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Guidelines Breast  
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FORSCHEN  
LEHREN  
HEILEN

# Diagnosis and Treatment of Patients with early and advanced Breast Cancer

## Neoadjuvant (Primary) Systemic Therapy



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## Neoadjuvant Systemic Therapy

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 Thill / Thomssen



Systematic review of published evidence

PUBMED 1999-2021

ASCO 1999-2021

SABCS 1999-2021

ECCO/ESMO 1999-2021

	<h1>Strategies for Differentiated Systemic Treatment in the Curative Situation</h1>	
© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.  Guidelines Breast Version 2022.1E	<b>If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred; study participation recommended</b>	
www.ago-online.de 	<b>„Low absolute risk implies low absolute benefit“</b>	
	■ HR+ / HER2- and „low-risk“	
	■ Endocrine therapy without chemotherapy	++
	■ HR+ / HER2- and „high-risk“	
	■ Conventionally dosed AT-based chemotherapy (q3w)	+
	■ Dose dense chemotherapy (including weekly schedule)	++
	■ Followed by endocrine endocrine-based therapy	++
	■ Triple-negative (TNBC)	
	■ Conventional dosed AT-based chemotherapy (q3w)	+
	■ Sequential AT-based chemotherapy (incl. weekly schedule)	++
	■ Neoadjuvant Neo-/adjuvant platinum-containing chemotherapy	+
	■ Neoadjuvant platinum-containing chemotherapy with ICPI (Pembrolizumab)	+
	■ HER2 negative, gBRCA1/2mut (ER pos. and TNBC respectively <sup>1</sup> )	
	■ Olaparib postneoadjuvant	+
	■ HER2+	
	■ Trastuzumab (plus Pertuzumab in N+ or NACT)	++
	■ Sequential AT-based chemotherapy with concurrent T + anti-HER2 therapy	+
	■ Anthracycline-free, chemotherapy + anti-HER2 therapy	++
<sup>1</sup> According to approval or study population (if not approved)		

## Systematic review of published evidence

PUBMED 1999-2021

ASCO 1999-2021

SABCS 1999-2021

ECCO/ESMO 1999-2021

## 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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Cancer. 2016 Jul;62:62-

#### Pertuzumab + Trastuzumab in combination with chemotherapy

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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]
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#### 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.
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#### Abemaciclib:

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#### 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.

#### Platin salts:

1. 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.
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4. 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
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	<b>Anthracycline-free Taxan / Carboplatin based Regimen for HER2+</b>			
<p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2022.1E</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	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: 93.5%
<p>T Docetaxel, Tx Paclitaxel, C Carboplatin, H Trastuzumab, P Pertuzumab</p>				

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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 randomized phase II Cardiac safety study (TRYPHAENA) Ann Oncol. 2013 Sep;24(9):2278-84. doi:10.1093/annonc/mdt182.
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Neoadjuvant Systemic Chemotherapy Clinical Benefit		
	Oxford	
	LoE	GR
Leads to improvement of prognosis by individualization of neoadjuvant and post-neoadjuvant therapy	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
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
3. Marm  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
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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.

Neoadjuvant Systemic Chemotherapy - Indications				
	Oxford			
	LoE	GR	AGO	
■ If similar postoperative adjuvant chemotherapy is indicated	1b	A	++	
■ To allow a risk adapted postoperative therapy	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.

If similar postoperative adjuvant chemotherapy is indicated

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	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 also 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, Zoumbros 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.

Neoadjuvant Systemic Chemotherapy (NACT) Predictive Factors for pCR II				
Factor	pCR* Probability	Oxford		
		LoE	GR	AGO
▪ Gene expression profiles (gene signatures) (Mammaprint®, Endopredict® Oncotype DX®, Prosigna®, Breast Cancer Index <sup>SM</sup> )	↑	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 (↑↑) probability of pCR, low (↓) or very low (↓↓) probability 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.
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
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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 neoadjuvant therapy. *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. doi: 10.1093/annonc/mdv175. Epub 2015 Apr 7.
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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 Jan 9. doi: 10.1093/annonc/mdy536. [Epub ahead of print]
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### 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.

