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Guidelines Breast
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LEITLINIEN
BREUSTEN

Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Neoadjuvante (Primäre) systemische Therapie

Neoadjuvante systemische Therapie



Versionen 2002–2020:

Bauerfeind / Blohmer / Costa / Dall / Fersis / Friedrich / Göhring / Harbeck / Heinrich / Huober / Jackisch / Kaufmann / Liedtke / Loibl / Lux / von Minckwitz / Müller / Mundhenke / Nitz / Schneeweiss / Schütz / Solomayer / Untch

Version 2021:

Fehm / Stickeler

Systematic review of published evidence

PUBMED 1999-2020

ASCO 1999-2020

SABCS 1999-2020

ECCO/ESMO 1999-2020

Subtyp-spezifische Strategien zur Systemtherapie

	AGO
Bei Indikation zur Chemotherapie neoadjuvante Applikation bevorzugt	
<ul style="list-style-type: none"> ▪ HR+/HER2- mit „niedrigem Risiko“ <ul style="list-style-type: none"> ▪ Endokrine Therapie ohne Chemotherapie 	++
<ul style="list-style-type: none"> ▪ HR+/HER2- mit „hohem Risiko“ <ul style="list-style-type: none"> ▪ Konventionell dosierte AT-basierte Chemotherapie (q3w) ▪ Dosisdichte Chemotherapie (inkl. weekly-Regime) ▪ Anschließend endokrine Therapie 	+ ++ ++
<ul style="list-style-type: none"> ▪ HER2+ <ul style="list-style-type: none"> ▪ Trastuzumab (plus Pertuzumab bei N+ oder NACT) <ul style="list-style-type: none"> ▪ Sequenzielles AT-basierte Chemotherapie mit simultaner Gabe von T + anti HER2-Therapie ▪ Anthracyclin-freie Chemotherapie mit anti HER2-Therapie 	++ ++ ++
<ul style="list-style-type: none"> ▪ Triple-negativ (TNBC) <ul style="list-style-type: none"> ▪ Konventionell dosierte AT-basierte Chemotherapie (q3w) ▪ Dosisdichte sequenzielle AT-basierte Chemotherapie (inkl. weekly Schemata) ▪ Neoadjuvante Platin-haltige Chemotherapie ▪ Neoadjuvante Chemotherapie mit ICI (Immun-Check-Point-Inhibitoren) 	+ ++ + +/*

* Studienteilnahme empfohlen


Systematic review of published evidence

PUBMED 1999-2020

ASCO 1999-2020

SABCS 1999-2020

ECCO/ESMO 1999-2020



Anthracycline-free Taxan/Carboplatin based regimen for Her2+

Regimen	Pts. (n=)	pCR rate (%)	OUTCOME
6 x TCH (TRIO B07)	34	47	Not published
6 x TCHP (TRYPHAENA)	75	64	3-yr-DFS: 90%
6 x TCHP (KRISTINE - TRIO - 021)	221	56	3-yr-EFS: 94.2
4 x TCHP (NSABP- B52; nur HR+)	155	41	Not published
9 x TxCHP (TRAIN-2)	206	68	3-yr-EFS: 93.5%

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 trastuzumab or lapatinib or th combination of trastuzumab and lapaitinib, followed by six cycls 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. *Lancet Oncol.* Dec;19(12):1630-1640; doi:10.1016/S1470-2045(18)30570-9.

HER2+ Early Breast Cancer Neo-/adjuvant and postneoadjuvant Therapy		
<p>AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2021.1D</p> <p>www.ago-online.de</p> <p>© 2021 AGO e. V. Alle Rechte vorbehalten. VDF 10 074</p>	<p>Adjuvant Therapy: low risk of recurrence <i>Rezidivrisiko</i> Paclitaxel^{1,2} + Trastuzumab³</p> <ul style="list-style-type: none"> elderly or fragile patients or pT1, pN0 	<p>Neoadjuvant Therapy⁴ Trastuzumab + Pertuzumab</p> <ul style="list-style-type: none"> Node-positive (cN+/pN+) or cT \geq 2
	<p>Adjuvant Therapy: high risk of recurrence DTT + Trastuzumab + Pertuzumab⁵</p> <ul style="list-style-type: none"> Node-positive (pN+) Irrespective of ER-status⁵ 	<p>Postneoadjuvant Therapy⁴ Trastuzumab +/- Pertuzumab or T-DM1</p> <p>In case of pCR:</p> <ul style="list-style-type: none"> Trastuzumab Trastuzumab + Pertuzumab <ul style="list-style-type: none"> Node-positive prior NACT Irrespective of ER-status <p>In case of non-pCR:</p> <ul style="list-style-type: none"> T-DM1
<p>Total duration of anti-HER2-therapy: 1 year</p> <p><small>1. Tolanev SM, et al. J Clin Oncol April 2019; 37:122-131 (inkl. Suppl.) 2. von Minckwitz G, et al. N Engl J Med 2017; 377:122-131 (inkl. Suppl.) 3. Gianni L, et al. Lancet Oncol 2012; 13:25-32 4. von Minckwitz G, et al. N Engl J Med 2019; 380:617-628 5. Piccart M, et al. SABCS 2019 (abs GS1-04)</small></p>		

