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Guidelines Breast
Version 2021.1D

FORSCHEN
LEHREN
HEILEN

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Neoadjuvant (Primary) Systemic Therapy

<u>Systematic review of published evidence</u>
PUBMED 1999-2020
ASCO 1999-2020
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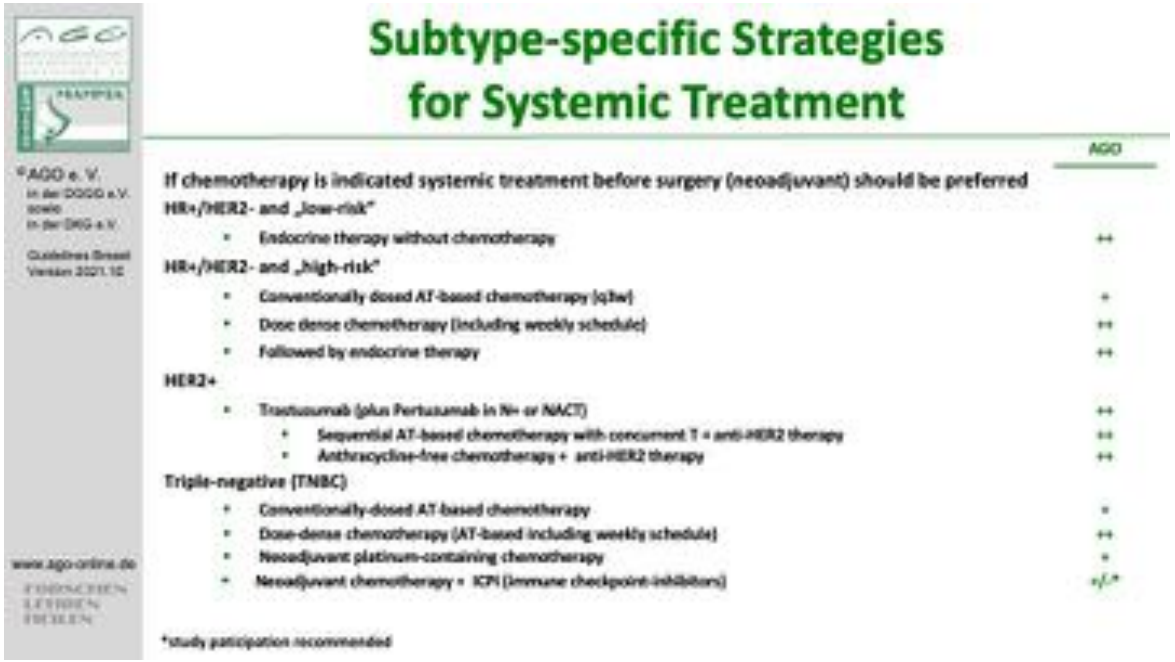
ECCO/ESMO 1999-2020



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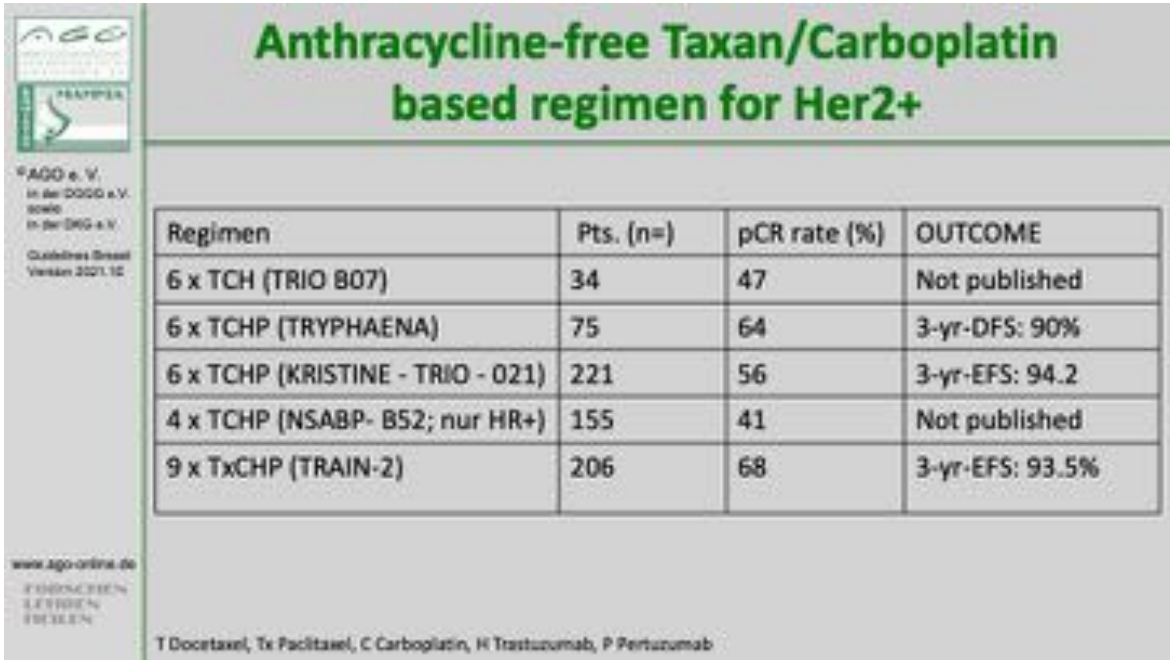
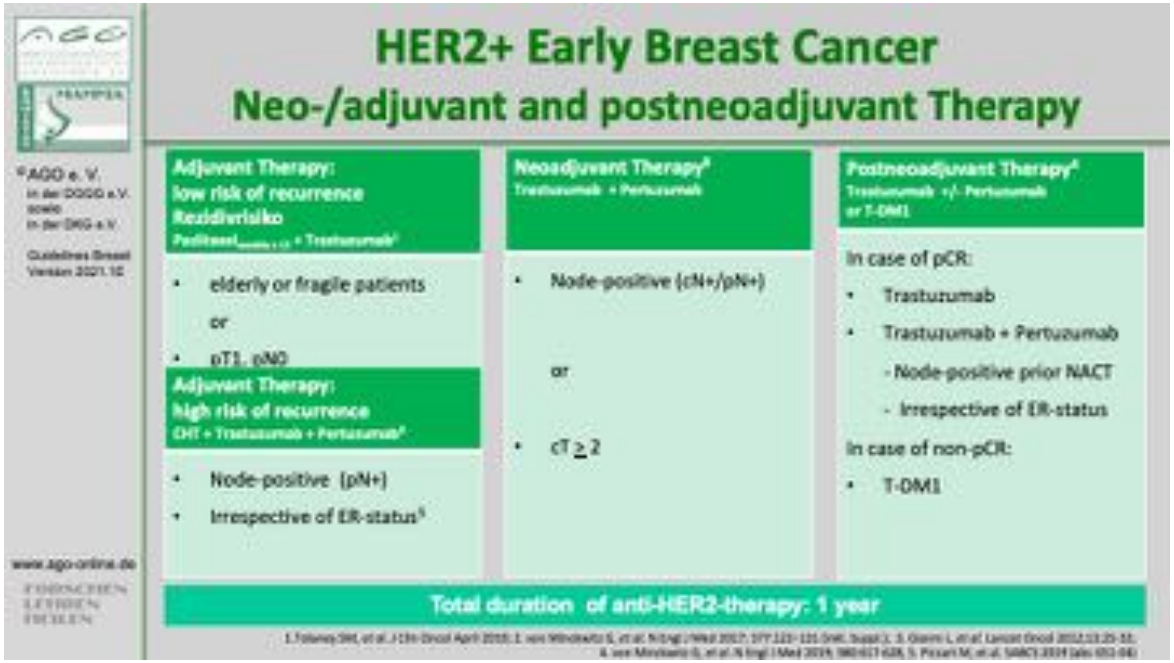


Regimen	Pts. (n=)	pCR rate (%)	OUTCOME
6 x TCH (TRIO B07)	34	47	Not published
6 x TCHP (TRYPHAENA)	75	64	3-yr-DFS: 90%
6 x TCHP (KRISTINE - TRIO - 021)	221	56	3-yr-EFS: 94.2
4 x TCHP (NSABP- B52; nur HR+)	155	41	Not published
9 x TxCHP (TRAIN-2)	206	68	3-yr-EFS: 93.5%

1. Hurvitz SA, Miller JM, Dichmann R et al. Final analysis of a phase II 3 arm randomized trial of neoadjuvant tratuzumab or lapatinib or th combination of trastuzumab and lapaitinib, followed by six cycels of docetaxel and carboplatin with trastuzumab and/or lapatinib in patients with Her2+ breast cancer (TRIO-US B07). Cancer Res 2013, 73(24 suppl). S1-02.
2. Schneeweiss A, Chia S, Hickish T et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with Her2-positive early breast cancer: a randomied phae II Cardiac safety study (TRYPHAENA) Ann Oncol. 2013 Sep;24(9):2278-84. doi:10.1093/annonc/mdt182.
3. Hurvitz SA, Martin M, Symmans WF et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with Her2-positive breast cancer (KRISTINE): a randomized, open-label, multicentre, phase 3 trial. Lancet oncol, 2018 Jan;19(1):115-126. doi:10.1016/S1470-2045(17)30716-7.
4. Rimawi MF, Cecchini RS, Rastogi P et al. A phase II trial evaluating pCR in patients with HR+ Her-positive breast cancer treated with neoadjuvant docetaxel, carboplatin, trastuzumab, pertuzumab (TCHP) +/- estrogen dbrivation: NRG Oncology/NSABP B-52 Cancer Res 2017;77(4 suppl):S3-06.
5. Van Ramshorst MS, van der Voort A, van Werkhoven ED et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual Her2 blockade for Her2-positive breast cancer (TRAIn-2): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. Dec;19(12):1630-1640; doi:10.1016/S1470-2045(18)30570-9.



