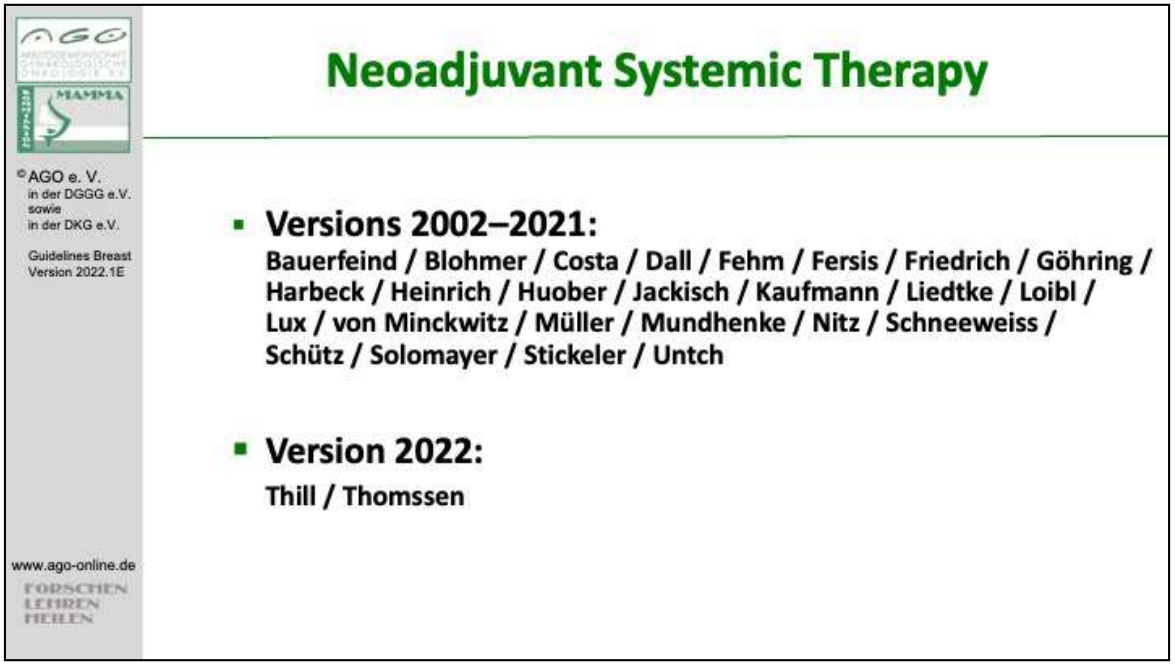
# Diagnosis and Treatment of Patients with early and advanced Breast Cancer

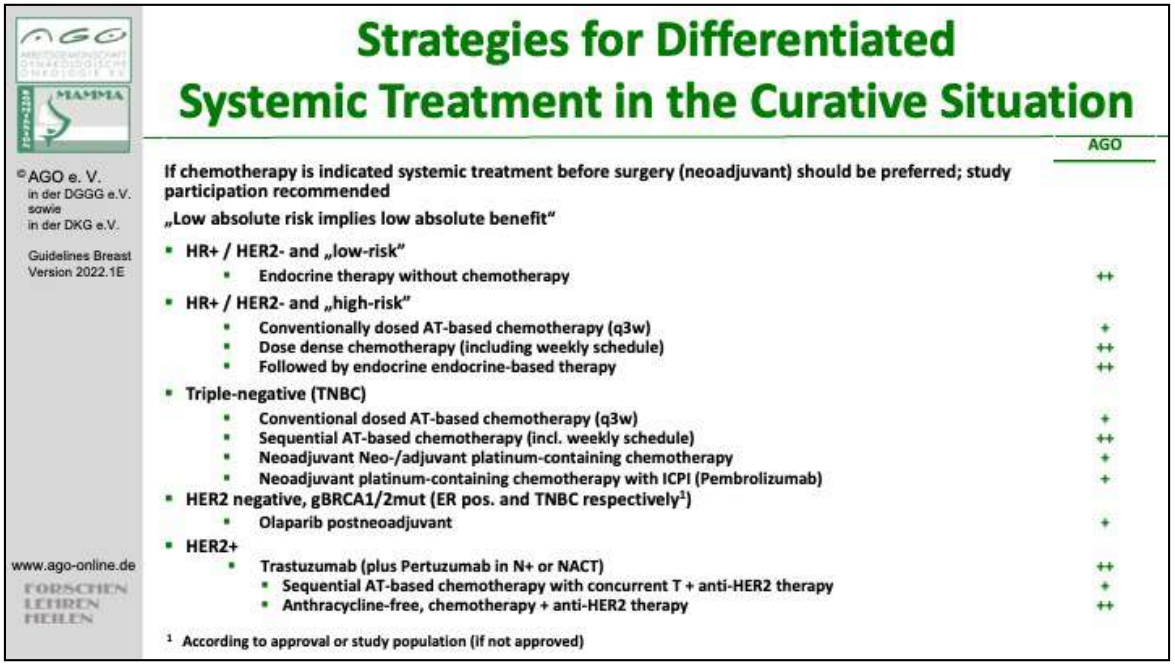


Guidelines Breast
Version 2022.1E

## Neoadjuvant
## (Primary) Systemic Therapy




Systematic review of published evidence
PUBMED 1999-2021
ASCO 1999-2021
SABCS 1999-2021
ECCO/ESMO 1999-2021