1. Tolanev SM, *et al.* J Clin Oncol April 2019
2. von Minckwitz G, *et al.* N Engl J Med 2017 377:122–131 (inkl. Suppl.)
3. Gianni L, *et al.* Lancet Oncol 2012;13:25-32
4. von Minckwitz G, *et al.* N Engl J Med 2019; 380:617-628
5. Piccart M, *et al.* SABCS 2019 (abs GS1-04)

Neoadjuvante systemische Chemotherapie – Klinischer Benefit

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

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

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

Pathological complete response is associated with improved survival in all subgroups

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

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 neoad
5. Cortazar P, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014: 384; 164
6. 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
7. 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 pii: S1526-8209(17)30565-7, 2017 [Epub ahead of print]
2. Reimer T et al. Avoiding axillary sentinel node biopsy after neoadjuvant systemic therapy in breast cancer: rationale for the prospective, multicentric EUBREAST-01 trial. Cancers 2020:3698; doi:10.3390/cancers12123698

Allows individualization of therapy according to mid-course treatment effect

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

Allows individualization of post-neoadjuvant treatment

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

Neoadjuvante systemische Chemotherapie – Indikationen

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

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 pii: S1470-2045(17)30777-5, 2017 [Epub ahead of print]

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

Neoadjuvante Chemotherapie (NACT) Prädiktive Faktoren für pCR I

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

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

General evidence

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

Lobular cancer

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

Metaplastic breast cancer

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



Neoadjuvante systemische Chemotherapie Prädiktion des Ansprechens II

Faktor	LoE ₂₀₀₉	CTS	GR	AGO
• Multigensignaturen	II	B	B	+/-
• Ki-67	I	B	A	+
• Tumor infiltrierende Lymphozyten*	I	B	B	+
• PIK3CA Mutation beim HER2-positiven Mammakarzinom	I	B	B	+/-
• gBRCA	II	B	B	+
• Defizienz der homologen Rekombination	IV	C	C	+/-
• PD-L1-Status (TNBC)	II	B	B	+/-

*LPBC ist definiert als dichtes lymphozytenreiches, die Tumorzellen umgebendes Binnenstroma außerhalb der Randzone (Lymphozyten >50% der Stromafäche)
Siehe auch Kapitel „Prognostische und prädiktive Faktoren“

Multigene signature

1. Pease AM, Riba LA, Gruner RA, Tung NM, James TA. Oncotype DX® Recurrence Score as a Predictor of Response to Neoadjuvant Chemotherapy. *Ann Surg Oncol*. 2019;26(2):366-371. doi: 10.1245/s10434-018-07107-8. Epub 2018 Dec 12. PMID: 30542840.
2. Iwata H, Masuda N, Yamamoto Y et al. Validation of the 21-gene test as a predictor of clinical response to neoadjuvant hormonal therapy for ER+, HER2-negative breast cancer: the TransNEOS study. *Breast Cancer Res Treat*. 2019 Jan;173(1):123-133. doi: 10.1007/s10549-018-4964-y. Epub 2018 Sep 21. PMID: 30242578; PMCID: PMC6394785.
3. Kuemmel S, Gluz O, Nitz U et al. Neoadjuvant nab-paclitaxel weekly versus dose-dense paclitaxel followed by dose-dense EC in high risk HR+/HER2- early BC by: Results from the neoadjuvant part of ADAPT HR+/HER2- trial. *SABCS 2020*; GS4-03.

Ki-67

1. Denkert C, et al. Ki67 levels as predictive and prognostic parameters in pretherapeutic breast cancer core biopsies: a translational investigation in the neoadjuvant GeparTrio trial. *Ann Oncol* 2013; 24; 2786
2. Chen X, et al. The predictive value of Ki-67 before neoadjuvant chemotherapy for breast cancer: a systematic review and meta-analysis. *Future Oncol* 13(9):843-857, 2017

Tumour infiltrating lymphocytes

1. Mao 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; 9; e115103
2. Miyshita M, et al. Tumor-infiltrating CD8+ and FOXP3+ lymphocytes in triple-negative breast cancer: its correlation with pathological complete response to neoadjuvant chemotherapy. *Breast Cancer Res Treat* 2014; 148; 525
3. Denkert C, 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. *JCO*; 32: 2014
4. Ingold Heppner B, et al. Tumor-Infiltrating Lymphocytes: A Predictive and Prognostic Biomarker in Neoadjuvant-Treated HER2-Positive Breast Cancer. *Clin Cancer Res*. 2016 Dec 1;22(23):5747-5754.
5. Denkert C, 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 mutation

1. Loibl S, 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; 32; 3212
2. Sueta A, 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; 9; e116054
3. Loibl S, Integrated Analysis of PTEN and p4EBP1 Protein Expression as Predictors for pCR in HER2-Positive Breast Cancer. *Clin Cancer Res*. 2016 1;22(11):2675-83.
4. Loibl S, 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;27(8):1519-25.