1. Tolaney 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)

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 Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and cycle number)
2. Fisher B, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998: 16; 2672

3. Van der Hage JA, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001: 19; 4224
4. Rastogi P, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008: 26; 778
5. EBCTCG. Long-term outcomes for neoad
6. Cortazar P, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014: 384; 164
7. Berruti A, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: a meta-regression of 29 randomized prospective studies. J Clin Oncol 2014: 32; 3883
8. Yee D, et al. Pathological complete response predicts event-free and distant disease free survival in the I-SPY 2 Trial. SABCS 2017 (abs GS3-08)

Can achieve operability in primary inoperable tumors

1. Makhoul I, et al. Neoadjuvant systemic treatment of breast cancer. J Surg Oncol 2011: 103; 348
2. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

Improved options for breast conserving surgery

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

Reduces the rate of lymphadenectomies

1. Fernandez-Gonzalez S, et al. The Shift From Sentinel Lymph Node Biopsy Performed Either Before or After Neoadjuvant Systemic Therapy in the Clinical Negative Nodes of Breast Cancer Patients. Results, and the Advantages and Disadvantages of Both Procedures. Clin Breast Cancer pii: S1526-8209(17)30565-7, 2017 [Epub ahead of print]
2. Reimer T et al. Avoiding axillary sentinel node biopsy after neoadjuvant systemic therapy in breast cancer: rationale for the prospective, multicentric EUBREAST-01 trial. Cancers 2020:3698; doi:10.3390/cancers12123698

Allows individualization of therapy according to mid-course treatment effect

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

Allows individualization of post-neoadjuvant treatment

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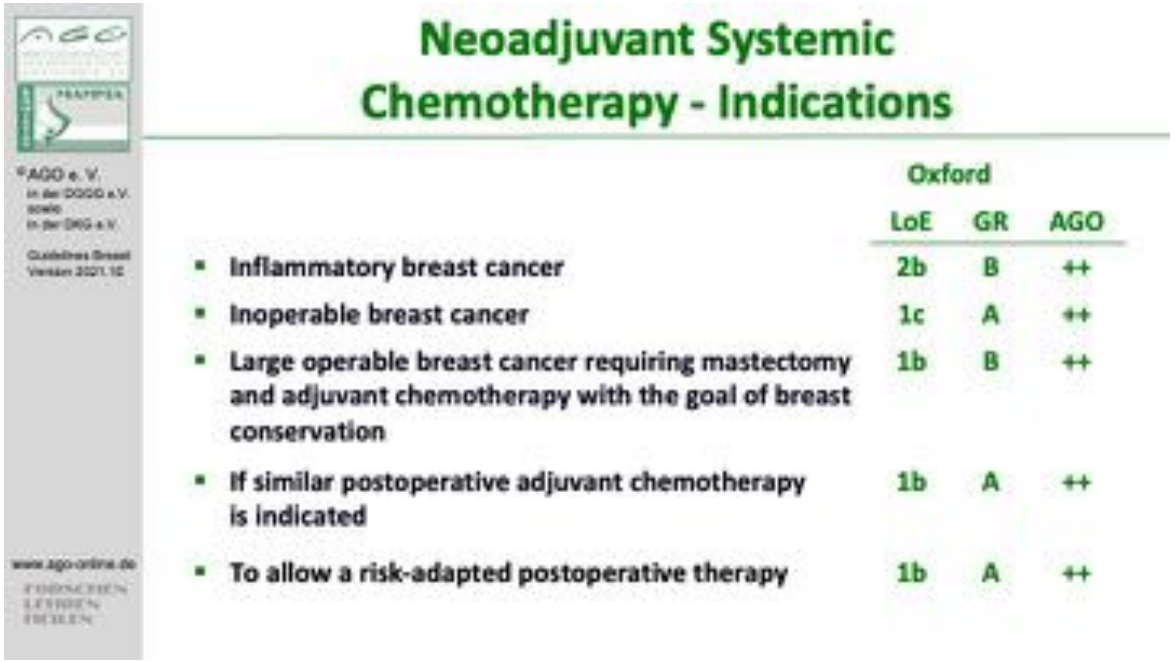
6. Masuda N, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med 376, 2147–2159, 2017
7. von Minckwitz G, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019;380(7):617-628.



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

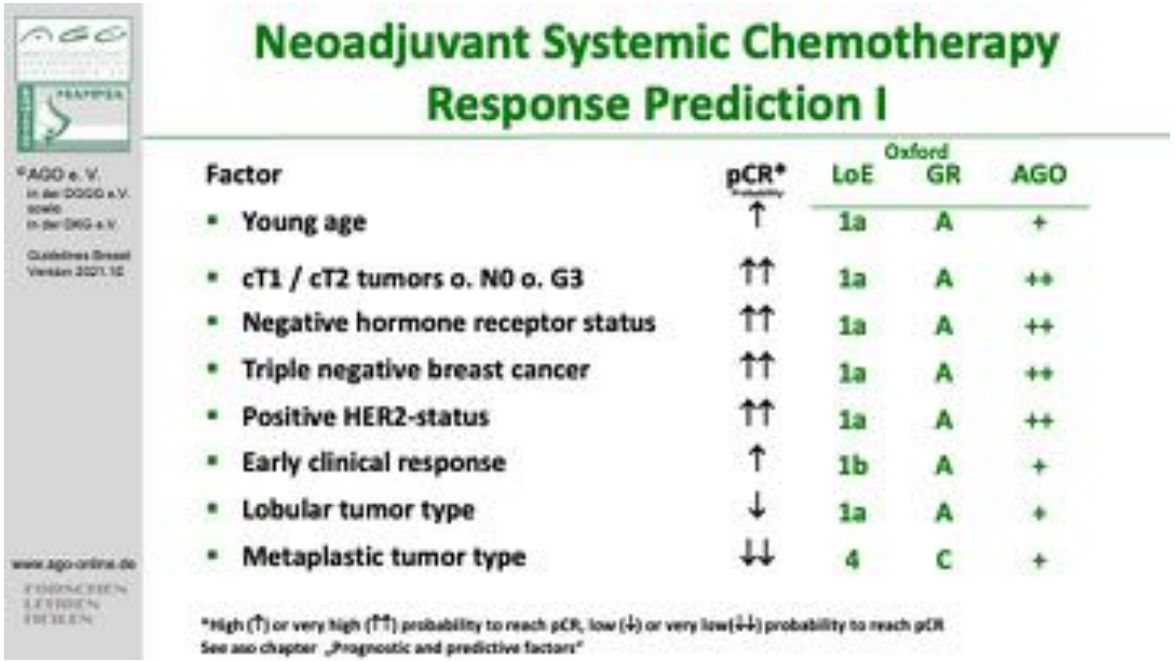
Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation

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]

<u>If similar postoperative adjuvant chemotherapy is indicated</u>

1. Untch M, et al. Neoadjuvant chemotherapy: early response as a guide for further treatment: clinical, radiological, and biological. J Natl Cancer Inst Monogr 2011: 43; 138
2. Loibl S, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012: 13 ; 887



