


Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Neoadjuvant (Primary) Systemic Therapy



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Neoadjuvant Systemic Therapy

- **Versions 2002–2019:**
 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 2020:**
 Jackisch / Schneeweiss


Systematic review of published evidence

PUBMED 1999-2020

ASCO 1999-2019

SABCS 1999-2019

ECCO/ESMO 1999-2019

Subtype-specific Strategies for Systemic Treatment	
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	If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred
	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 therapy ++
	HER2+
	▪ Trastuzumab (plus Pertuzumab in N+ or NST) ++
	▪ Sequential A/T-based regimen with concurrent T + anti-HER2 therapy ++
	▪ Anthracycline-free, platinum-containing regimen +
	▪ Anthracycline-free, taxane-containing regimen +
	Triple-negative (TNBC)
	▪ Conventionally dosed AT-based chemotherapy +
	▪ Dose dense chemotherapy (AT - based including weekly schedule) ++
	▪ Neoadjuvant platinum-containing chemotherapy +


Systematic review of published evidence

PUBMED 1999-2010

ASCO 1999-2019

SABCS 1999-2019

ECCO/ESMO 1999-2019

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	<p>Adjuvant Therapy: low risk of recurrence Rezidivrisiko Paclitaxel_{weekly x 12} + Trastuzumab¹</p> <ul style="list-style-type: none"> elderly or fragile patients or pT1, pN0 <p>Adjuvant Therapy: high risk of recurrence CHT + Trastuzumab + Pertuzumab²</p> <ul style="list-style-type: none"> Node-positive (pN+) Irrespective of ER-status⁵ 	<p>Neoadjuvant Therapy³ Trastuzumab + Pertuzumab</p> <ul style="list-style-type: none"> Node-positive (cN+/pN+) or cT ≥ 2 	<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 NST - Irrespective of ER-status <p>In case of non-pCR:</p> <ul style="list-style-type: none"> T-DM1
	<p style="text-align: center;">Total duration of anti-HER2-therapy: 1 year</p> <p style="font-size: small;">1. Tolane 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)</p>		

1. Tolane 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)

Neoadjuvant Systemic Chemotherapy Clinical Benefit			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Leads to improvement of prognosis by individualization of post-neoadjuvant therapy 	1b	A	
<ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> Pathological complete response is associated with improved survival 	1b	A	
<ul style="list-style-type: none"> Can achieve operability in primary inoperable tumors 	1b	A	
<ul style="list-style-type: none"> Improved options for breast conserving surgery 	1b	A	
<ul style="list-style-type: none"> Decreases rate of axillary lymph node dissection 	3b	C	
<ul style="list-style-type: none"> Allows individualization of therapy according to mid-course treatment effect 	1b	B	

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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. Cortazar P, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014: 384; 164
3. 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
4. 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]

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.

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

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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

Neoadjuvant Systemic Chemotherapy Response Prediction I				
Factor	LoE _{Ox2} 001	CTS	GR	AGO
• Young age	1a	B	A	+
• cT1 / cT2 tumors o. N0 o. G3	1a	B	A	++
• Negative hormone receptor status	1a	B	A	++
• ER+ and negative PgR-status	2a	B	B	++
• Triple negative breast cancer	1a	B	A	++
• Positive HER2 status	1a	B	A	++
• Non-lobular tumor type	1a	B	A	+
• Early clinical response	1b	B	A	+

Young age

1. von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145
2. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010: 124; 133
3. Loibl S, et al. Outcome after neoadjuvant chemotherapy in young breast cancer patients: a pooled analysis of individual patient data from eight prospectively randomized controlled trials. Breast Cancer Res Treat. 2015;152(2):377-87.

cT1 / cT2 tumors o. N0 o. G3

1. von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145
2. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010: 124; 133

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

Negative ER and PgR status

1. von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145
2. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010: 124; 133
3. Loibl S, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014: 144; 153
4. van Mackelenbergh MT, 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 2018 Jan;167(1):59-71