gBRCA mutation

1. Spugnesi L, et al. Germline mutations in DNA repair genes may predict neoadjuvant therapy response in triple negative breast patients. *Genes Chromosomes Cancer*. 2016 ;55(12):915-924.
2. Hahnen E, et al. Germline Mutation Status, Pathological Complete Response, and Disease-Free Survival in Triple-Negative Breast Cancer: Secondary Analysis of the GeparSixto Randomized Clinical Trial. *JAMA Oncol* 3(10):1378-1385, 2017
3. Fasching P, et al. BRCA1/2 Mutations and Bevacizumab in the Neoadjuvant Treatment of Breast Cancer: Response and Prognosis Results in Patients With Triple-Negative Breast Cancer From the GeparQuinto Study. *J Clin Oncol*. 2018 ;36(22):2281-2287.

HRD

1. Telli ML, et al. Homologous recombination deficiency (HRD) status predicts response to standard neoadjuvant chemotherapy in patients with triple-negative or BRCA1/2 mutation-associated breast cancer. *Breast Cancer Res Treat* 2017.
2. Loibl S et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. *Ann Oncol* 2018;29(12):2341-2347

PDL-1-Status (TNBC):

1. Asano Y, Kashiwagi S, Goto W, Takada K, Takahashi K, Morisaki T, Fujita H, Takashima T, Tomita S, Ohsawa M, Hirakawa K, Ohira M. Prediction of treatment responses to neoadjuvant chemotherapy in triple-negative breast cancer by analysis of immune checkpoint protein expression. *J Transl Med*. 2018 Apr 4;16(1):87. doi: 10.1186/s12967-018-1458-y. PMID: 29615063; PMCID: PMC5883348.
2. 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.
3. Schmid P, Cortes J, Puztai 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.

Neoadjuvante systemische Chemotherapie Empfohlene Schemata und Schedules

	Oxford		
	LoE	GR	AGO
▪ Analog zu adjuvanten Standardschemata*	1a	A	++
▪ Taxan gefolgt von Anthrazyklin (umgekehrte Reihenfolge)	1a	A	+
▪ Platinsalze beim TNBC (unabh. des BRCA-Status)	1a	A	+
▪ Nab-Paclitaxel qw anstatt Paclitaxel qw	1a	A	+
▪ Checkpointinhibitoren in Kombination mit Chemotherapie (TNBC)	1b	B	+/-**

* Siehe Kapitel adjuvante Chemotherapie; ** Studienteilnahme erwünscht

Use of adjuvant standard regimens for NACT

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

Taxane followed by anthracycline sequence

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

Platinum in TNBC (irrespective of BRCA status)

1. Alba E, et al. A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from


- the GEICAM/2006-03, multicenter study. *Breast Cancer Res Treat* 2012; 136; 487
2. Von Minckwitz G , et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol* 2014; 15; 747
 3. Ando M, et al. Randomized phase II study of weekly paclitaxel with and without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA breast cancer without HER2 overexpression. *Breast Cancer Res Treat* 2014; 145; 401
 4. Petrelli F, et al. The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2014; 144; 223
 5. Sikov WM, et al. Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance). *J Clin Oncol* 2015; 33; 13
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Nab-Paclitaxel weekly instead of Paclitaxel weekly

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ICPi in combination with chemotherapy

1. Mittendorf EA, Zhang H, Barrios Chet al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. *Lancet*. 2020 Oct 10;396(10257):1090-1100. doi: 10.1016/S0140-6736(20)31953-X.
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ICPi plus neoadjuvant chemotherapy for triple negative breast cancer patients

	GeparNuevo	IMpassion031	Keynote 522	NeoTRIP
Phase	II	III	III	II
n	171	111	601	280
Prim. Endpunkt	pCR	pCR	pCR + EFS	EFS
CPY	Durvalumab (14 26 Wo)	Atezolizumab (11)	Pembrolizumab (11)	Atezolizumab (24 30w)
Chemo	Nab P + EC	Nab P + doAC	Flu+Carbo + AC oder EC	Nab P + Carbo
PDL-1 positiv	87%	88%	88%	50%
pCR (II)	57% vs. 44% Δ 13% (n.s.)	58% vs. 41% Δ 17% (p<0.01)	65% vs. 57% Δ 8% (p=0.001)	44% vs. 41% Δ 3% (n.s.)
pCR PER 3 positiv	54% vs. 50%	60% vs. 49%	69% vs. 55%	57% vs. 48%
pCR PDL-1 negativ	47% vs. 38%	48% vs. 34%	47% vs. 30%	32% vs. 32%
Follow-up (Mth) / HR EFS	-	38 mth / 0,74 (n.s.)	35 mth / 0,63 (n.s.)	-

Quelle: Breast Cancer 2021; 17(12):1983-1994

1. Loibl S, Untch M, Burchardi N et al. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. *Ann Oncol.* 2019;30(8):1279-1288. doi: 10.1093/annonc/mdz158.
2. 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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4. Gianni L, Huang CS, Egle I, et al. Pathologic complete response (pCR) to neoadjuvant treatment with or without atezolizumab in triple negative, early high-risk and locally advanced breast cancer. NeoTRIPaPDL1 Michelangelo randomized study: SABCs 2019 GS3-04