<u>Systematic review of published evidence</u>
PUBMED 1999-2021
ASCO 1999-2021
SABCS 1999-2021
ECCO/ESMO 1999-2021
<u>Trastuzumab in combination with chemotherapy</u>


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. Jackisch C, et al. HannaH phase III randomised study: Association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. Eur J

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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
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.

Her2+ Antrazyklin-freie Chemotherapie:

1. Ramphorstet MS, van der Voort A, Workhoven ED al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of

dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018 Dec;19(12):1630-1640. doi: 10.1016/S1470-2045(18)30570-9.
2. Anna van der Voort, Mette S. van Ramshorst, Erik D. van Werkhoven et al. J Clin Oncol 38: 2020 (suppl; abstr 501)

TNBC neoadjuvant chemotherapy with ICP

1. Mittendorf EA, Zhang H, Barrios Chet al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020 Oct 10;396(10257):1090-1100. doi: 10.1016/S0140-6736(20)31953-X.
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.
3. Schmid P, Cortes J, Dent R et al. KEYNOTE-522: Phase 3 study of pembrolizumab + chemotherapy vs placebo + chemotherapy as neoadjuvant treatment, followed by pembrolizumab vs placebo as adjuvant treatment for early triple-negative breast cancer (TNBC). ESMO 2021 Abstract #VP7_2021

Abemaciclib:

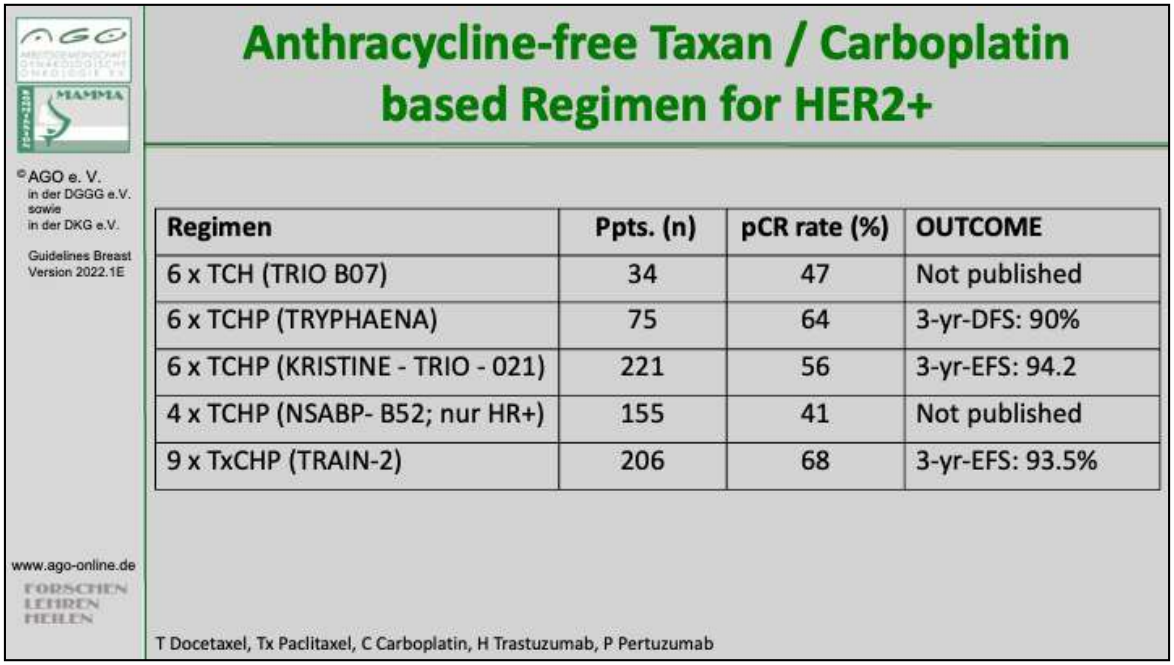
1. Harbeck N, Rastogi P, Martin M et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol. 2021 Dec;32(12):1571-1581. doi: 10.1016/j.annonc.2021.09.015. Epub 2021 Oct 14. PMID: 34656740.

Olaparib

1. Tutt ANJ, Garber JE, Kaufman B et al. Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer. N Engl J Med. 2021 Jun 24;384(25):2394-2405. doi: 10.1056/NEJMoa2105215. Epub 2021 Jun 3. PMID: 34081848.