Triple negative breast cancer (TNBC)

1. von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145
2. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010: 124; 133
3. Loibl S, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014: 144; 153

Positive HER2 status

1. von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of

the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145


2. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010: 124; 133
3. Loibl S, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014: 144; 153

Non-lobular tumor type

1. von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145
2. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010: 124; 133
3. Loibl S, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014: 144; 153

Early clinical response

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. von Minckwitz G, et al. Response-guided neoadjuvant chemotherapy for breast cancer. J Clin Oncol. 2013;31(29):3623-30

<div>  <h2>Neoadjuvant Systemic Therapy Response Prediction II</h2> </div>				
Factor	LoE ₂₀₀₉	CTS	GR	AGO
▪ Multigene signatures	III	C	B	+/-
▪ Ki-67	I	B	A	+
▪ Tumor infiltrating lymphocytes*	I	B	B	+
▪ PIK3CA mutation in HER2 positive BC	I	B	B	+/-
▪ gBRCA	II	B	B	+
▪ Homologous recombination deficiency	IV	C	C	+/-

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* LPBC is defined as dense lymphocytic infiltration of inner peritumoral stroma outside of invasion front
 (> 50% of stromal area are covered by lymphocytes)

Multigene signature

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, JCOm 32:
2. Masuda H, et al. Differential response to neoadjuvant chemotherapy among 7 triple-negative breast cancer molecular subtypes. Clin Cancer Res 2013; 19; 5533-40
3. Stover DG, Coloff JL, Barry WT et al.: Role of Proliferation in Determining Response to Neoadjuvant Chemotherapy in Breast Cancer: A Gene Expression-Based Meta-Analysis. Clin Cancer Res. 2016 Dec 15;22(24):6039-6050
4. Ali HR, Chlon L, Pharoah PD et al.: Patterns of Immune Infiltration in Breast Cancer and Their Clinical Implications: A Gene-Expression-Based Retrospective Study. PLoS Med. 2016 Dec 13;13(12):e1002194. doi: 10.1371/journal.pmed.1002194
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.

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. Spugnese 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

Neoadjuvant Systemic Chemotherapy Recommended Regimens and Schedules			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Standard protocols used in the adjuvant setting with a duration of at least 18 weeks* 	1a	A	++
<ul style="list-style-type: none"> Taxane followed by anthracycline 	1a	A	+
<ul style="list-style-type: none"> Platinum in TNBC (irrespective of BRCA status) 	1a	B	+
<ul style="list-style-type: none"> Nab-Paclitaxel weekly instead of Paclitaxel weekly 	1b	B	+

* See chapter Adjuvant Chemotherapy



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Standard regimens used in the adjuvant setting with a duration of at least 18 weeks

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

AC or EC → D q3w or P q1w

1. 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
2. von Minckwitz G, et al. Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARDUO study of the German Breast Group. J Clin Oncol 2005; 23; 2676
3. Gray R, et al. Increasing the dose intensity of adjuvant chemotherapy: an EBCTCG meta-analysis. SABCS 2017 (abs GS1-01)

Taxane followed by anthracycline sequence

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

Platinum in TNBC (irrespective of BRCA status)


1. Alba E, et al. A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from the GEICAM/2006-03, multicenter study. Breast Cancer Res Treat 2012: 136; 487
2. Von Minckwitz G, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol 2014: 15; 747
3. Ando M, et al. Randomized phase II study of weekly paclitaxel with and without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA breast cancer without HER2 overexpression. Breast Cancer Res Treat 2014: 145; 401
4. Petrelli F, et al. The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat 2014: 144; 223
5. Sikov WM, et al. Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance). J Clin Oncol 2015: 33; 13
6. Byrski T, et al. Pathologic complete response to neoadjuvant cisplatin in BRCA1-positive breast cancer patients. Breast Cancer Res Treat 2014: 147; 401
7. Sikov WM, Berry DA, Perou CM, et al: Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week

Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance). J Clin Oncol, 2014

8. Loibl S, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. Lancet Oncol. 2018;19(4):497-509.
9. Loibl S et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. Ann Oncol 2018;29(12):2341-2347

Nab-Paclitaxel weekly instead of Paclitaxel weekly

1. M Untch et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto—GBG 69): a randomised, phase 3 trial. Lancet Oncol. 2016 Mar;17(3):345-56
2. Gianni L, et al. Comparing Neoadjuvant Nab-paclitaxel vs Paclitaxel Both Followed by Anthracycline Regimens in Women With ERBB2/HER2-Negative Breast Cancer-The Evaluating Treatment With Neoadjuvant Abraxane (ETNA) Trial: A Randomized Phase 3 Clinical Trial. JAMA Oncol 2017; 4: 302-08
3. Futamura M, et al. Preoperative neoadjuvant chemotherapy using nanoparticle albumin-bound paclitaxel followed by epirubicin and cyclophosphamide for operable breast cancer: a multicenter phase II trial. Breast Cancer. 2017 Jan 3. doi:
4. Zong Y, et al. Nanoparticle albumin-bound paclitaxel as neoadjuvant chemotherapy of breast cancer: a systematic review and meta-analysis. Oncotarget 8(10):17360-17372, 2017
5. Schneeweiss A, et al. Survival analysis of the prospectively randomized phase III GeparSepto trial comparing neoadjuvant chemotherapy with weekly nab-paclitaxel with solvent-based paclitaxel followed by anthracycline/cyclophosphamide for patients with early breast cancer – GBG69. SABCS 2017 (abs GS3-05)
6. Untch M et al. Comparing Neoadjuvant Nab-paclitaxel vs Paclitaxel Both Followed by Anthracycline Regimens in Women With ERBB2/HER2-Negative Breast Cancer-The Evaluating Treatment With Neoadjuvant Abraxane (ETNA) Trial: A Randomized Phase 3 Clinical Trial. J Clin Oncol 2019 in press



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Neoadjuvant Systemic Therapy

Recommended Methods of Monitoring of Response

	Oxford		
	LoE	GR	AGO
▪ Breast ultrasound	2b	B	++
▪ Palpation	2b	B	++
▪ Mammography	2b	B	++
▪ MRI	2b	B	+
▪ PET(-CT)	2b	B	+/-
▪ Clip tumor region	5	D	++
▪ Clip placement in pN+	3	C	+/-

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

Breast ultrasound

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. 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
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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
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PET(-CT)

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Clip tumour region

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Neoadjuvant Targeted Therapy in HER2 Positive Tumors

	Oxford	
	LoE	GR
		AGO
■ Trastuzumab in combination with chemotherapy	1b	A
■ Pertuzumab + trastuzumab in combination with chemotherapy	2b	B
■ Two anti-HER2 agents without chemotherapy	2b	B
		++
		++
		+/-

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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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
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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
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3. Nagayama A, et al. Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis. *J Natl Cancer Inst* 2014; 106(9): in print
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)
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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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Lapatinib in combination with chemotherapy

1. Untch M et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial. *Lancet Oncol* 2012; 13; 135 - 144
2. Robidoux A, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013; 14; 1183-1192
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4. Bonnefoi H, et al. Neoadjuvant treatment with docetaxel plus lapatinib, trastuzumab, or both followed by an anthracycline-based chemotherapy in HER2-positive breast cancer: results of the randomised phase II EORTC 10054 study. *Ann Oncol* 2014 [Epub ahead of print]
5. Nagayama A, et al. Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis. *J Natl Cancer Inst* 2014; 106(9): [Epub ahead of print]

Lapatinib + Trastuzumab in combination with chemotherapy


1. Robidoux A, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013; 14; 1183-1192
2. 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
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4. Nagayama A, et al. Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis. *J Natl Cancer Inst* 2014; 106(9): [Epub ahead of print]