Neoadjuvante systemische Therapie Empfohlene Methoden zur Überprüfung des Ansprechens

	Oxford		
	LoE	GR	AGO
▪ Mammasonographie	2b	B	++
▪ Palpation	2b	B	++
▪ Mammographie	2b	B	++
▪ MRT	2b	B	+
▪ PET(-CT)	2b	B	+/-
▪ Prätherapeutische Markierung der Tumorregion	5	D	++
▪ Prätherapeutische Markierung des pN+	2a	B	+*

*Studienteilnahme empfohlen (AXSANA /Eubrest 3 – Studie)

Breast ultrasound

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

Palpation

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

Mammography

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

MRI

1. Javid S, et al. Can breast MRI predict axillary lymph node metastasis in women undergoing neoadjuvant chemotherapy. *Ann Surg Oncol* 2010; 17; 1841
2. Morrow M, et al. MRI for breast cancer screening, diagnosis, and treatment. *Lancet* 2011; 378; 1804
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PET(-CT)

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2. Coudert B, et al. Use of [(18)F]-FDG PET to predict response to neoadjuvant trastuzumab and docetaxel in patients with HER2-positive breast cancer, and addition of bevacizumab to neoadjuvant trastuzumab and docetaxel in [(18)F]-FDG PET-predicted non-responders (AVATAXHER): an open-label, randomised phase 2 trial. *Lancet Oncol* 2014; 15; 1493
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Clip pN+

1. Caudle AS, Yang WT, Krishnamurthy S et al.: Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection. *J Clin Oncol*. 2016;34(10):1072-8.
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4. Simons JM, et al. Diagnostic Accuracy of Different Surgical Procedures for Axillary Staging After Neoadjuvant Systemic Therapy in Node-positive Breast Cancer: A Systematic Review and Metaanalysis. *Ann Surg Oncol* 2018 Oct 11. doi: 10.1097/SLA.0000000000003075. [Epub ahead of print]
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Neoadjuvante zielgerichtete Therapie bei HER2-positiven Tumoren

	Oxford		
	LoE	GR	AGO
▪ Pertuzumab + Trastuzumab in Kombination mit Chemotherapie (high-risk bei cT2-4 und/oder cN+)	2b	B	++
▪ Trastuzumab in Kombination mit Standard-Kombinations-Chemotherapie (low-risk)*	1b	A	+
▪ HER2 gerichtete Substanzen ohne Chemotherapie	2b	B	+/-**

* Studienteilnahme empfohlen
 ** Trastuzumab + Monochemotherapie bevorzugt in der adjuvanten Therapie einzusetzen

Pertuzumab + Trastuzumab in combination with chemotherapy

1. Gianni L, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2012; 13; 25-32
2. Schneeweiss A, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Annals Oncol* 2013; 24; 2278-84
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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]

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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.

Trastuzumab in combination with chemotherapy

1. Gianni L, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet* 2010: 375; 377
2. Untch M, et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. *J Clin Oncol* 2011: 29; 3351
3. Gianni L, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet Oncol* 2014: 15; 640
4. De Azambuja E, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. *Lancet Oncol* 2014: 15; 1137
5. Jackisch C, et al. HannaH phase III randomised study: Association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. *Eur J Cancer*. 2016 Jul;62:62-

Anti-HER2 agents without chemotherapy

1. Gianni L, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012: 13; 25-32
2. 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

3. 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

Neoadjuvante Chemotherapie – Vorgehen je nach Ansprechen

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

Completion of neoadjuvant chemotherapy

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

In case of no change:

Completion of NACT, followed by surgery

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

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

Continuation of NST with non-cross-resistant regimen

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

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

DAC2x -> NX x 4

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

In case of progressive disease:

Stop of NACT and immediate surgery or radiotherapy

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

Additional adjuvant chemotherapy with non-cross-resistant regimen

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

Axilläre operative Interventionen bei NACT						Oxford		
						LoE	GR	AGO
SLNE nach NACT						2b	B	++
SLNE vor NACT						2b	B	-
cN Status (vor NACT)	pN Status (vor NACT)	cN Status (nach NACT)	Axilläre operative Intervention (nach NACT)	pN Status (nach NACT und Operation)	Operative Konsequenz aus Metastasefund			
cN0	---	ypN0	SLNE alleine	ypN0 (n)	---	2b	B	++***
				ypN0 (n)	ALND	2b	C	= (n?) bei (n)
				ypN1-2a (n)	Keine**	5	D	+/-
				ypN0 (n)	ALND	2b	C	++
cN+	pN1-2a	ypN0	SLNE alleine* TAD (TUNE + SLNE)* ALND*	ypN0	---	2b	B	+/-***
				ypN0	ALND	2b	B	++***
				ypN0	ALND	2b	B	++***
				ypN+ inkl. ypN0 (n)	ALND	2b	B	= (n?) bei (n)
cN+	pN1-2a	ypN+	ALND	ypN+	---	2b	B	++
				n.d.	Keine**	5	D	-
				ALND	ypN+ inkl. ypN0 (n)	---	2b	B
cN+	pN1-2a	ypN+	Keine	n.d.	Keine**	5	D	-

