


Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Neoadjuvante (Primäre) systemische Therapie



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Neoadjuvante systemische Therapie

- **Versionen 2002–2018:**
 Bauerfeind / Blohmer / Costa / Dall / Fersis / Friedrich /
 Göhring / Harbeck / Heinrich / Huober / Jackisch /
 Kaufmann / Liedtke / Lux / von Minckwitz /
 Müller / Mundhenke / Nitz / Schneeweiss / Schütz /
 Solomayer
- **Version 2019:**
 Loibl / Untch


Systematic review of published evidence

PUBMED 1999-2018

ASCO 1999-2018

SABCS 1999-2018

ECCO/ESMO 1999-2018

	<h1>Subtyp-spezifische Strategien zur Systemtherapie</h1>	
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<p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<ul style="list-style-type: none"> ■ Bei Indikation zur Chemotherapie neoadjuvante Applikation bevorzugt ■ HR+/HER2- mit „niedrigem Risiko“ <ul style="list-style-type: none"> ■ Endokrine Therapie ohne Chemotherapie ■ 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 ■ HER2+ <ul style="list-style-type: none"> ■ Trastuzumab (plus Pertuzumab neoadjuvant bei hohem Risiko) <ul style="list-style-type: none"> ■ Sequentielles A/T-basiertes Regime mit simultaner Gabe von T + anti HER2-Th. ■ Anthrazyklin-freies, Platin-haltige Regime ■ Anthrazyklin-freies, Taxan-haltige Regime ■ Triple-negativ (TNBC) <ul style="list-style-type: none"> ■ Konventionell dosierte AT-basierte Chemotherapie (q3w) ■ Dosisdichte sequentielle A/T-basierte Chemotherapie (inkl. weekly Schemata) ■ Neoadjuvante Platin-haltige Chemotherapie 	

Systematic review of published evidence

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Dosisdichte Paclitaxel

Schema	ED [mg/m ²]	Gaben	kumulativ	mg/m ² /week
EC-Pac q3w	175	4	700	58,33
ddEC-ddPac	175	4	700	87,5
ddEC-Pw	80	12	960	80

Dosisdichte Schemata sind folgende Schemata

- 1) q3w gegebene Dosis als q2w gegeben mit primärem G-CSF Support.
Z.B. Paclitaxel 175mg/m² q2w == Paclitaxel 87,5 mg/m²/week (Pq2w)
- 2) Wöchentliche Schemata, die im Vergleich zum parallelen q3w-Schema eine relativ hohe Dosisverdichtung aufweist.
Z.B. Paclitaxel weekly 80-90 mg/m² (week(Pw))

Neoadjuvante systemische Chemotherapie – Klinischer Benefit			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Überleben ist gleich nach neoadjuvanter (präoperativer, primärer) und adjuvanter systemischer Therapie (bei gleichem Regime und gleicher Zyklenzahl) 	1a	A	
<ul style="list-style-type: none"> Pathologische Komplettremission ist mit einem besseren Überleben assoziiert 	1b	A	
<ul style="list-style-type: none"> Kann Operabilität bei primär inoperablen Tumoren erreichen 	1b	A	
<ul style="list-style-type: none"> Verbessert die Optionen für eine brusterhaltende Operation 	1b	A	
<ul style="list-style-type: none"> Senkt die Rate an axillären Lymphonodektomien 	3b	C	
<ul style="list-style-type: none"> Erlaubt Individualisierung der Therapie nach dem Interims-Ansprechen 	1b	B	
<ul style="list-style-type: none"> Erlaubt Individualisierung der post-neoadjuvanten Behandlung* 	1b	B	
* Studienteilnahme empfohlen			

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.* 2018 Dec 5. doi: 10.1056/NEJMoa1814017. [Epub ahead of print]

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	++



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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