Two 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

Anti-HER2 agent in combination with endocrine treatment

1. Rimawi MF, et al. SABCS 2014 (S6-02)
2. Guarneri V, et al. Double-blind, placebo-controlled, multicenter, randomized, phase IIb neoadjuvant study of letrozole-lapatinib in postmenopausal hormone receptor-positive, human epidermal growth factor receptor 2-negative, operable breast cancer. *J Clin Oncol* 2014; 32; 1050
3. Gianni L Neoadjuvant treatment with trastuzumab and pertuzumab plus palbociclib and fulvestrant in HER2-positive, ER-positive breast cancer (NA-PHER2): an exploratory, open-label, phase 2 study. *Lancet Oncol.* 2018 Feb;19(2):249-256.


 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	Neoadjuvant Systemic Therapy Procedures in Case of Early Response		
	Oxford		
	LoE	GR	AGO
In case of early response following 6 to 12 weeks of neoadjuvant chemotherapy:			
▪ Complete all chemotherapy before surgery i.e. ≥ 18 weeks of treatment	1b	A	++
▪ In case of response after 2 cycles of TAC in HR positive breast cancer consider 8 instead of 6 cycles of TAC	2b	C	+

Complete all chemotherapy before surgery i.e. ≥ 18 weeks of treatment

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 response after 2 cycles of DAC in HR positive breast cancer consider 8 instead of 6 cycles of DAC

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

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

In case of no change:

Completion of NST, 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

DAC x 2 → 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 NST 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
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Axillary Interventions in NST				Oxford		AGO
				LoE	GR	
SLNE following NST				2b	B	++
SLNE prior NST				2b	B	+/-
Further surgical procedures depending on SLNE status						
cN-status (before NST)	pN-status (before NST)	N-status (after NST)	Surgical Procedure (after NST)			
cN0	pN0(sn)	ycN0	None	1a	A	+
cN0	pN+(sn) according to ACOSOG Z0011	ycN0	None	1b	B	+
cN0	pN+(sn) not according to ACOSOG Z0011	ycN0	ALND or Axillary RT	2b	B	+
cN0	Not done	ypN0 (sn)	SLNE only	2b	B	++
		ypN1 _{mic} (sn)	ALND Axillary RT	2b 5	C D	++ +/-
		ypN1 (sn)	ALND Axillary RT	2b 5	C D	++ +/-
cN+	pN+ _{CNB}	ycN0	SLNE only*	2b	B	+/-
			TAD (TLNE + SLNE)*	2b	B	+
			ALND*	2b	B	+
cN+	pN+ _{CNB}	ycN+	ALND	2	B	++
			Axillary RT	5	D	-

NST=Neoadjuvant Systemic Therapy; ALND=Axillary Lymph Node Dissection; SLNE=Sentinel Lymph Node Excision;
TAD=Targeted Axillary Dissection; TLNE=Targeted Lymph Node Excision; RT=Radiotherapy – *Trial participation recommended

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

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.


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.
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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.
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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.
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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



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Neoadjuvant Systemic Therapy

Loco-regional Surgery

Oxford		
LoE	GR	AGO
5	D	++
2b	C	++
2	B	++
2	B	+

- **Clip tumor region before NST**
- **Appropriate surgery following NST**
- **Microscopically clear margins**
- **Tumor resection according to most recent imaging result**

Mark previous tumor region

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. Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. Cancer 2010; 116: 1184
3. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012; 19: 1508

Surgery

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. Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. Cancer 2010; 116: 1184

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

Microscopically clear margins

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. Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. Cancer 2010: 116; 1184
3. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

Tumor resection according to imaging result

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. Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. Cancer 2010: 116; 1184
3. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer.. Ann Surg Oncol 2012: 19; 1508

Sentinel node biopsy (see chapter “Surgery”)


1. Kühn 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
2. Boughhey JC 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