AGO e. V.
in der DGO e. V.
sowie
in der DKG e. V.
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EVIDENZ-
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BREUSTEN

*Studienbeteiligung an Axilla empfohlen; ** = Empfehlungen Kapitel Strahlentherapie, alleinige Radio bei ypN0(n), ypN+ nicht empfohlen ;
*** Empfehlungsgrad bezieht sich auf Staging bei cN0 und cN+ ypN0

Complete Axillary lymph node dissection after positive sentinel lymph node may be omitted in certain cases due to lack of benefit in prospectively randomized studies

1. Reimer T, Gerber B. Quality-of-life considerations in the treatment of early-stage breast cancer in the elderly. *Drugs Aging*. 2010 Oct 1;27(10):791-800.
2. Tuttle TM, Shamliyan T, Virnig BA, et al. The impact of sentinel lymph node biopsy and magnetic resonance imaging on important outcomes among patients with ductal carcinoma in situ. *J Natl Cancer Inst Monogr*. 2010;2010(41):117-20. Review.
3. Gerber B, Heintze K, Stubert J, et al. Axillary lymph node dissection in early-stage invasive breast cancer: is it still standard today? *Breast Cancer Res Treat*. 2011 Aug;128(3):613-24.
4. D'Angelo-Donovan DD, Dickson-Witmer D, Petrelli NJ. Sentinel lymph node biopsy in breast cancer: A history and current clinical recommendations. *Surg Oncol*. 2012 Jan 9.
5. Galimberti V, Cole BF, Zurrada S, et al. International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol*. 2013 Apr;14(4):297-305.
6. 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 Sep 12;318(10):918-926.

Statement surgical intervention in the axilla before or after neoadjuvant chemotherapy

1. Kuehn T, Bauerfeind I, Fehm T, et al.: Sentinel-lymph-node biopsy with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective multi-center cohort study. *Lancet Oncol* 2013;14(7):609-18.
2. Boughey JC, Suman VJ, Mittendorf EA, et al.: Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA* 2013;310(14):1455-61.
3. Fu JF, Chen HL, Yang J, et al. Feasibility and accuracy of sentinel lymph node biopsy in clinically node-positive breast cancer after neoadjuvant chemotherapy: a meta-analysis. *PLoS One*. 2014 Sep 11;9(9):e105316
4. Lee HD, Ahn SG, Lee SA, et al. Prospective Evaluation of the Feasibility of Sentinel Lymph Node Biopsy in Breast Cancer Patients with Negative Axillary Conversion after Neoadjuvant Chemotherapy. *Cancer Res Treat*. 2014 Aug 29. doi: 10.4143/crt.2013.208. [Epub ahead of print]
5. Boileau JF, Poirier B, Basik M, et al. Sentinel Node Biopsy After Neoadjuvant Chemotherapy in Biopsy-Proven Node-Positive Breast Cancer: The SN FNAC Study. *J Clin Oncol*. 2015;33(3):258-264.
6. Boughey JC, Ballman KV, Le-Petross HAT et al. Identification and Resection of Clipped Node Decreases the False-negative Rate of Sentinel Lymph Node Surgery in Patients Presenting With Node-positive Breast Cancer (T0-T4, N1-N2) Who Receive Neoadjuvant Chemotherapy: Results From ACOSOG Z1071 (Alliance). *Ann Surg*. 2015 Nov 26. [Epub ahead of print]
7. Ryu JM, Lee SK, Kim JY, et al. Predictive Factors for Nonsentinel Lymph Node Metastasis in Patients With Positive Sentinel Lymph Nodes After Neoadjuvant Chemotherapy: Nomogram for Predicting Nonsentinel Lymph Node Metastasis. *Clin Breast Cancer*. 2017 Nov;17(7):550-55
8. Galimberti V, Ribeiro Fontana SK, Maisonneuve P. Sentinel node biopsy after neoadjuvant treatment in breast cancer: five-year follow-up of patients with clinically node-negative or node-positive disease before treatment. *Eur J Surg Oncol* 2016;42(3) 361-8
9. Martelli G, Miceli R, Folli S, et al. Sentinel node biopsy after primary chemotherapy in cT2 N0/1 breast cancer patients: Long-term results of a retrospective study. *Eur J Surg Oncol*. 2017 Nov;43(11):2012-2020.
10. Palmer JAV, Flippo-Morton T, Walsh KK, et al. Application of ACOSOG Z1071: Effect of Results on Patient Care and Surgical Decision-Making. *Clin Breast Cancer*. 2017 Oct 12. pii: S1526-8209(17)30492-5.
11. Fernandez-Gonzalez S, Falo C, Pla MJ, 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*. 2017 Sep 4. pii: S1526-8209(17)30565-7. doi: 10.1016/j.clbc.2017.08.014. [Epub ahead of print]

12. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. Classe JM, Loaec C, Gimbergues P et al. *Breast Cancer Res Treat* 2018; doi.org/10.1007/s10549-5004-7
13. Kahler-Ribeiro-Fontana S, Pagan E, Magnoni F, et al.: Long-term standard sentinel node biopsy after neoadjuvant treatment in breast cancer: a single institution ten-year follow-up, *Eur J Surg Oncol*. 2020 Oct 15;S0748-7983(20)30846-5.