General evidence

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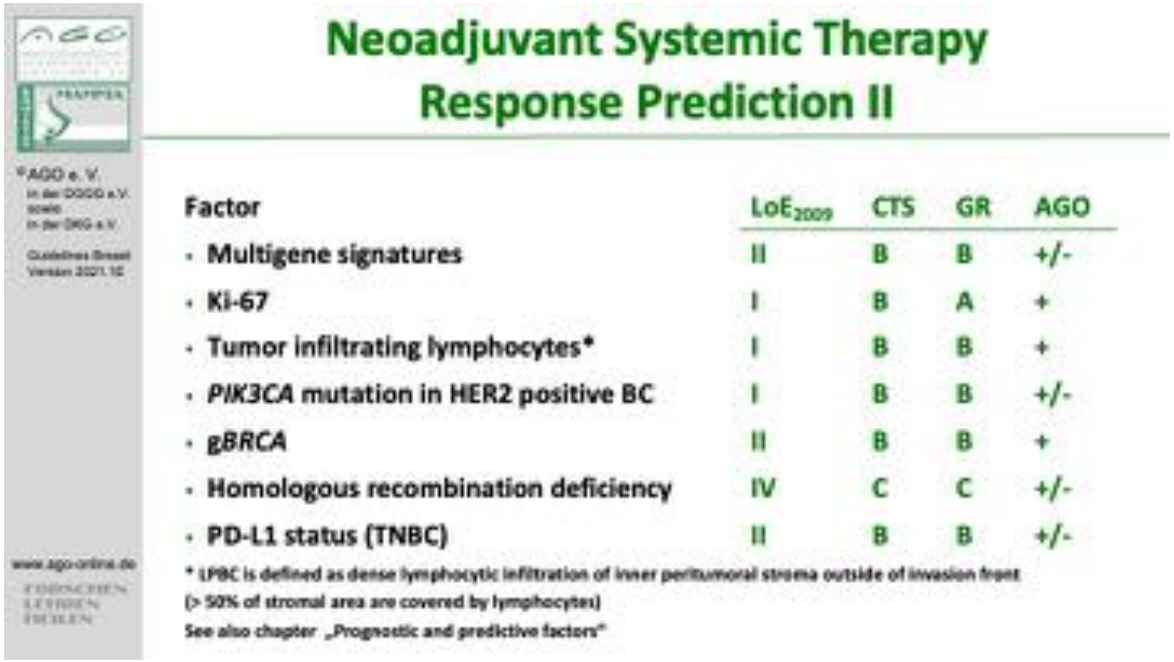
2. Gerber B, Loibl S, Eidtmann H, et al. Neoadjuvant bevacizumab and anthracycline-taxane-based chemotherapy in 678 triple-negative primary breast cancers; results from the geparquinto study (GBG 44). Ann Oncol 2013;24: 2978-84.
3. van Mackelenbergh MT, Denkert C, Nekljudova V, et al. Outcome after neoadjuvant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

Lobular cancer

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

Metaplastic breast cancer

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



Multigene signature

1. Pease AM, Riba LA, Gruner RA, Tung NM, James TA. Oncotype DX® Recurrence Score as a Predictor of Response to Neoadjuvant Chemotherapy. Ann Surg Oncol. 2019;26(2):366-371. doi: 10.1245/s10434-018-07107-8. Epub 2018 Dec 12. PMID: 30542840.
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Ki-67

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

Tumour infiltrating lymphocytes

1. Mao Y, et al. The Value of Tumor Infiltrating Lymphocytes (TILs) for Predicting Response to Neoadjuvant Chemotherapy in Breast Cancer: A Systematic Review and Meta-Analysis. PloS One 2014: 9; e115103
2. Miyshita M, et al. Tumor-infiltrating CD8+ and FOXP3+ lymphocytes in triple-negative breast cancer: its correlation with pathological complete response to neoadjuvant chemotherapy. Breast Cancer Res Treat 2014: 148; 525
3. Denkert C, et al . Tumor-Infiltrating Lymphocytes and Response to Neoadjuvant Chemotherapy With or Without Carboplatin in Human Epidermal Growth Factor Receptor 2–Positive and Triple-Negative Primary Breast Cancers. JCO; 32: 2014
4. Ingold Heppner B, et al. Tumor-Infiltrating Lymphocytes: A Predictive and Prognostic Biomarker in Neoadjuvant-Treated HER2-Positive Breast Cancer. Clin Cancer Res. 2016 Dec 1;22(23):5747-5754.
5. Denkert C, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. Lancet Oncol. 2018 ;19(1):40-50

PIK3CA mutation

1. Loibl S, et al. PIK3CA mutations are associated with lower rates of pathologic complete response to anti-human epidermal growth factor receptor 2 (her2) therapy in primary HER2-overexpressing breast cancer. J Clin Oncol 2014: 32; 3212
2. Sueta A, et al. An Integrative Analysis of PIK3CA Mutation, PTEN, and INPP4B Expression in Terms of Trastuzumab Efficacy in HER2-Positive Breast Cancer. PloS One 2014: 9; e116054
3. Loibl S, Integrated Analysis of PTEN and p4EBP1 Protein Expression as Predictors for pCR in HER2-Positive Breast Cancer. Clin Cancer Res. 2016 1;22(11):2675-83.
4. Loibl S, PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol. 2016;27(8):1519-25.

gBRCA mutation

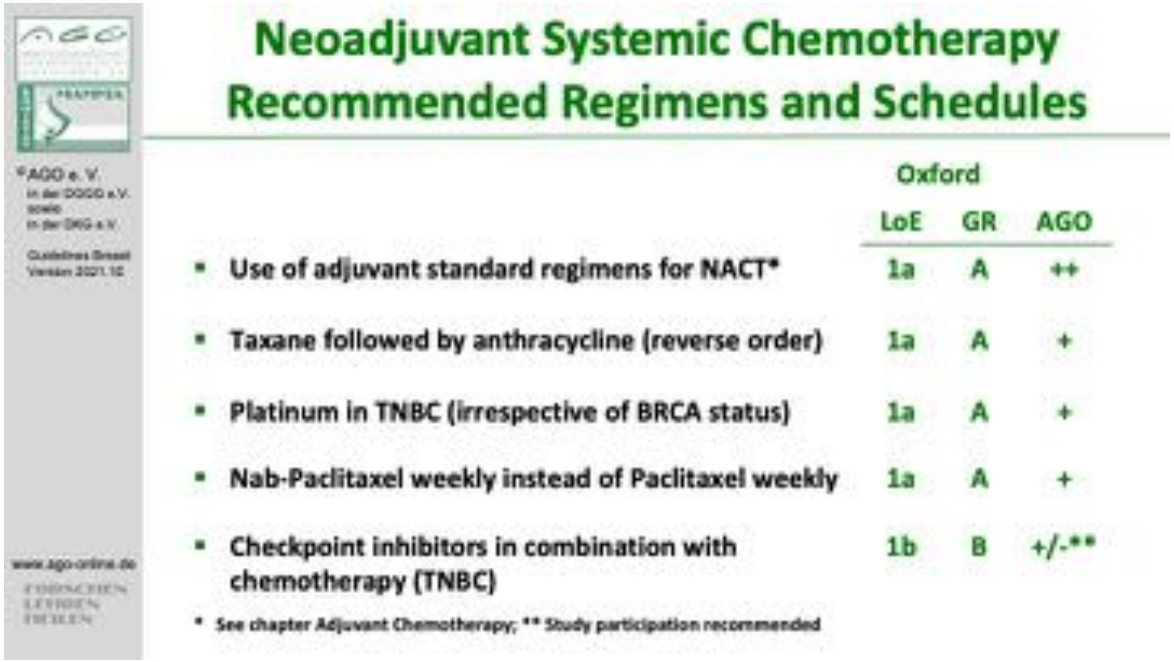
1. Spugnesi L, et al. Germline mutations in DNA repair genes may predict neoadjuvant therapy response in triple negative breast patients. Genes Chromosomes Cancer. 2016 ;55(12):915-924.
2. Hahnen E, et al. Germline Mutation Status, Pathological Complete Response, and Disease-Free Survival in Triple-Negative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

HRD

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

PDL-1-Status (TNBC):

1. Asano Y, Kashiwagi S, Goto W, Takada K, Takahashi K, Morisaki T, Fujita H, Takashima T, Tomita S, Ohsawa M, Hirakawa K, Ohira M. Prediction of treatment responses to neoadjuvant chemotherapy in triple-negative breast cancer by analysis of immune checkpoint protein expression. J Transl Med. 2018 Apr 4;16(1):87. doi: 10.1186/s12967-018-1458-y. PMID: 29615063; PMCID: PMC5883348.
2. Mittendorf EA, Zhang H, Barrios Chet al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020 Oct 10;396(10257):1090-1100. doi: 10.1016/S0140-6736(20)31953-X.
3. Schmid P, Cortes J, Pusztai L et al. ; KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810-821. doi: 10.1056/NEJMoa1910549.