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



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### Use of adjuvant standard regimens for NACT

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<https://doi.org/10.1016/j.annonc.2021.06.014>

Recommended Regimen in Triple Negative Breast Cancer			
	Oxford		
	LoE	GR	AGO
<b>Non-platinum-containing regimen</b>			
▪ ddEC x 4 → pacli <sub>80</sub> q1w x 12	1b	B	++
▪ NabPac <sub>125</sub> q1w x 12 → E <sub>90</sub> C q(2)3w x 4	1b	B	+/-
<b>Platinum-containing regimen</b>			
▪ NabPac <sub>125</sub> / carbo <sub>AUC 2</sub> q1w x 8 → ddEC x 4	1b	B	+
▪ Pacli <sub>80</sub> q1w x 12 / carbo <sub>AUC 6</sub> q3w x 4 → ddAC / ddEC x 4	1b	B	+
▪ Docetaxel / carbo <sub>AUC 6</sub> q3w x 6 or paclitaxel/carbo <sub>AUC 1,5</sub> q1w x 18	2b	B	+
▪ NabPac <sub>100</sub> / carbo <sub>AUC 6</sub> q4w x 4	2b	C	+
<b>Checkpoint inhibitors</b>			
▪ Pembro <sub>200</sub> q3w + Pac <sub>80</sub> / carbo <sub>AUC 1,5</sub> q1w x 12 → E <sub>90</sub> C q3w x 4	1b	B	+
▪ Pembro <sub>200</sub> q3w + Pac <sub>80</sub> q1w x 12 / carbo <sub>AUC 5</sub> q3w → E <sub>90</sub> C q3w x 4	1b	B	+

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MAMMA

# ICPi plus Neoadjuvant Chemotherapy for Triple Negative Breast Cancer Patients

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	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 (1y)	Pembrolizumab (1y)	Atezolizumab (24 weeks)
Chemo	NabPac <sub>125</sub> q1w x12 → EC q2w x4	NabPac <sub>125</sub> q1w x12 → EC q2w x4	Pac q1w x12 + carbo q3w AUC 5 or q1w AUC 1,5 → AC/EC q3w x4	NabPac <sub>125</sub> + 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)	43.5% vs. 40.8% Δ 2.6% (n.s.)
pCR PD-L1 positive	58% vs. 50%	69% vs. 49%	69% vs. 55%	52% vs. 48%
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)	20 months EFS: 0.76 (n.s.)	39.1 months EFS: 15.7 vs. 23.8 m 0.63 (p = 0.00031)	---
EFS/IDFS adjusted to pCR/non-pCR	pCR 95.5% vs. 86.1% npCR 76.3% vs. 69.7%	---	pCR 94.4% vs. 92.5% npCR 67.4% vs. 56.8%	---

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# Neoadjuvant Systemic Therapy

## Recommended Methods of Monitoring of Response

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- **Breast ultrasound**
- **Palpation**
- **Mammography**
- **MRI**
- **PET(-CT)**
- **Pretherapeutical marking of tumor region**
- **Pretherapeutical marking of pN+**

Oxford		
LoE	GR	AGO
2b	B	++
2b	B	++
2b	B	++
2b	B	+
2b	B	+/-
5	D	++
2a	B	+*

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\*study participation recommended (AXSANA /Eubrest 3 Trial)

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

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



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#### 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  $\pm$  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

Neoadjuvant Chemotherapy Treatment Strategies Based on Clinical Response			
	Oxford		
	LoE	GR	AGO
<b>In case of early response</b>			
▪ Completion of neoadjuvant chemotherapy	1b	A	++
<b>In case of no change:</b>			
▪ 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	+
<b>In case of disease progression</b>			
▪ 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
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.