Neoadjuvante systemische Chemotherapie Prädiktion des Ansprechens I				
Faktor	LoE ₀ x2001	CTS	GR	AGO
▪ Junges Alter	1a	B	A	+
▪ cT1 / cT2-Tumore o. N0 o. G3	1a	B	A	++
▪ Negativer Hormonrezeptorstatus	1a	B	A	++
▪ ER+ und negativer PgR-Status	2a	B	B	++
▪ Triple-negatives Mammakarzinom	1a	B	A	++
▪ Positiver HER2 Status	1a	B	A	++
▪ Nicht-lobuläre Histologie	1a	B	A	+
▪ Frühes klinisches Ansprechen	1b	B	A	+



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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

Neoadjuvante systemische Chemotherapie Prädiktion des Ansprechens II				
Faktor	LoE ₂₀₀₉	CTS	GR	AGO
▪ Multigensignaturen	III	C	B	+/-
▪ Ki-67	I	B	A	+
▪ Tumor infiltrierende Lymphozyten*	I	B	B	+
▪ PIK3CA Mutation beim HER2-positiven Mammakarzinom	I	B	B	+/-
▪ gBRCA in TNBC	II	B	B	+
▪ Defizienz der homologen Rekombination	IV	C	C	+/-

* LPBC ist definiert als dichtes lymphozytenreiches, die Tumorzellen umgebendes Binnenstroma außerhalb der Randzone (Lymphozyten >50% der Stromafäche)



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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, Colloff JL, Barry WT, Brugge JS, Winer EP, Selfors LM. The 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, Markowitz F, Caldas C. 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



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Neoadjuvante systemische Chemotherapie

Empfohlene Regime und Schedules

	Oxford		
	LoE	GR	AGO
▪ Adjuvante Standardregime mit einer Dauer von mindestens 18 Wochen*	1a	A	++
▪ Taxan gefolgt von Anthrazyklin	1a	A	+
▪ Platinsalze beim TNBC (unabh. des BRCA-Status)	2b	B	+
▪ Nab-Paclitaxel qw anstatt Paclitaxel qw	1b	B	+

* Siehe Kapitel adjuvante Chemotherapie

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 GEPAR DUO 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


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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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	+/-
▪ Clipmarkierung der Tumorregion	5	D	++
▪ Clipmarkierung des 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
4. Schwentner L, et al. Using ultrasound and palpation for predicting axillary lymph node status following neoadjuvant chemotherapy - Results from the multi-center SENTINA trial. Breast. 2017 Feb;31:202-207.

Palpation

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

Mammography

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

MRI

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


PET(-CT)

1. Dose-Schwarz J, et al. Assessment of residual tumour by FDG-PET: conventional imaging and clinical examination following primary chemotherapy of large and locally advanced breast cancer. Br J Cancer 2010; 102; 35
2. Coudert B, et al. Use of [(18)F]-FDG PET to predict response to neoadjuvant trastuzumab and docetaxel in patients with HER2-positive breast cancer, and addition of bevacizumab to neoadjuvant trastuzumab and docetaxel in [(18)F]-FDG PET-predicted non-responders (AVATAXHER): an open-label, randomised phase 2 trial. Lancet Oncol 2014; 15; 1493

3. Groheux D, et al. ¹⁸F-FDG-PET/CT for predicting the outcome in ER+/HER2- breast cancer patients: comparison of clinicopathological parameters and PET image-derived indices including tumor texture analysis. Breast Cancer Res. 2017 Jan 5;19(1):3

Clip tumour region

1. Caudle AS, Yang WT, Krishnamurthy S et al.: Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection. J Clin Oncol. 2016;34(10):1072-8.
2. Hartmann et al. Wire localization of clip-marked axillary lymph nodes in breast cancer patients treated with primary systemic therapy. Eur J Surg Oncol. 2018 ;44:1307-1311
3. Siso C et al. Intraoperative Ultrasound-Guided Excision of Axillary Clip in Patients with Node-Positive Breast Cancer Treated with Neoadjuvant Therapy (ILINA Trial). Ann Surg Oncol 2018; 25:784–791
4. Simons JM, et al. Diagnostic Accuracy of Different Surgical Procedures for Axillary Staging After Neoadjuvant Systemic Therapy in Node-positive Breast Cancer: A Systematic Review and Metaanalysis. Ann Surg Oncol 2018 Oct 11. doi: 10.1097/SLA.0000000000003075. [Epub ahead of print]



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Neoadjuvante zielgerichtete Therapie bei HER2-positiven Tumoren

- **Trastuzumab in Kombination mit Chemotherapie**
- **Pertuzumab + Trastuzumab in Kombination mit Chemotherapie**
- **Zwei gegen HER2 gerichtete Substanzen ohne Chemotherapie**

	Oxford		
	LoE	GR	AGO
1b	1b	A	++
2b	2b	B	++
2b	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
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.