Axillary intervention after PST

1. Tee SR, Devane LA, Evoy D et al. Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. *Br J Surg*. 2018 Nov;105(12):1541-1552.
2. Balic M, Thomssen C, Würstlein R, Gnant M, Harbeck N. St. Gallen/Vienna 2019: A Brief Summary of the Consensus Discussion on the Optimal Primary Breast Cancer Treatment. *Breast Care (Basel)*. 2019 Apr;14(2):103-110.
3. Classe JM, Loaec C, Gimbergues P et al. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. *Breast Cancer Res Treat*. 2019 Jan;173(2):343-352.
4. Moo TA, Edelweiss M, Hajiyeva S, et al. Is Low-Volume Disease in the Sentinel Node After Neoadjuvant Chemotherapy an Indication for Axillary Dissection? [published correction appears in *Ann Surg Oncol*. 2020 Feb 21;:]. *Ann Surg Oncol*. 2018;25(6):1488–1494.

TAD (+SLNE) after PST, if pN1 (CNB prior to PST and ycN0

1. Allweis TM, Menes T, Rotbart N et al. Ultrasound guided tattooing of axillary lymph nodes in breast cancer patients prior to neoadjuvant therapy, and identification of tattooed nodes at the time of surgery. *Eur J Surg Oncol*. 2019 Nov 16. pii: S0748-7983(19)31445-3.
2. Balasubramian R, Morgan C, Shaari E et al. Wire guided localisation for targeted axillary node dissection is accurate in axillary staging in node positive breast cancer following neoadjuvant chemotherapy. *Eur J Surg Oncol*. 2019 Dec 11. pii: S0748-7983(19)31500-8.
3. Coufal O, Zapletal O, Gabrielová L et al. Targeted axillary dissection and sentinel lymph node biopsy in breast cancer patients after neoadjuvant chemotherapy - a retrospective study. *Rozhl Chir*. Winter 2018;97(12):551-557.
4. Ditsch N, Rubio IT, Gasparri ML et al.. Breast and axillary surgery in malignant breast disease: a review focused on literature of 2018 and 2019. *Curr Opin Obstet Gynecol*. 2020 Feb;32(1):91-99.
5. Flores-Funes D, Aguilar-Jiménez J, Martínez-Gálvez M et al. Validation of the targeted axillary dissection technique in the axillary staging of breast cancer after neoadjuvant therapy: Preliminary results. *Surg Oncol*. 2019 Sep;30:52-57. doi: 10.1016/j.suronc.2019.05.019

6. Gandhi A, Coles C, Makris A et al. Axillary Surgery Following Neoadjuvant Chemotherapy - Multidisciplinary Guidance From the Association of Breast Surgery, Faculty of Clinical Oncology of the Royal College of Radiologists, UK Breast Cancer Group, National Coordinating Committee for Breast Pathology and British Society of Breast Radiology. *Clin Oncol (R Coll Radiol)*. 2019 Sep;31(9):664-668.
7. García-Moreno JL, Benjumeda-Gonzalez AM, Amerigo-Góngora M et al. Targeted axillary dissection in breast cancer by marking lymph node metastasis with a magnetic seed before starting neoadjuvant treatment. *J Surg Case Rep*. 2019 Dec 4;2019(11):rjz344.
8. Greenwood HI, Wong JM, Mukhtar RA et al. Feasibility of Magnetic Seeds for Preoperative Localization of Axillary Lymph Nodes in Breast Cancer Treatment. *AJR Am J Roentgenol*. 2019 Oct;213(4):953-957.
9. Hellingman D, Donswijk ML, Winter-Warnars GAO et al. Feasibility of radioguided occult lesion localization of clip-marked lymph nodes for tailored axillary treatment in breast cancer patients treated with neoadjuvant systemic therapy. *EJNMMI Res*. 2019 Oct 24;9(1):94.
10. Kanesalingam K, Sriram N, Heilat G et al. Targeted axillary dissection after neoadjuvant systemic therapy in patients with node-positive breast cancer. *ANZ J Surg*. 2019 Dec 17. doi: 10.1111/ans.15604.
11. Natsiopoulos I, Intzes S, Liappis T et al. Axillary Lymph Node Tattooing and Targeted Axillary Dissection in Breast Cancer Patients Who Presented as cN+ Before Neoadjuvant Chemotherapy and Became cN0 After Treatment. *Clin Breast Cancer*. 2019 Jun;19(3):208-215.
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 Mar;269(3):432-442.
13. Simons JM, van Pelt MLMA, Marinelli AWKS et al. Excision of both pretreatment marked positive nodes and sentinel nodes improves axillary staging after neoadjuvant systemic therapy in breast cancer. *Br J Surg*. 2019 Nov;106(12):1632-1639.
14. Tee SR, Devane LA, Evoy D et al. Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. *Br J Surg*. 2018 Nov;105(12):1541-1552
15. Lee J, Jung JH, Kim WW, et al: 5-year oncological outcomes of targeted axillary sampling in pT1-2N1 breast cancer. *Asian J Surg* 2019 Jun;42(6):681-687. doi: 10.1016/j.asjsur.2018.10.004. Epub 2018 Nov 22.
16. Simons J, v Nijnatten JA, Koppert LB, et al: Radioactive Iodine Seed placement in the Axilla with Sentinel lymph node biopsy after neoadjuvant chemotherapy in breast cancer: Results of the prospective multicenter RISAS trial. *SABCS 2020, GS1-10*

ypN0 (i+)