Use of adjuvant standard regimens for NACT

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

Taxane followed by anthracycline sequence

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

Platinum in TNBC (irrespective of BRCA status)

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

the GEICAM/2006-03, multicenter study. Breast Cancer Res Treat 2012: 136; 487
2. Von Minckwitz G , et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol 2014: 15; 747
3. Ando M, et al. Randomized phase II study of weekly paclitaxel with and without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA breast cancer without HER2 overexpression. Breast Cancer Res Treat 2014: 145; 401
4. Petrelli F, et al. The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat 2014: 144; 223
5. Sikov WM, et al. Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance). J Clin Oncol 2015: 33; 13
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
10. Li ZY, Zhang Z, Cao XZ, Feng Y, Ren SS. Platinum-based neoadjuvant chemotherapy for triple-negative breast cancer: a systematic review and meta-analysis. J Int Med Res. 2020 Oct;48(10):300060520964340. doi: 10.1177/0300060520964340. PMID: 33100072; PMCID: PMC7645412.
11. Iwase M, Ando M, Aogi K, Aruga T, Inoue K, Shimomura A, Tokunaga E, Masuda N, Yamauchi H, Yamashita T, Iwata H. Long-term survival analysis of addition of carboplatin to neoadjuvant chemotherapy in HER2-negative breast cancer. Breast Cancer Res Treat. 2020 Apr;180(3):687-694. doi: 10.1007/s10549-020-05580-y. Epub 2020 Mar 5. PMID: 32140811

<u>Nab-Paclitaxel weekly instead of Paclitaxel weekly</u>

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
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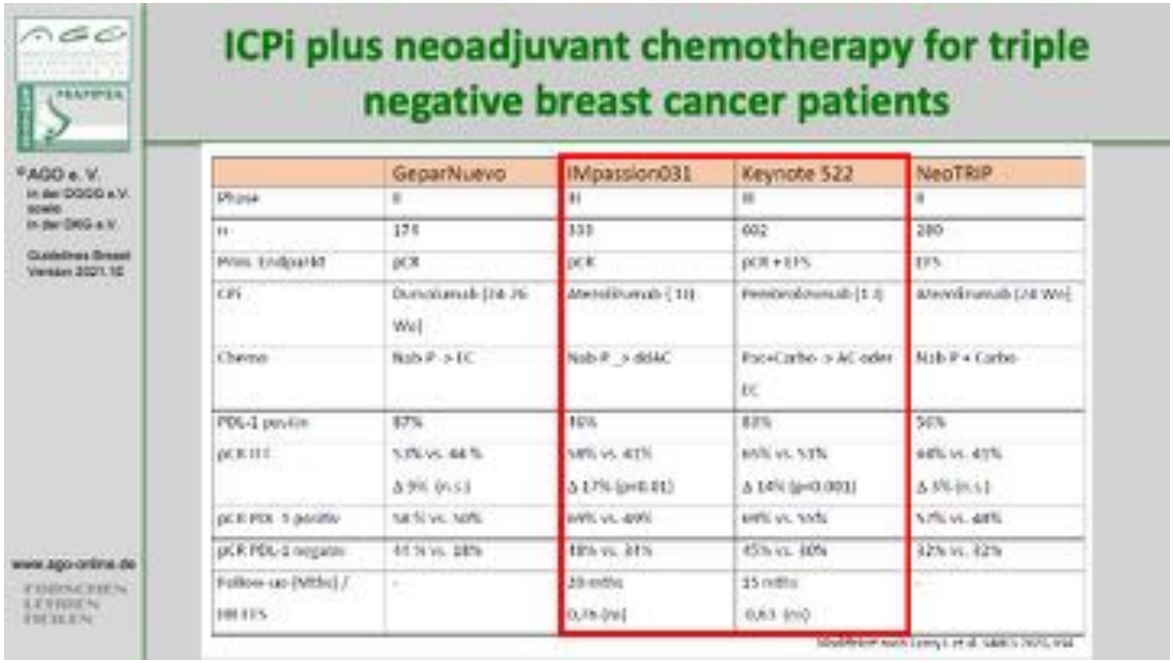
3. Futamura M, et al.Preoperative neoadjuvant chemotherapy using nanoparticle albumin-bound paclitaxel followed by epirubicin and cyclophosphamide for operable breast cancer: a multicenter phase II trial.Breast Cancer. 2017 Jan 3. doi:
4. Zong Y, et al. Nanoparticle albumin-bound paclitaxel as neoadjuvant 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
7. Li Y, et al. Is nab paclitaxel better thean conventional taxanes as neoadjuvant therapy for breast cancer? A meta-analysis. J Int Med Res. 2020 Aug;48(8):300060520943473. doi: 10.1177/0300060520943473. PMID: 32762463; PMCID: PMC7416144.

ICPi in combination with chemotherapy

1. Mittendorf EA, Zhang H, Barrios Chet al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020 Oct 10;396(10257):1090-1100. doi: 10.1016/S0140-6736(20)31953-X.
2. Schmid P, Cortes J, Pusztai L et al. ; KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810-821. doi: 10.1056/NEJMoa1910549.



1. Loibl S, Untch M, Burchardi N et al. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol. 2019;30(8):1279-1288. doi: 10.1093/annonc/mdz158.
2. Mittendorf EA, Zhang H, Barrios Chet al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020 Oct 10;396(10257):1090-1100. doi: 10.1016/S0140-6736(20)31953-X.
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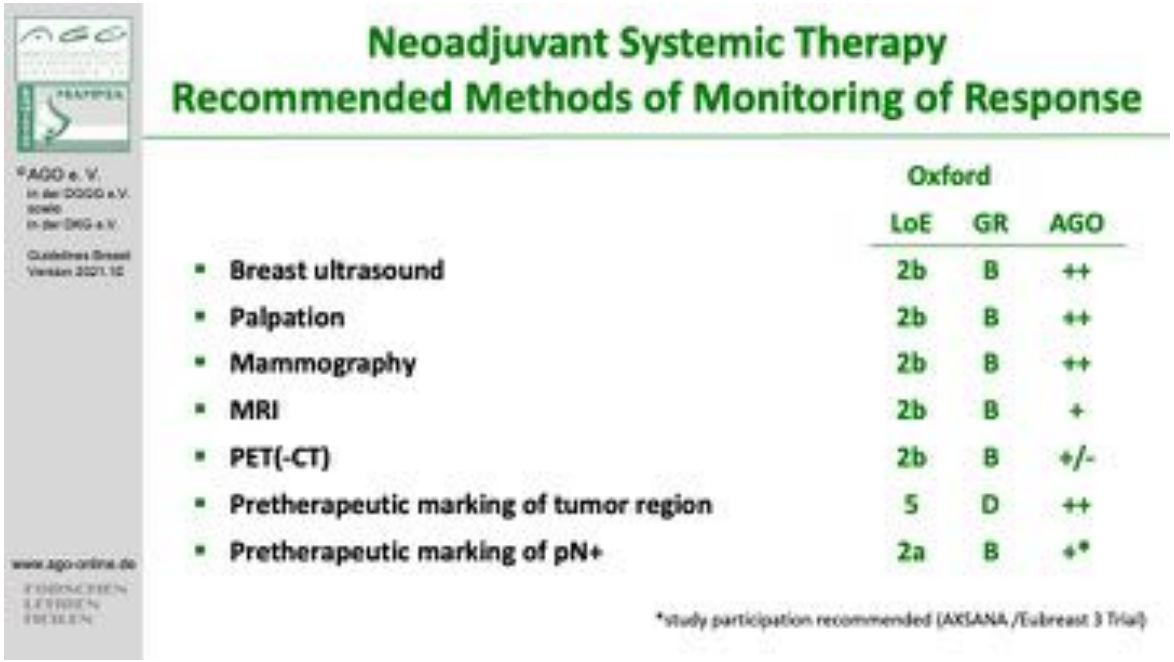