Pertuzumab + Trastuzumab in combination with chemotherapy

1. Gianni L, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012; 13; 25-32
2. Schneeweiss A, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Annals Oncol* 2013; 24; 2278-84
3. Nagayama A, et al. Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis. *J Natl Cancer Inst* 2014; 106(9): in print
4. Gianni L et al. Five-year analysis of the phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P). *J Clin Oncol* 33, 2015 (suppl; abstr 505)
5. Loibl S, et al. Dual HER2-blockade with pertuzumab and trastuzumab in HER2-positive early breast cancer: a subanalysis of data from the randomized phase III GeparSepto trial. *Ann Oncol*. 2017;28:497-504
6. Schneeweiss A et al. Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: Evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer. *Eur J Cancer* 89:27-35, 2017
7. Hurvitz SA, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol* 2017. pii: S1470-2045(17)30716-7 [Epub ahead of print]
8. Swain SM, et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. *Ann Oncol* 2017. doi: 10.1093/annonc/mdx773. [Epub ahead of print]
9. Von Minckwitz G, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med*. 2017 13;377(2):122-131.

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
3. Alba E, et al. Trastuzumab or lapatinib with standard chemotherapy for HER2-positive breast cancer: results from the GEICAM/2006-14 trial. *Br J Cancer* 2014; 110; 1139
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
3. 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]
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.



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Neoadjuvante systemische Therapie

Vorgehen bei einem frühen Ansprechen


	Oxford		
	LoE	GR	AGO
Bei frühem Ansprechen nach 6 bis 12 Wochen einer neoadjuvanten Chemotherapie: <ul style="list-style-type: none"> ■ Komplettierung der gesamten Chemotherapie vor der Operation d.h. ≥ 18 Wochen Behandlung ■ Beim Ansprechen nach 2 Zyklen TAC beim HR-positiven Mammakarzinom 8 statt 6 Zyklen TAC erwägen 	1b	A	++
	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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Neoadjuvante systemische Therapie

Vorgehen bei keinem frühen Ansprechen

	Oxford		
	LoE	GR	AGO
Bei keiner Änderung:			
▪ Komplettierung der neoadjuvanten Chemotherapie (NACT), anschl. Operation	2b	C	++
▪ Fortsetzen der NACT mit einem nicht-kreuzresistenten Regime	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:			
▪ Abbruch der NACT und Operation oder Bestrahlung	4	D	++
▪ Zusätzliche adjuvante Chemotherapie mit nicht-kreuzresistenten 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
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.



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Neoadjuvante systemische Therapie

Lokoregionäre Operationen

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

- Intraoperative Clipmarkierung der Tumorregion
- Adäquate Operation nach NACT
- Mikroskopisch freie Absetzungsränder
- Exzision innerhalb neuer Grenzen nach aktueller Bildgebung

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.
5. Mamtani A, et al. How Often Does Neoadjuvant Chemotherapy Avoid Axillary Dissection in Patients With Histologically Confirmed Nodal Metastases? Results of a Prospective Study. Ann Surg Oncol. 2016 Oct;23(11):3467-74.