Wong SM , 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 Oct;26(11):3502-3509.

Neoadjuvante systemische Therapie Lokoregionäre Operation (Mamma)

	Oxford		
	LoE	GR	AGO
▪ Frühzeitige Markierung des Tumors mit exakter topographischer Dokumentation	5	D	++
▪ Resektion des Tumors / repräsentative Exzision des posttherapeutischen, markierten Tumorareals	2b	C	++
▪ Exzision in neuen Tumorgrenzen	2b	C	++
▪ Freie Resektionsränder	2a	B	++

Mark previous tumor region

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

Surgery

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

Microscopically clear margins

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

Tumor resection according to imaging result

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

Neoadjuvante systemische Therapie Indikationen für Mastektomie

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

Positive margins after repeated excisions

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

Radiotherapy not feasible

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

In case of clinical complete response:

Inflammatory breast cancer in case of pCR

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

Multicentric lesions

1. Ataseven B, et al. Impact of Multifocal or Multicentric Disease on Surgery and Locoregional, Distant and Overall Survival of 6,134 Breast Cancer Patients Treated With Neoadjuvant Chemotherapy. Ann Surg Oncol 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

Neoadjuvante systemische Therapie Zeitablauf von Diagnosestellung, Operation und Radiotherapie

	Oxford		
	LoE	GR	AGO
Therapiebeginn der NACT <ul style="list-style-type: none"> Therapieverzögerungen (> 60 Tage) führen zu einer Prognoseverschlechterung 	2b	B	
Zeitpunkt der Operation nach NACT <ul style="list-style-type: none"> 4-8 Wochen nach dem letzten Chemotherapiezyklus 	2b	B	++
Radiotherapie innerhalb von 2 Monaten nach der Operation	2b	B	++

Initiation of chemotherapy after histologic diagnosis

- de Melo Gagliato D, Lei X, Giordano SH, Valero V, Barcenas CH, Hortobagyi GN, Chavez-MacGregor M. 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

- 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.
- 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. doi: 10.1159/000504964.
- 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. doi: 10.1016/j.clinimag.2020.10.043.

Radiotherapy 2 mths after surgery BCS

- Silva SB, Pereira AAL, Marta GN, de Barros Lima KML, de Freitas TB, Matutino ARB, de Azevedo Souza MCL, de Azevedo RGMV, de Viveiros PAH, da Silva Lima JM, Filassi JR, de Andrade Carvalho H, Piatto JRM, Mano MS. Clinical impact of adjuvant radiation therapy

delay after neoadjuvant chemotherapy in locally advanced breast cancer. *Breast*. 2018;38:39-44. doi: 10.1016/j.breast.2017.11.012.



Neoadjuvante endokrine Therapie (NET) - Gute klinische Praxis -

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

1. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009; 18; 339
2. 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
3. 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
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.
5. 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
6. 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
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. Ian Smith 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
9. 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 23;12:1758835920973130
10. Harbeck N. Risk-adapted adjuvant therapy of luminal early breast cancer in 2020. *Curr Opin Obstet Gynecol.* 2021 Feb 1;33(1):53-58.

NET bei Patienten mit endokrin-sensitivem Mammakarzinom

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> • Postmenopausale Patienten <ul style="list-style-type: none"> • Verbessert die Optionen für brusterhaltende Operationen • Aromataseinhibitoren (mindestens 6 Monate) • Aromataseinhibitor + Lapatinib (HER2+ Mammakarzinom) 	1b	A	+
	1a*	B	+
	2b	B	+/-
<ul style="list-style-type: none"> • Prämenopausale Patientinnen <ul style="list-style-type: none"> • Tamoxifen • Aromataseinhibitoren + LHRHa 	2b	C	+
	1b	C	+/-
<ul style="list-style-type: none"> • Simultane chemo-endokrine Therapie 	1b	A	-
<ul style="list-style-type: none"> • Präoperative ET (Tam/AI) mit KI-67 Bestimmung nach 2-4 Wochen (prognostische/prädiktive Evaluation) 	1b	B	+
<ul style="list-style-type: none"> • Prognostischer Score: <ul style="list-style-type: none"> • PEPI: pTN-Stadium, ER-Expression und KI-67 Expression nach neoadjuvanter endokriner Therapie 	1b	B	+

* Keine Langzeitergebnisse zur neoadjuvanter endokriner Therapie (vs. adjuvanter endokriner Therapie)

