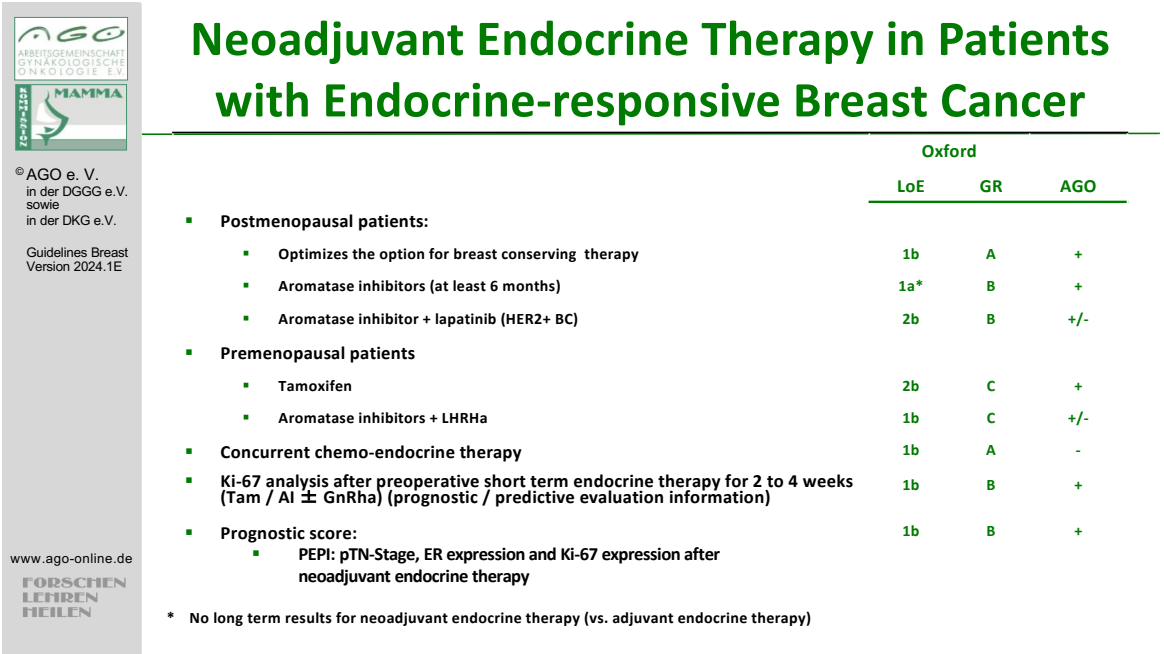
Neoadjuvant endocrine Therapy (NET)
- Good clinical practice -

Guidelines Breast
Version 2024.1E

- **Suitable for patients who are**
  - **inoperable**
  - **not able or willing to undergo chemotherapy**
- **Data for premenopausal in contrast to postmenopausal patients is limited**
- **Optimale duration of NET is at least 4-6 months or until best repsonse or progression**
- **Choice of endocrine therapy is based on the menopausal status**
- **Ki-67 analysis after preoperative short term endocrine therapy for 2 to 4 weeks may predict response to endocrine treatment (prognostic / predictive 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).



Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer

	Oxford LoE	GR	AGO
▪ **Postmenopausal patients:**			
▪ Optimizes the option for breast conserving therapy	1b	A	+
▪ Aromatase inhibitors (at least 6 months)	1a*	B	+
▪ Aromatase inhibitor + lapatinib (HER2+ BC)	2b	B	+/-
▪ **Premenopausal patients**			
▪ Tamoxifen	2b	C	+
▪ Aromatase inhibitors + LHRHa	1b	C	+/-
▪ **Concurrent chemo-endocrine therapy**	1b	A	-
▪ **Ki-67 analysis after preoperative short term endocrine therapy for 2 to 4 weeks (Tam / AI ± GnRha) (prognostic / predictive evaluation information)**	1b	B	+
▪ **Prognostic score:** ▪ **PEPI: pTN-Stage, ER expression and Ki-67 expression after neoadjuvant endocrine therapy**	1b	B	+

* No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)

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.