Axillary surgery and NACT							Oxford		
							LoE	GR	AGO
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			
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	++
cN+ **	pN+ <sub>oxa</sub>	ycN0	ALND	+	ypN0 / ypN+	none	2b	B	++
			TAD	+	ypN0	none	2b	B	+
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ incl. ypN1mi	ALND	2b	B	+
			SLNE	+/-	ypN0	none	2b	B	+/-
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ incl. ypN1mi	ALND	2b	B	+
		ycN+	ALND	++	ypN0 / ypN+	none	2b	B	++

\* Study participation in EUBREAST-01 recommended; \*\* Study participation in AXSANA 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
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 conserving 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, fertilité & 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. Boughhey 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 eubrest-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.
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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.
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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.
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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 excision 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
▪ <b>Positive margins after repeated excisions</b>	<b>3b</b>	<b>C</b>	<b>++</b>
▪ <b>Radiotherapy not feasible</b>	<b>5</b>	<b>D</b>	<b>++</b>
▪ <b>In case of clinical complete response</b>			
▪ <b>Inflammatory breast cancer (in case of pCR)</b>	<b>2b</b>	<b>C</b>	<b>+/-</b>
▪ <b>Multicentric lesions</b>	<b>2b</b>	<b>C</b>	<b>+/-</b>
▪ <b>cT4a-c breast cancer</b>	<b>2b</b>	<b>B</b>	<b>+/-</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 2014 [Epub ahead of print]

#### 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 2014

 <b>Neoadjuvant Systemic Therapy</b> <b>Timing of Diagnosis, Surgery and Radiotherapy</b>			
	Oxford		
	LoE	GR	AGO
<b>Initiation of therapy</b> Delay of therapy (> 60 days) associated with worse prognosis	2b	B	
<b>Timing of surgery</b> 4-8 weeks after last course of chemotherapy	2a	B	++
<b>Radiotherapy within 2 months after surgery</b>	2b	B	++

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 LEHREN  
 HEILEN

#### 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.

#### 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.



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## Neoadjuvant endocrine Therapy (NET)

### - Good clinical practice -

- **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 response 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. 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 postmenopausal 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 Nov;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

Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer			
	Oxford		
	LoE	GR	AGO
<b>Postmenopausal patients:</b> <ul style="list-style-type: none"> <li>Optimizes the option for breast conserving therapy</li> <li>Aromatase inhibitors (at least 6 months)</li> <li>Aromatase inhibitor + lapatinib (HER2+ BC)</li> </ul>	1b	A	+
	1a*	B	+
	2b	B	+/-
<b>Premenopausal patients</b> <ul style="list-style-type: none"> <li>Tamoxifen</li> <li>Aromatase inhibitors + LHRHa</li> </ul>	2b	C	+
	1b	C	+/-
<b>Concurrent chemo-endocrine therapy</b> <ul style="list-style-type: none"> <li>Ki-67 analysis after preoperative short term endocrine therapy for 2 to 4 weeks (Tam / AI ± GnRha) (prognostic / predictive evaluation information)</li> </ul>	1b	A	-
	1b	B	+
<b>Prognostic score:</b> <ul style="list-style-type: none"> <li>PEPI: pTN-Stage, ER expression and Ki-67 expression after neoadjuvant endocrine therapy</li> </ul>	1b	B	+
* Optimal duration of neoadjuvant endocrine therapy is unknown. 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: 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. 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; 339  
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LEHREN  
HEILEN

# Postneoadjuvant Therapy HR+ / HER2-

## HR positive (pCR and non-pCR)

	Oxford		
	LoE	GR	AGO
▪ Endocrine therapy according to menopausal state (s. chap. 10)	1a	A	++
▪ Abemaciclib for 2 yrs + endocrine therapy if high risk of recurrence <sup>1</sup>	1b	B	+
▪ Palbociclib for 1-2 yrs + endocrine therapy	1b	B	-
▪ Olaparib for 1 yr + endocrine therapy (gBRCA1/2 <sup>MUT</sup> , if non-pCR and CPS-EG Score ≥ 3) <sup>2</sup>	1b	B	+
▪ Capecitabine (non-pCR)	3b	C	+/-