Breast ultrasound

1. Rauch GM, et al. Multimodality Imaging for Evaluating Response to Neoadjuvant Chemotherapy in Breast Cancer. AJR Am J Roentgenol. 2016 Nov 3:1-10
2. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508
3. Von Minckwitz G, et al. Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. J Natl Cancer Inst 2008: 100; 542
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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
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Clip pN+
1. Caudle AS, Yang WT, Krishnamurthy S et al.: Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection. J Clin Oncol. 2016;34(10):1072-8.
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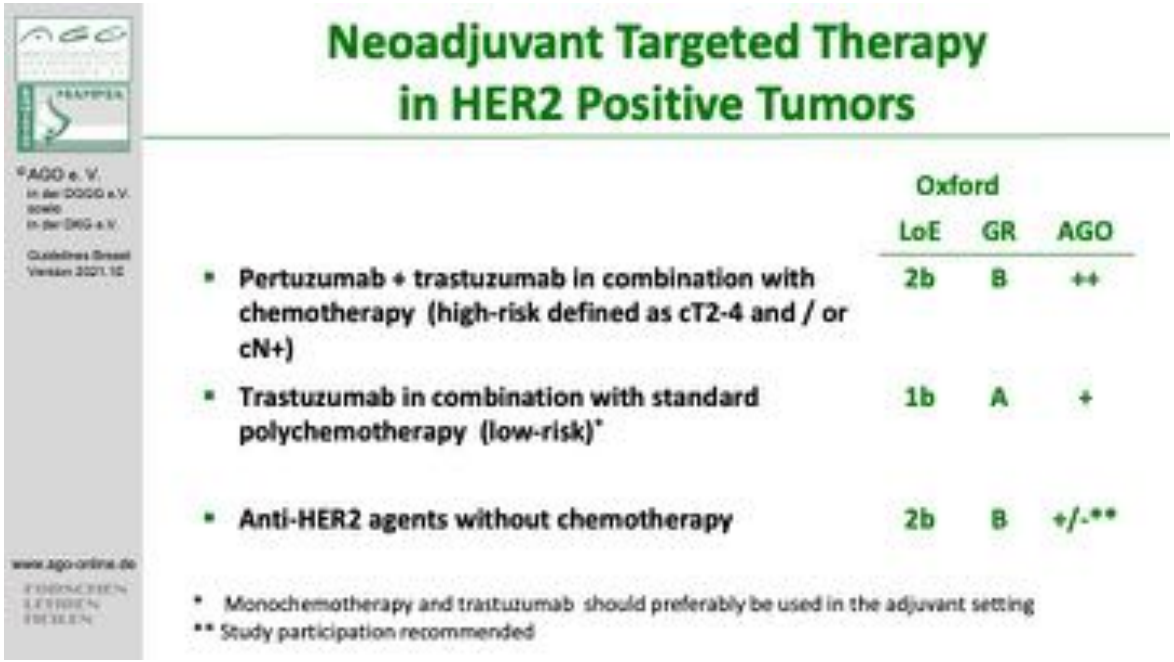

Pertuzumab + Trastuzumab in combination with chemotherapy

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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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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Anti-HER2 agents without chemotherapy

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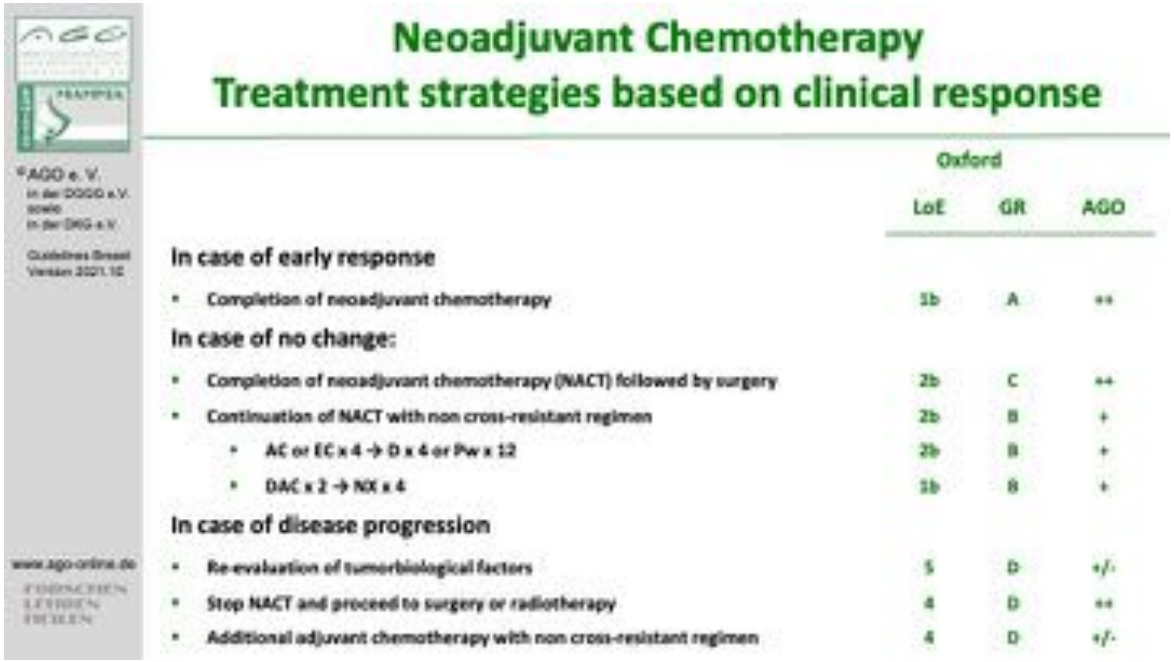

Completin of neoadjuvant chemotherapy

1. Von Minckwitz G, et al. Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: a randomized, controlled, open phase IIb study. J Clin Oncol 2001: 19; 3506
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4. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

In case of no change:

Completion of NACT, followed by surgery

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

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

Continuation of NST with non-cross-resistant regimen

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

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

DAC2x -> NX x 4

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

In case of progressive disease:

Stop of NACT and immediate surgery or radiotherapy

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

Additional adjuvant chemotherapy with non-cross-resistant regimen

1. Mittendorf EA, et al. Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. J Clin Oncol 29, 1956, 2011
2. Lee S-J et al. A phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after neoadjuvant chemotherapy (CREATE-X/JBCRG-04). San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, TX. Abstract: S1-07
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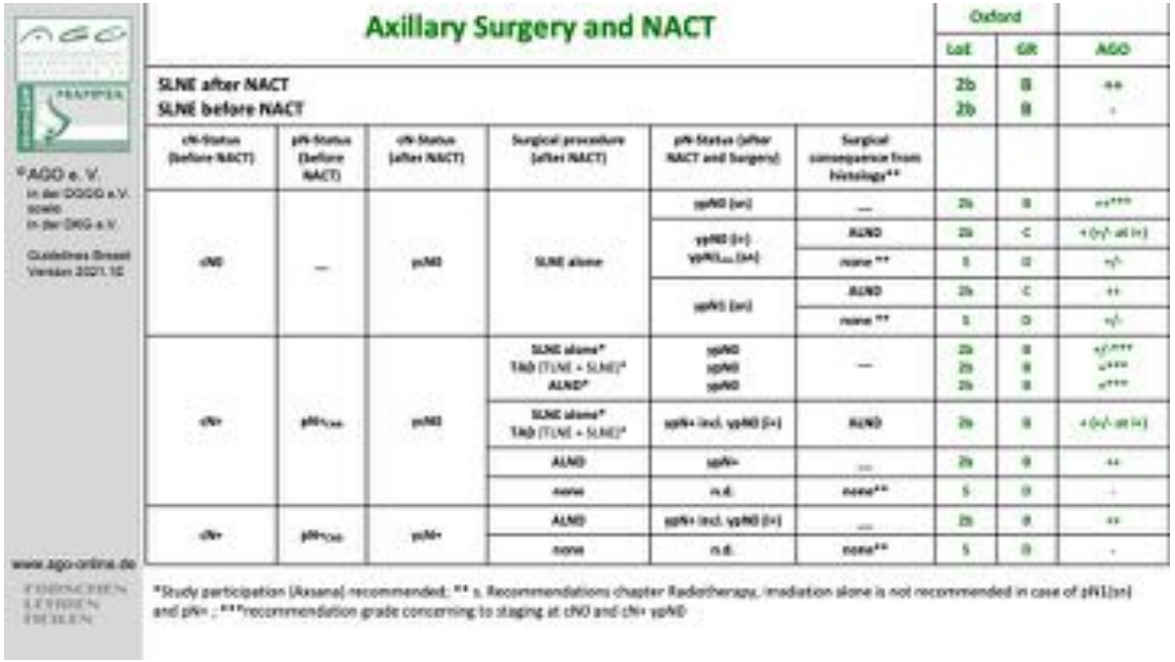