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Operatives Vorgehen in der Axilla und NACT						
SLNB vor oder nach NACT bei cN0						
SLNB vor NACT				2b	B	+/-
SLNB nach NACT				2b	B	+
Weitere operative Therapie in Abhängigkeit von SLNB						
cN-Status (vor Therapie)	pN-Status (vor Therapie)	N-Status (nach Therapie)	operatives Vorgehen nach Therapie			
cN0	pN0(sn)	-	Nihil	1a	A	+
cN0	pN+(sn) analog ACOSOG Z0011	ycN0	Nihil	5	D	+
			Re-SN alleine	2b	B	-
cN0	pN+(sn) nicht analog ACOSOG Z0011	ycN0	ALND	3	B	-
			Re-SN alleine	2b	B	-
cN0	Nicht durchgeführt	ypN0(sn) ypN1(sn)	ALND	2b	B	+
			Axilla XRT	2b	B	+
			SN alleine	2b	B	+
			ALND	2b	B	+
cN+	pN+ (CNB)	ycN0	ALND	5	B	+
			SN alleine	2b	B	+/-
			TAD inkl. SN	3b	C	+
cN+	pN+ (CNB)	ypN1 (CNB)	ALND	2b	B	+/-
			ALND	2b	B	++

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



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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, Michael Dixon J. 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			
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	LoE	GR	AGO
	Therapiebeginn		
	<ul style="list-style-type: none"> Notwendige Therapieverzögerung führt nicht zu einer Prognoseverschlechterung (ggf. >4 Wochen) 		
Operation	<ul style="list-style-type: none"> Nach Leukozyten-Nadir (2 bis 4 Wochen nach dem letzten Chemotherapiezyklus) 		
	2b	B	++
Radiotherapie innerhalb von 2–3 Monaten nach Operation			
	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?
Int J Radiat Oncol Biol Phys 2011; 79; 1452-145

Neoadjuvante endokrine Therapie bei Patienten mit endokrin-sensitivem Mammakarzinom			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Postmenopausale Patienten <ul style="list-style-type: none"> die inoperabel sind und keine Chemotherapie möchten / haben können Verbessert die Optionen für brusterhaltende Operationen Aromataseinhibitoren (für > 3 Monate) Aromataseinhibitor + Lapatinib (HER2+ Mammakarzinom) Prämenopausale Patientinnen <ul style="list-style-type: none"> die inoperabel sind und keine Chemotherapie möchten / haben können Tamoxifen Aromataseinhibitoren + LHRHa Simultane chemo-endokrine Therapie Prognostischer Score: <ul style="list-style-type: none"> PEPI: pTN-Stadium, ER-Expression und Ki-67 Expression nach neoadjuvanter endokriner Therapie 	2a 1b 1a ^a 2b	B A B B	+ + + +/-
^a Optimale Dauer der neoadjuvanten endokrinen Therapie ist unbekannt. Keine Langzeitergebnisse zur neoadjuvanten endokrinen Therapie (vs. adjuvante endokrine Therapie)	1b	B	+

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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 positiv (pCR und non-pCR)*			
▪ Endokrine Therapie nach Menopausenstatus (s. Kap. 10)	1a	A	++
▪ Capecitabin (bei non-pCR)	3b	C	+/-
HER2 positiv (bei pCR)			
▪ Low risk: Trastuzumab (bis 12 Mon. komplett)	2a	C	++
▪ High risk (z.B. HR-/N+): Trastuzumab + Pertuzumab (bis 12 Mon. komplett)	2b	C	+
HER2 positiv (bei non-pCR)			
▪ T-DM1 (bis zu 14 Gaben anti-HER2-Therapie komplett)	1b	B	+
▪ Neratinib nach 1 Jahr Trastuzumab (nur bei HR-positiv)	4	C	+/-
▪ Trastuzumab + Pertuzumab (bis 12 Mon. komplett)	2b	C	+/-
Tripelnegativ (TNBC) (bei non-pCR)			
▪ Capecitabin (bis zu 8 Kurse)	1b	B	+

*Studienteilnahme empfohlen

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.

etc.

Statement HER2 positiv (bei pCR): Low risk: Trastuzumab (bis 12 Mon. komplett)

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.

etc.

Statement HER2 positiv (bei pCR): pN+ oder HR-: Trastuzumab + Pertuzumab (bis 12 Mon. komplett)

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.

Statement HER2 positiv (bei non-pCR) T-DM1 (bis 12 Mon. anti-HER2-Therapie komplett)

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.

Statement HER2 positiv (bei non-pCR) Neratinib nach 1 Jahr Trastuzumab (nur bei HR-positiv)

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 Tripelnegativ (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.