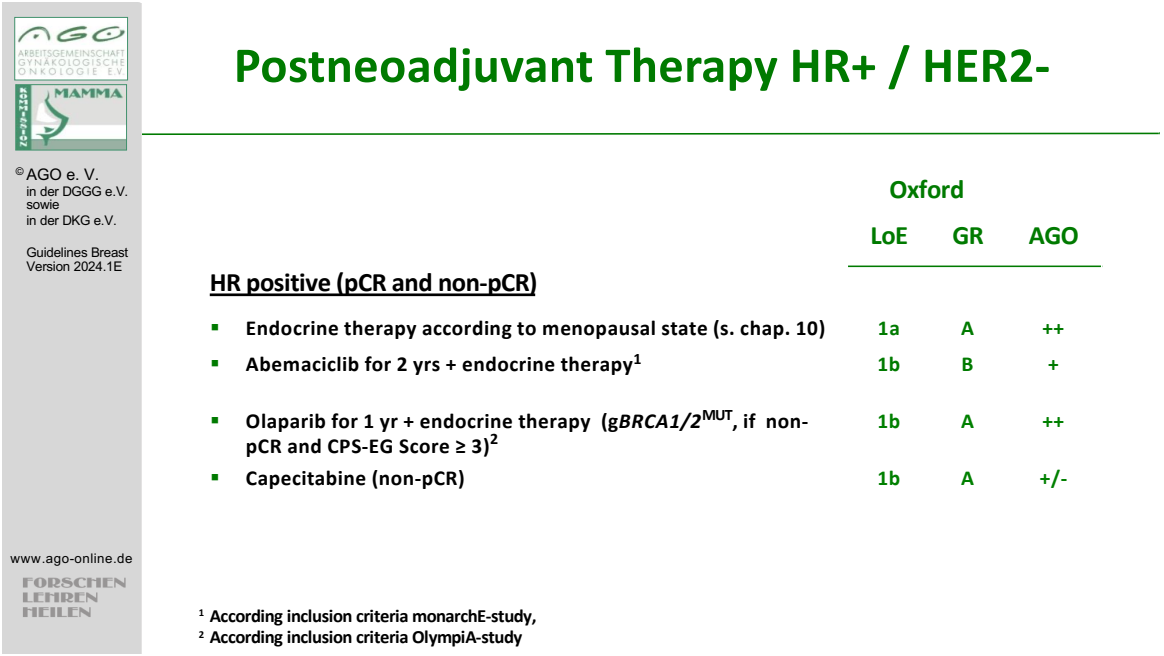
Preoperative ET and Ki67 measurement:

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).

Prognostic scores following NST

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



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>

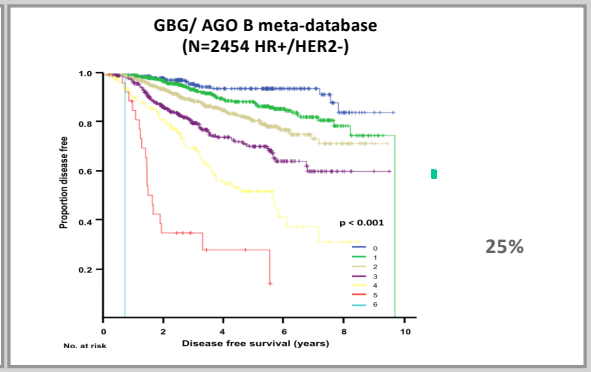
1. Joensuu H, Kellokumpu-Lehtinen PL, Huovinen R et al. Adjuvant Capecitabine for Early Breast Cancer: 15-Year Overall Survival Results From a Randomized Trial. J Clin Oncol. 2022 Jan 12:JCO2102054.

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.

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

Guidelines Breast
Version 2024.1E

	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

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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)

Postneoadjuvant Therapy TNBC

	Oxford LoE	Oxford GR	AGO
pCR			
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	+
Non-pCR			
▪ Capecitabine (q3w up to 8 courses)[1]			
▪ With non-pCR after A-T-containing chemotherapy[1]	1a	A	++
▪ With non-pCR after platinum +/- pembrolizumab-containing therapy	5	D	+/-
▪ Platinum salts (carboplatin or cisplatin) q3w after AT-pretreatment	1b	B	+/-
▪ Olaparib (*gBRCA*^{MUT})[2]	1b	A	++
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	++

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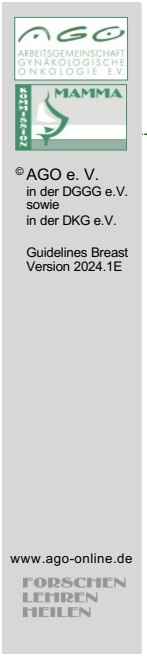

Postneoadjuvant Therapy HER2-positive

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

* In combination with standard endocrine treatment

Statement HER2 positiv (pCR):

1. Piccart M et al.; APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. J Clin Oncol. 2021 May 1;39(13):1448-1457.
2. Chan A, Moy B, Mansi J et al.: ExteNET Study Group. Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial. Clin Breast Cancer. 2020 Oct 6:S1526-8209(20)30258-5. doi: 10.1016/j.clbc.2020.09.014.
3. Martin M et al.; ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(12):1688-1700
4. von Minckwitz G, Procter M, de Azambuja E, et al. APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017 Jul 13;377(2):122-131.
5. Goldhirsch A et al.; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet. 2013;382(9897):1021-8.
6. Swain S, Macharia H, Cortes J et al. Event-free survival in patients with early HER2-positive breast cancer with a pathologic complete response after HER2-targeted therapy: A pooled analysis. Cancers 2022;14(20):5051. doi: 10.3390/cancers14205051.

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.
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<u>Statement rastuzumab + Pertuzumab in N+:</u>

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.