Axillary Surgery and NACT

						Oxford		
						LoE	GR	AGO
SLNE after NACT						2b	B	++
SLNE before NACT						2b	B	+
cN-Status (before NACT)	pN-Status (before NACT)	cN-Status (after NACT)	Surgical procedure (after NACT)	pN-Status (after NACT and Surgery)	Surgical consequence from histology**			
cN0	—	pN0	SLNE alone	ypN0 (sn)	—	2b	B	++***
				ypN0 (i+) ypN1(sn) (SA)	ALND	2b	C	+ (+)* at i+
					none **	1	D	+/-
				ypN1 (sn)	ALND	2b	C	++
					none **	1	D	+/-
cN+	pN+(sn)	pN0	SLNE alone* TAD (T/NE + SLNE)* ALND*	ypN0 ypN0 ypN0	—	2b 2b 2b	B B B	+/-*** +*** +***
			SLNE alone* TAD (T/NE + SLNE)*	ypN+ incl. ypN0 (i+)	ALND	2b	B	+ (+)* at i+
			ALND	ypN+	—	2b	B	++
			none	n.d.	none**	1	D	-
cN+	pN+(sn)	pN+	ALND	ypN+ incl. ypN0 (i+)	—	2b	B	++
			none	n.d.	none**	1	D	-

*Study participation (Axsana) recommended; ** s. Recommendations chapter Radiotherapy, irradiation alone is not recommended in case of pN1(sn) and pN+ ; ***recommendation grade concerning to staging at cN0 and cN+ ypN0

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

1. Reimer T, Gerber B. Quality-of-life considerations in the treatment of early-stage breast cancer in the elderly. Drugs Aging. 2010 Oct 1;27(10):791-800.
2. Tuttle TM, Shamliyan T, Virnig BA, et al. The impact of sentinel lymph node biopsy and magnetic resonance imaging on important outcomes among patients with ductal carcinoma in situ. J Natl Cancer Inst Monogr. 2010;2010(41):117-20. Review.
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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.
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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.
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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.
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6. Gandhi A, Coles C, Makris A et al. Axillary Surgery Following Neoadjuvant Chemotherapy - Multidisciplinary Guidance From the Association of Breast Surgery, Faculty of Clinical Oncology of the Royal College of Radiologists, UK Breast Cancer Group, National Coordinating Committee for Breast Pathology and British Society of Breast Radiology. Clin Oncol (R Coll Radiol). 2019 Sep;31(9):664-668.
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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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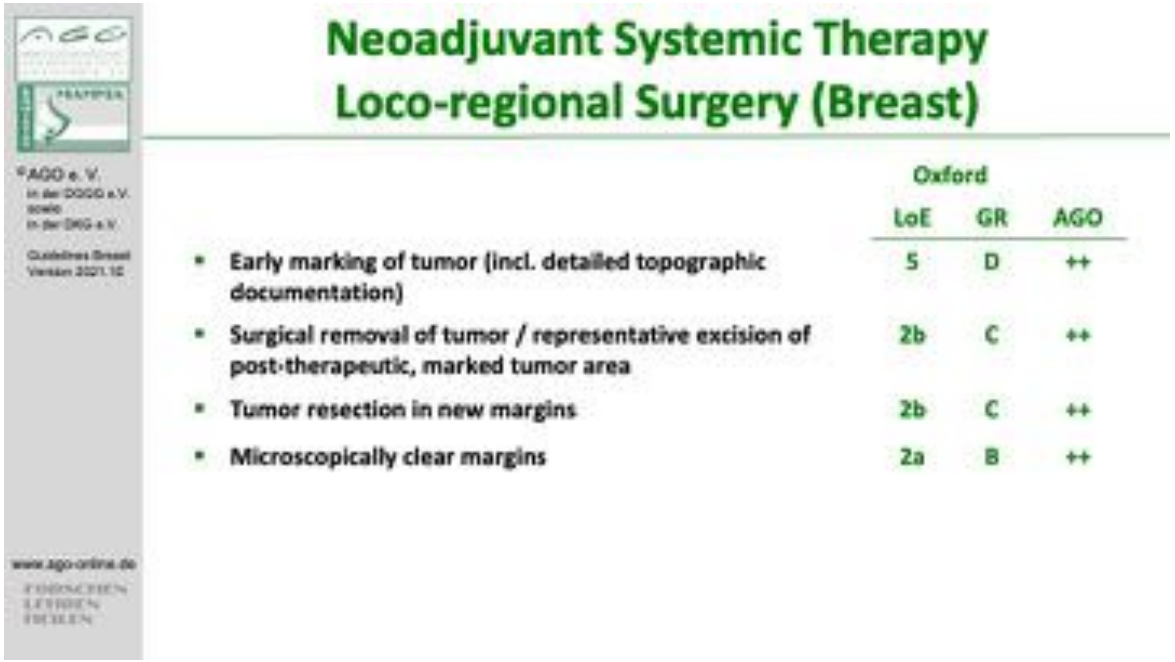
16. Simons J, v Nijnatten JA, Koppert LB, et al: Radioactive Iodine Seed placement in the Axilla with Sentinel lymph node biopsy after neoadjuvant chemotherapy in breast cancer: Results of the prospective multicenter RISAS trial. SABCS 2020, GS1-10

<u>ypN0 (i+)</u>

1. Wong SM , Almana N , Choi J et al: Prognostic Significance of Residual Axillary Nodal Micrometastases and Isolated Tumor Cells After Neoadjuvant Chemotherapy for Breast Cancer, Ann Surg Oncol. 2019 Oct;26(11):3502-3509.



Mark previous tumor region

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

Surgery

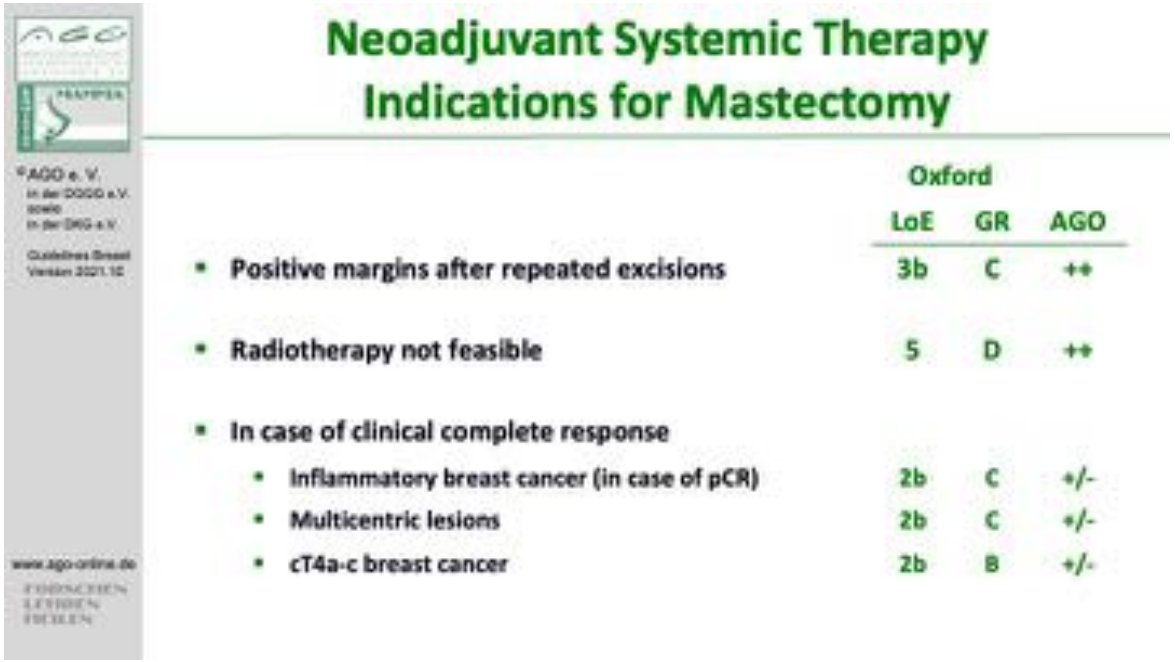
1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

Microscopically clear margins

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

Tumor resection according to imaging result

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



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

Initiation of chemotherapy after histologic diagnosis

1. de Melo Gagliato D, Lei X, Giordano SH, Valero V, Barcenas CH, Hortobagyi GN, Chavez-MacGregor M. Impact of Delayed Neoadjuvant Systemic Chemotherapy on Overall Survival Among Patients with Breast Cancer. Oncologist. 2020;25(9):749-757. doi: 10.1634/theoncologist.2019-0744.