3. Classe JM, Bordes V, Campion L et al.: Sentinel lymph node biopsy after neoadjuvant chemotherapy for advanced breast cancer: results of Ganglion. J Clin Oncol. 2009 Feb 10;27(5):726-32
4. El Hage Chehade H, Headon H, El Tokhy O et al.: Is sentinel lymph node biopsy a viable alternative to complete axillary dissection following neoadjuvant chemotherapy in women with node-positive breast cancer at diagnosis? An updated meta-analysis involving 3,398 patients. Am J Surg. 2016 Nov;212(5):969-981.
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Verzicht auf operative Sanierung nach NACT

1. Yau C et al. SABCS 2019 (abs GS5-01)
2. Radovic M et al. SABCS 2019 (abs GS5-02)
3. Heil J et al. SABCS 2019 (abs GS5-03)
4. Tasulis M et al. SABCS 2019 (abs GS5-04)
5. Basik M et al. SABCS 2019 (abs GS5-05)
6. Vrancken Peeters MTFD et al. SABCS 2019 (abs GS5-06)

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

Positive margins after repeated excisions

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

Radiotherapy not feasible

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

In case of clinical complete response:

Inflammatory breast cancer in case of pCR

1. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and

treatment. Ann Oncol 2011; 22; 515

2. Brzezinska M, Williams LJ, Thomas J et al.: Outcomes of patients with inflammatory breast cancer treated by breast-conserving surgery. Breast Cancer Res Treat 2016;160(3):387-91.

Multicentric lesions

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

	Oxford		
	LoE	GR	AGO
Initiation of therapy Necessary delay of therapy does not impact prognosis (even if > 4 weeks)	2b	B	
Surgery After nadir of leucocyte count (2 to 4 weeks after last course of chemotherapy)	2b	B	++
Radiotherapy within 2–3 months after surgery	2b	B	++

Initiation of therapy after histologic diagnosis

1. Loibl S, et al. Impact in delay of start of chemotherapy and surgery on pCR and survival in breast cancer – a pooled analysis of individual patient data from six prospectively randomized neoadjuvant trials. ASCO 2017 (abs 171)


Surgery after the nadir of the leucocyte count (2 to 4 weeks after last course of chemotherapy)

1. 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.
2. Omarini C, et al. Impact of time to surgery after neoadjuvant chemotherapy in operable breast cancer patients. Eur J Surg Oncol 43(4):613-618, 2017

Radiotherapy after surgery 2–3 weeks after surgery BCS

1. Ring A, et al. Is surgery necessary after complete clinical remission following neoadjuvant chemotherapy for early breast cancer? J Clin Oncol 2003; 21; 4540

2. Daveau C, et al. Is radiotherapy an option for early breast cancers with complete clinical response after neoadjuvant chemotherapy?
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Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer

		Oxford		
		LoE	GR	AGO
■	Postmenopausal patients:			
■	Who are inoperable and cannot / will not receive chemotherapy	2a	B	+
■	Optimizes the option for breast conserving therapy	1b	A	+
■	Aromatase inhibitors (for > 3 months)	1a ^a	B	+
■	Aromatase inhibitor + lapatinib (HER2+ BC)	2b	B	+/-
■	Premenopausal patients			
■	Who are inoperable and cannot / will not receive chemotherapy	5	C	+
■	Tamoxifen	2b	C	+
■	Aromatase inhibitors + LHRHa	1b	C	+/-
■	Concurrent chemo-endocrine therapy	1b	A	-
■	Prognostic score:			
■	PEPI: pTN-Stage, ER expression and Ki-67 expression after neoadjuvant endocrine therapy	1b	B	+
■	^a Optimal duration of neoadjuvant endocrine therapy is unknown. No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)			

Postmenopausal patients:

Who are inoperable and can / will not receive chemotherapy

1. Semiglazov VF, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer 2007: 110; 244

Optimizes the option for breast conserving therapy

Eiermann W, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study. Ann Oncol 2001: 12; 1527

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. Semiglazov VF, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer 2007: 110; 244

3. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009: 18; 339
4. 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

Aromatase inhibitors (for > 3 months)

1. Eiermann W, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study. Ann Oncol 2001: 12; 1527
2. 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
3. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009: 18; 339
4. 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
5. Spring LM, Gupta A, Reynolds KL et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA oncology 2016;2(11):1477-86.