<sup>1</sup> According inclusion criteria monarchE-study

<sup>2</sup> According inclusion criteria OlympiA-study

<sup>1</sup> According inclusion criteria monarchE-study  
<sup>2</sup> According inclusion criteria OlympiA-study

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

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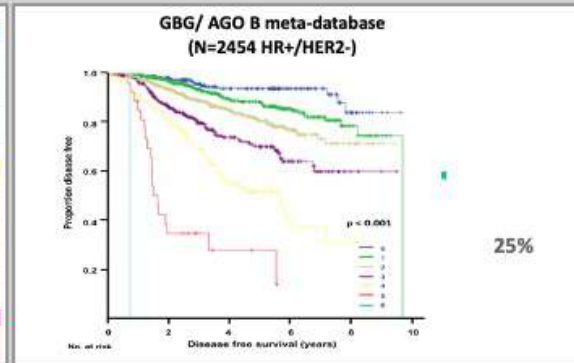
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#### Statement Capecitabine (bei non-pCR; 8 Kurse)

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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.
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## How to Calculate CPS+EG Score?

Point assignment for CPS+EG score		
Clinical Stage		
I	0	T1N0; T0N1m; T1N1m
IIA	0	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	2	T0-2N2
IIB	2	T4N0-2
IIIC	2	Any T N3
Pathologic Stage		
0	0	TU/NO
I	0	T1N0; T0N1m; T1N1m
IIA	1	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2 N2
IIB	1	T4 N0-N2
IIIC	2	Any T N3
Tumor Biologic Factors		
ER negative	1	
Nuclear grade 3	1	



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

Adjuvant / Post-Neoadjuvant Treatment with CDK4/6i			
	monarchE	PALLAS	PENELOPE <sup>B</sup>
N	5,637	5,600	1,250
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib
% of pts. with NACT	37%	n.r.	100%
Duration of CDK4/6i treatment	24 mths	24 mths	12 mths
Follow-up	27.1 mths	24 mths	43 mths
Discontinuation rate	28%	42%	20%
Discontinuation rate due to AE <sub>CDKi</sub>	17%	27%	5%
IDFS-HR (95%-CI)	0.70 (0.59-0.82) p < 0.0001	0.96 (0.81-1.14) p = 0.65	0.93 (0.74-1.16) p = 0.525
2-yrs IDFS	92.7% vs. 90.0%	n.r.	88% vs. 78%
3-yrs IDFS	88.8% vs. 83.4%	88% vs. 89%	81% vs. 78%
4-yrs IDFS	n.r.	84.2% vs. 84.5%	73% vs. 72%
IDFS: invasive disease-free survival			

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Postneoadjuvant Therapy TNBC			
	Oxford		
	LoE	GR	AGO
<b>pCR</b>			
Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	+
<b>Non-pCR</b>			
Capecitabine (q3w up to 8 courses)*	1a	A	+
Olaparib ( <i>gBRCA<sup>MUT</sup></i> ) <sup>1</sup>	1b	B	+
Continuation of pembrolizumab, if started with neoadj. therapy (q3w up to 9 courses)	1b	B	++

<sup>1</sup> According inclusion criteria of OlympiA trial  
\* without platin based previous therapy

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

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#### Pembrolizumab in combination with chemotherapy

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

Postneoadjuvant Therapy: HER2-positive			
	Oxford		
	LoE	GR	AGO
<b>pCR</b>			
▪ 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)*	2b	B	-
<b>non-pCR</b>			
▪ 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)*	2b	B	+
▪ Neratinib after other HER2-directed therapies (HR-positive*)	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.
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#### 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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