Postmenopausal patients:

Aromatase inhibitors (for up to 6 months)

1. Smith I, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol 2005; 23; 5108
2. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009; 18; 339
3. Ellis MJ, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype--ACOSOG Z1031. J Clin Oncol 2011; 29; 2342
4. Spring LM et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA oncology 2016;2(11):1477-86.
5. Madigan LI et al. Neoadjuvant endocrine therapy in locally advanced estrogen and progesterone receptor-positive breast cancer: 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 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; 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, et al. 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. Ian Smith 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
2. 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;23(12):1758835920973130
3. Harbeck N. Risk-adapted adjuvant therapy of luminal early breast cancer in 2020. *Curr Opin Obstet Gynecol*. 2021 Feb 1;33(1):53-58.

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.

Postneoadjuvante Therapie HER2-negativ

	Oxford		
	LoE	GR	AGO
HR positiv (pCR und non-pCR)			
• Endokrine Therapie nach Menopausenstatus (s. Kap. 10)	1a	A	++
• Capecitabin (bei non-pCR)	3b	C	+/-
• Endokrine Therapie + Abemaciclib	2b	B	+/-*
• Endokrine Therapie + Palbociclib	1b*	B	-*
Triple negative (TNBC) (bei non-pCR)			
• Capecitabin (bis zu 8 Kurse)**	1b	B	+
• Experimentelle postneoadjuvante Therapien innerhalb von Studien	S	D	+*

* Studienteilnahme empfohlen
 ** Studientage ohne platinbasierte Vortherapie

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.
3. 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.
4. Mayer EL, Gnant MI, DeMichele A et al. PALLAS: A randomized phase III trial of adjuvant palbociclib with endocrine therapy versus endocrine therapy alone for HR+/HER2- early breast cancer. Ann Oncol (2020) 31 (suppl_4): S1142-S1215. 10.1016/annonc/annonc325
5. Loibl S, Marmé F, Martin M et al. Phase III study of palbociclib combined with endocrine therapy (ET) in patients with hormone-receptor-positive (HR+), HER2-negative primary breast cancer and with high relapse risk after neoadjuvant chemotherapy (NACT): First results from PENELOPE-B. SABCS 2020: GS1-02.

Statement Tripel negativ (TNBC) (bei non-pCR) Capecitabine (8 Kurse)

1. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med. 2017 Jun

1;376(22):2147-2159.

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)



Postneoadjuvant treatment with CDK 4/6i

	MonarchE	PALLAS	Penelope ^a
N	5637	5600	1250
CDK	Abemaciclib	Palbociclib	Palbociclib
% of pts with NACT	87%	n.r.	100%
Duration of CDK 4/6i treatment	24 mths	24 mths	12 mths
Follow-up	19 mths	24 mths	43 mths
Discontinuation rate	28%	42%	20%
IDFS-HR (95%-CI)	0.713 (0.583 - 0.871) p = 0.0009	0.93 (0.76-1.15) p = 0.51	0.93 (0.74-1.16) p=0.525
2-yr IDFS	92% vs. 89%	n.r.	88% vs. 84%
3-yr IDFS	n.r.	88% vs. 89%	81% vs. 78%
4-yr IDFS	n.r.	n.r.	73% vs. 72%

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IDFS: invasive disease-free survival

1. 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.
2. Mayer EL, Gnant MI, DeMichele A et al. PALLAS: A randomized phase III trial of adjuvant palbociclib with endocrine therapy versus endocrine therapy alone for HR+/HER2- early breast cancer. Ann Oncol (2020) 31 (suppl_4): S1142-S1215. 10.1016/annonc/annonc325
3. Loibl S, Marmé F, Martin M et al. Phase III study of palbociclib combined with endocrine therapy (ET) in patients with hormone-receptor-positive (HR+), HER2-negative primary breast cancer and with high relapse risk after neoadjuvant chemotherapy (NACT): First results from PENELOPE-B. SABCs 2020: GS1-02.

Postneoadjuvante Therapie HER2-positiv

	Oxford		
	LoE	GR	AGO
pCR			
• Low risk: Trastuzumab (bis 12 Mon. komplett)	2a	C	++
• High risk (cN+): Trastuzumab + Pertuzumab (bis 12 Mon. komplett)	2b	C	+
• Neratinib nach 1 Jahr* Trastuzumab (HR-positiv)*	2b	B	-
non-pCR			
• T-DM1	1b	B	+
• Neratinib nach 1 Jahr* Trastuzumab (HR-positiv)	2b	B	+/-
• Trastuzumab + Pertuzumab (bis 12 Mon. komplett)	2b	C	+/-
* kombiniert mit Standard endokriner Therapie			

Statement HER2 positiv (bei pCR):

1. Goldhirsch A et al.; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. *Lancet*. 2013;382(9897):1021-8.
2. 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.
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. 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.

Statement HER2 positiv (bei non-pCR) :

1. von Minckwitz G, Huang CS, Mano MS et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med*. 2018 Dec 5. doi: 10.1056/NEJMoa1814017.
2. 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

3. 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.