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.

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; 1380
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

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	LoE	GR	AGO
HR-positive (pCR and non-pCR)			
▪ Endocrine therapy according to menopausal status (see. ch. 10)	1a	A	++
▪ Capecitabine (in case of non-pCR)	3b	C	+/-
HER2-positive (in case of pCR)			
▪ Low-risk: Trastuzumab (to complete 12 months)	2a	C	++
▪ High-risk (N+): Trastuzumab + Pertuzumab (to complete 12 months)	2b	C	+
HER2-positive (in case of non-pCR)			
▪ T-DM1	1b	B	+
▪ Neratinib after 1 year* Trastuzumab (HR-positive)	3b	B	+/-
▪ Trastuzumab + Pertuzumab (to complete 12 months)	2b	C	+/-
Triple negative (TNBC) (if non-pCR)			
▪ Capecitabine (up to 8 courses)**	1b	B	+
* in combination with standard endocrine therapy ** without platin based previous therapy			

Statement ER and/or PgR positiv (pCR and non-pCR) Endocrine treatment according to menopausal status (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;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;386(10001):1341-1352.

Statement HER2 positive (after pCR): Low risk: Trastuzumab (to complete 12 mths)

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

Statement HER2 positive (after pCR): High risk (N+) Trastuzumab + Pertuzumab (to complete 12 mths)

1. von Minckwitz G, Procter M, de Azambuja E, et al. APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017 Jul 13;377(2):122-131.

2. Piccart M , Procter M, Fumagalli D et al. Interim overall survival analysis of APHINITY (BIG 4-11): A randomized multicenter, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab versus chemotherapy plus trastuzumab plus placebo as adjuvant therapy in patients with operable HER2-positive early breast cancer. SABCS 2019; abstr. GS 01-04

Statement HER2 positive (if non-pCR) T-DM1

1. von Minckwitz G, Huang CS, Mano MS et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019;380(7):617-628

Statement HER2 positive (if non-pCR) Neratinib (one year) after completing a year of adjuvant trastuzumab (if HR positive)

1. 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

Statement HER2 positive (if non-pCR): Trastuzumab + Pertuzumab (to complete 12 mths)

1. von Minckwitz G, Procter M, de Azambuja E, et al. APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017 Jul 13;377(2):122-131.
2. Piccart M , Procter M, Fumagalli D et al. Interim overall survival analysis of APHINITY (BIG 4-11): A randomized multicenter, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab versus chemotherapy plus trastuzumab plus placebo as adjuvant therapy in patients with operable HER2-positive early breast cancer. SABCS 2019; abstr. GS 01-04

Statement Triplet negative (TNBC) (if non-pCR) Capecitabine (8 courses)

1. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med. 2017;376(22):2147-2159.
2. Lluch A, Barrios CH, Torrecillas L, 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;38(3):203–213.

doi:10.1200/JCO.19.00904

3. Van Mackelenbergh M Seiter F, Möbus V et al. Effects of capecitabine as part of neo-/adjuvant chemotherapy. A meta-analysis of individual patient data from 12 randomized trials including 15,457 patients. SABCS 2019, abstr. GS1-07

Take Home Message - NST

- **Neoadjuvant systemic therapy offers an established treatment option for patients with early breast cancer if chemotherapy is indicated**
- **The pathologic response offers important prognostic information**
- **Surgical procedures after NST follows the same guidelines as compared to upfront surgery**
- **The options in axillary interventions follow a complex algorithm (see slide 16 of this chapter**
- **In case of non-pCR there is the option to improve prognosis by postneoadjuvant treatment in HER2+, TNBC or high-risk HR+ HER2- breast cancer by adapted postneoadjuvant therapy**
- **If postneoadjuvante endocrine therapy is indicated therapy is independend of the response to NST**