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Radiotherapy 2 mths after surgery BCS

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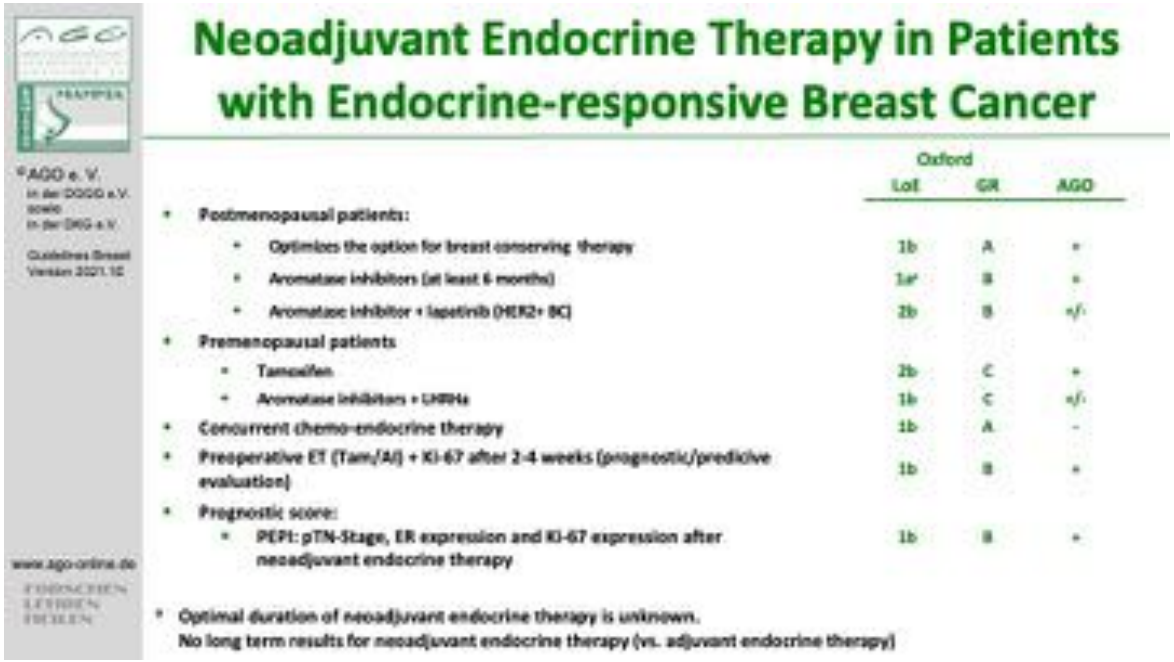
delay after neoadjuvant chemotherapy in locally advanced breast cancer. Breast. 2018;38:39-44. doi: 10.1016/j.breast.2017.11.012.

1. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009: 18; 339
2. Madigan LI et al. Neoadjuvant endocrine therapy in locally advanced estrogen and progesterone receptor-positive breast cancer: determining the optimal endocrine agent and treatment duration in postmenopausal women-a literature review and proposed guidelines. Breast Cancer Res. 2020 Jul 20;22(1):77. doi: 10.1186/s13058-020-01314-6
3. Fontein DB, et al. Efficacy of six month neoadjuvant endocrine therapy in postmenopausal, hormone receptor-positive breast cancer patients--a phase II trial. Eur J Cancer 2014: 50; 2190
4. Spring LM, et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA Oncol. 2016 Nov 1;2(11):1477-1486.
5. Marmé F, et al. Utility of the CPS+EG staging system in hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer treated with neoadjuvant chemotherapy. Eur J Cancer 53:65-74, 2015
6. Ellis MJ et al. Ki67 proliferation index as a tool for chemotherapy decisions during and after neoadjuvant aromatase inhibitor treatment of breast cancer: results from the American College of Surgeons Oncology Group Z1031 Trial (Alliance). J Clin Oncol. 2017;35(10):1061–9
7. Kurozumi S et al. Impact of combining the progesterone receptor and preoperative endocrine prognostic index (PEPI) as a prognostic factor after neoadjuvant endocrine therapy using aromatase inhibitors in postmenopausal ER positive and HER2 negative breast cancer. PLoS One. 2018;13(8):e0201846.

8. Ian Smith et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy on postmemopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentric, parallel-group, randomized phase 3 trial . Lancet Oncol. 2020 Nov;21(11):1443-1454
9. Nitz U et al. The run-in phase of the prospective WSG-ADAPT HR+/Her2- trial demonstrates the feasibility of a study design combining static and dynamic biomarker assessments for individualized therapy in early breast cancer. Ther Adv Med Oncol. 2020 Nov23:12:1758835920973130
10. Harbeck N Rid-adapted adjuvant therapy of luminal early breast cancer in 2020. Curr Opin Obstet Gynecol. 2021 Feb 1;33(1):53-58.



<u>Postmenopausal patients:</u>

<u>Aromatase inhibitors (for up to 6 months)</u>

1. Smith I, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol 2005: 23; 5108
2. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009: 18; 339
3. Ellis MJ, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype--ACOSOG Z1031. J Clin Oncol 2011: 29; 2342
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<u>AI and fulvestrant</u>

1. Lerebours F, et al. Randomized phase 2 neoadjuvant trial evaluating anastrozole and fulvestrant efficacy for postmenopausal, estrogen receptor-positive, human epidermal growth factor receptor 2-negative breast cancer patients: Results of the UNICANCER CARMINA 02 French trial (UCBG 0609). Cancer. 2016 Oct;122(19):3032-40.

Concurrent chemo-endocrine therapy

1. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009: 18; 339Von Minckwitz G, et al. Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: a randomized, controlled, open phase IIb study. J Clin Oncol 2001: 15; 3506
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3. Rimawi M, al. e. A phase III trial evaluating pCR in patients with HR+, HER2-positive breast cancer treated with neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) +/- estrogen deprivation: NRG oncology/NSABP B-52. San Antonio Breast Cancer Symposium 2016:Abstract S3-06.
4. Spring LM, et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA Oncol. 2016 Nov 1;2(11):1477-1486.

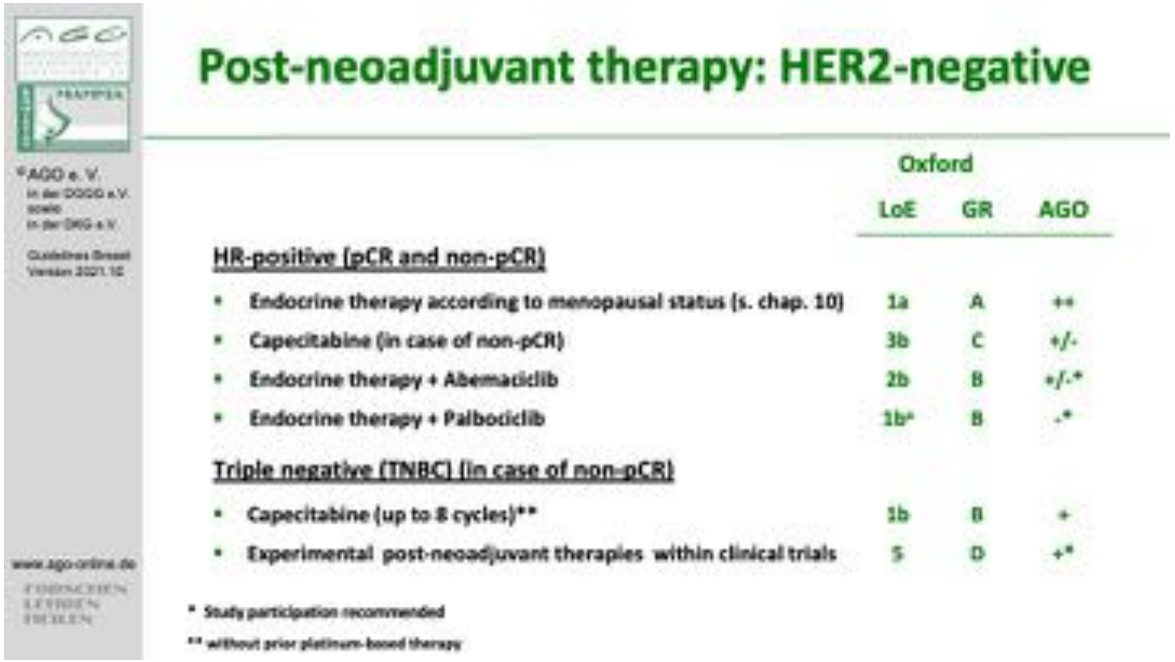
Preoperative ET and Ki67 measurement:

1. Ian Smith et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy on postmemopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentric, parallel-group, randomized phase 3 trial . Lancet Oncol. 2020 Nov;21(11):1443-1454
2. Nitz U et al. The run-in phase of the prospective WSG-ADAPT HR+/Her2- trial demonstrates the feasibility of a study design combining static and dynamic biomarker assessments for individualized therapy in early breast cancer. Ther Adv Med Oncol. 2020 Nov23:12:1758835920973130
3. Harbeck N Rid-adapted adjuvant therapy of luminal early breast cancer in 2020. Curr Opin Obstet Gynecol. 2021 Feb 1;33(1):53-58.

Prognostic scores following NST

1. Ellis MJ et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. J Natl Cancer Inst. 2008;100(19):1380–8.

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



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

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005 May 14-20;365(9472):1687-717.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015 Oct 3;386(10001):1341-1352.
3. O'Shaughnessy JA , Johnston S, Harbeck N et al. Primary outcome analysis of invasive disease-free survival for monarchE: abemaciclib combined with adjuvant endocrine therapy for high risk early breast cancer. SABCS 2020:GS1-01.
4. Mayer EL, Gnant MI, DeMichele A et al. PALLAS: A randomized phase III trial of adjuvant palbociclib with endocrine therapy versus endocrine therapy alone for HR+/HER2- early breast cancer. Ann Oncol (2020) 31 (suppl_4): S1142-S1215. 10.1016/annonc/annonc325
5. Loibl S, Marmé F, Martin M et al. Phase III study of palbociclib combined with endocrine therapy (ET) in patients with hormone-receptor-positive (HR+), HER2-negative primary breast cancerand with high relapse risk after neoadjuvant chemotherapy (NACT): First results from PENELOPE-B. SABCS 2020: GS1-02.

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

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

1;376(22):2147-2159.
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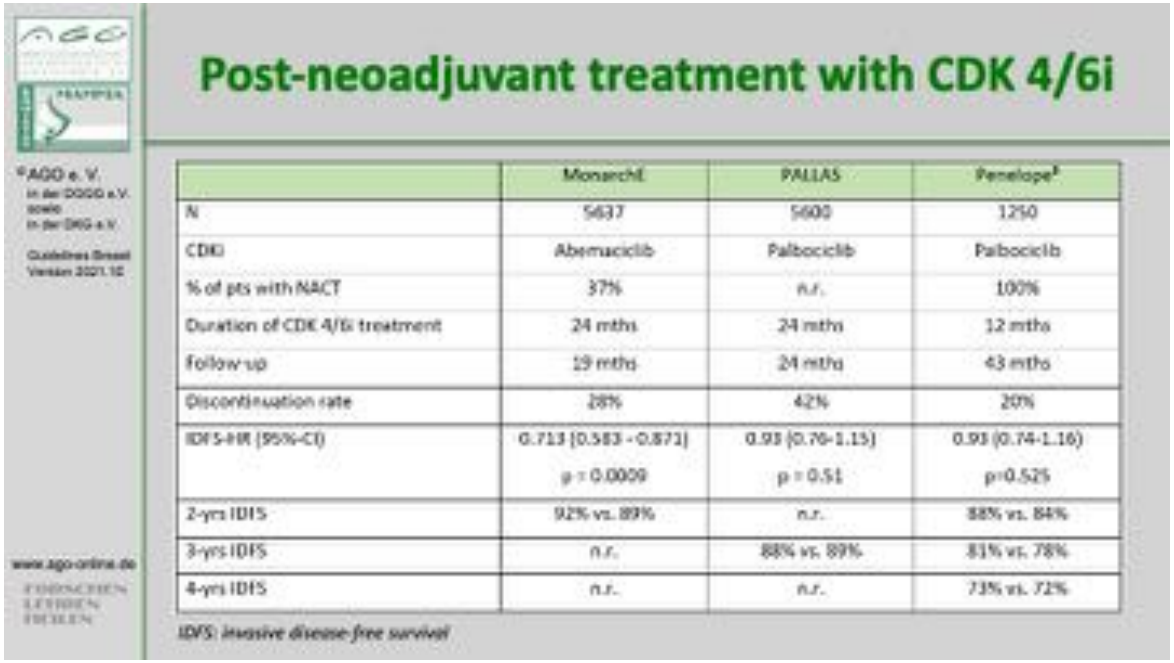

	Monarch[1]	PALLAS	Penelope[3]
N	5637	5600	1250
CDKi	Abemaciclib	Palbociclib	Palbociclib
% of pts with NACT	37%	n.r.	100%
Duration of CDK 4/6i treatment	24 mths	24 mths	12 mths
Follow up	19 mths	24 mths	43 mths
Discontinuation rate	28%	42%	20%
IDFS-HR (95%-CI)	0.713 (0.583 - 0.871) p = 0.0009	0.93 (0.76-1.15) p = 0.51	0.93 (0.74-1.16) p=0.525
2-yrs IDFS	92% vs. 89%	n.r.	88% vs. 84%
3-yrs IDFS	n.r.	88% vs. 89%	81% vs. 78%
4-yrs IDFS	n.r.	n.r.	73% vs. 72%

1. O'Shaughnessy JA , Johnston S, Harbeck N et al. Primary outcome analysis of invasive disease-free survival for monarchE: abemaciclib combined with adjuvant endocrine therapy for high risk early breast cancer. SABCS 2020:GS1-01.
2. Mayer EL, Gnant MI, DeMichele A et al. PALLAS: A randomized phase III trial of adjuvant palbociclib with endocrine therapy versus endocrine therapy alone for HR+/HER2- early breast cancer. Ann Oncol (2020) 31 (suppl_4): S1142-S1215. 10.1016/annonc/annonc325
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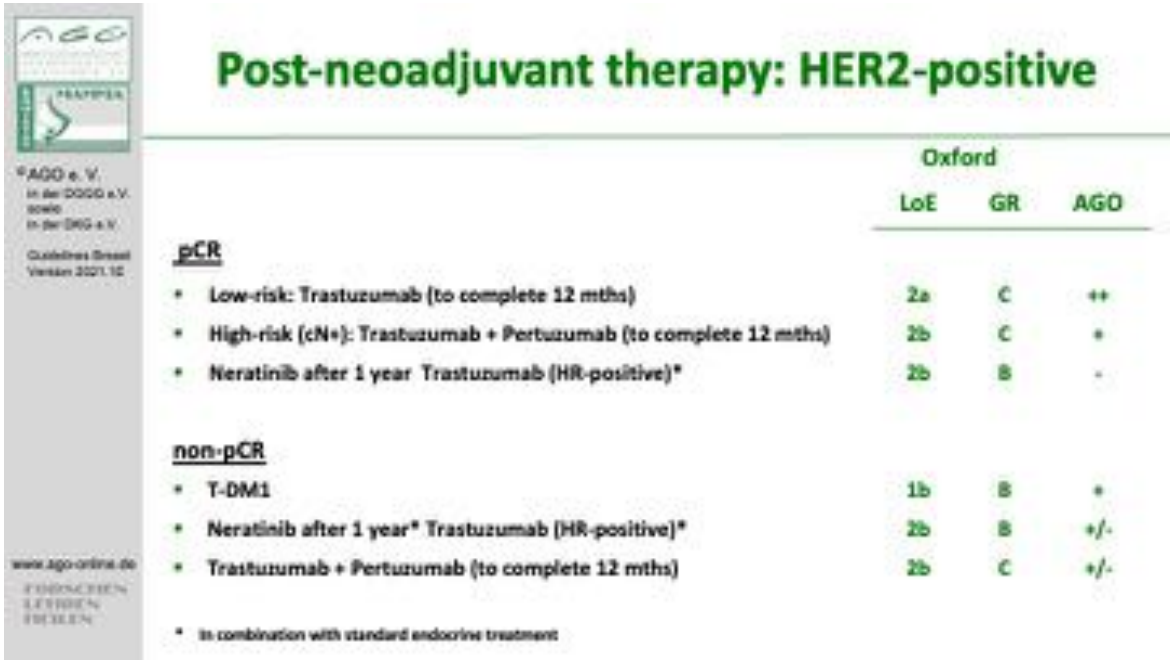

Statement HER2 positiv (bei pCR):

1. Goldhirsch A et al.; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet. 2013;382(9897):1021-8.
2. von Minckwitz G, Procter M, de Azambuja E, et al. APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017 Jul 13;377(2):122-131.
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4. Chan A, Moy B, Mansi J et al.: ExteNET Study Group. Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial. Clin Breast Cancer. 2020 Oct 6:S1526-8209(20)30258-5. doi: 10.1016/j.clbc.2020.09.014.

Statement HER2 positiv (bei non-pCR) :

1. von Minckwitz G, Huang CS, Mano MS et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2018 Dec 5. doi: 10.1056/NEJMoa1814017.
2. Martin M et al.; ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(12):1688-1700

3. Chan A, Moy B, Mansi J, et al.: ExteNET Study Group. Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial. Clin Breast Cancer. 2020 Oct 6:S1526-8209(20)30258-5. doi: 10.1016/j.clbc.2020.09.014.

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