Platin salts:

1. Loibl S, Sikov W, Huober J et al. Event-free survival (EFS), overall survival (OS), and safety of adding veliparib (V) plus carboplatin (Cb) or carboplatin alone to neoadjuvant chemotherapy in triple-negative breast cancer (TNBC) after ≥4 years of follow-up: BrighTNess, a randomized phase III trial. ESMO 2021 Abstract #1190. Annals of Oncology (2021) 32 (suppl_5): S407-S446. 10.1016/annonc/annonc687.

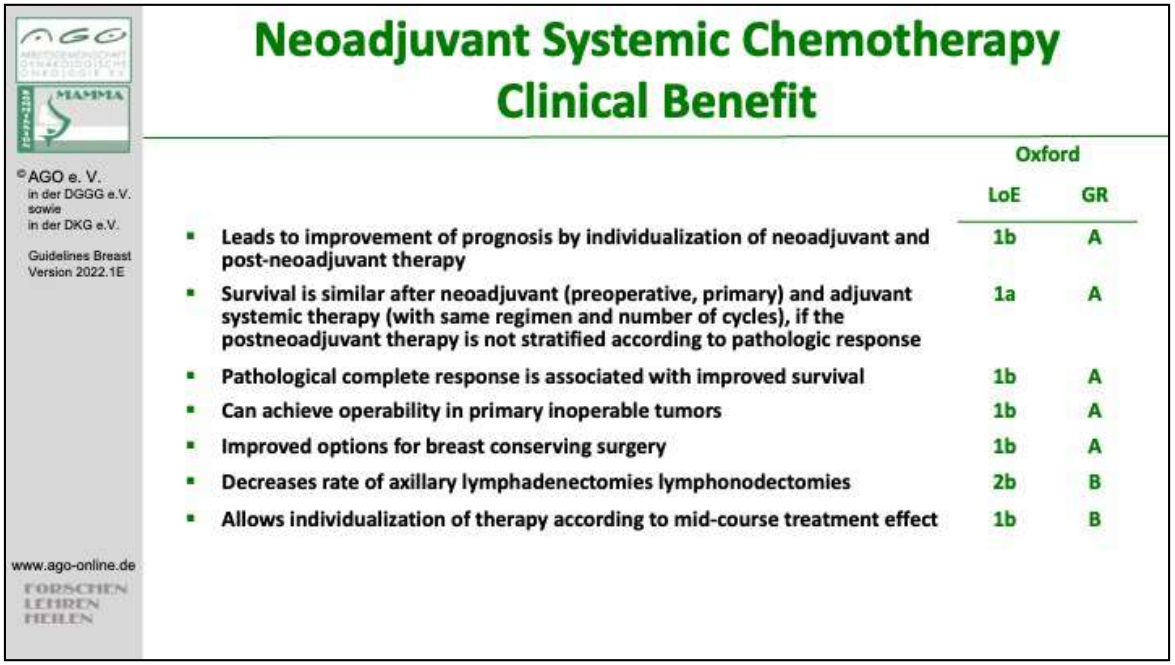



## Anthracycline-free Taxan / Carboplatin based Regimen for HER2+

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

T Docetaxel, Tx Paclitaxel, C Carboplatin, H Trastuzumab, P Pertuzumab


1. Hurvitz SA, Miller JM, Dichmann R et al. Final analysis of a phase II 3 arm randomized trial of neoadjuvant 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.




## Neoadjuvant Systemic Chemotherapy
## Clinical Benefit

| | Oxford LoE | Oxford GR |
|---|---|---|
| ▪ Leads to improvement of prognosis by individualization of neoadjuvant and post-neoadjuvant therapy | 1b | A |
| ▪ Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and number of cycles), if the postneoadjuvant therapy is not stratified according to pathologic response | 1a | A |
| ▪ Pathological complete response is associated with improved survival | 1b | A |
| ▪ Can achieve operability in primary inoperable tumors | 1b | A |
| ▪ Improved options for breast conserving surgery | 1b | A |
| ▪ Decreases rate of axillary lymphadenectomies lymphonodectomies | 2b | B |
| ▪ Allows individualization of therapy according to mid-course treatment effect | 1b | B |


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

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

Pathological complete response is associated with improved survival in all subgroups

1. von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012: 30; 1796
2. Fisher B, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998: 16; 2672
3. Van der Hage JA, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for

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

Can achieve operability in primary inoperable tumors

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

Improved options for breast conserving surgery

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

Reduces the rate of lymphadenectomies

1. Fernandez-Gonzalez S, et al. The Shift From Sentinel Lymph Node Biopsy Performed Either Before or After Neoadjuvant Systemic Therapy in the Clinical Negative Nodes of Breast Cancer Patients. Results, and the Advantages and Disadvantages of Both Procedures. Clin Breast Cancer 2018 Feb;18(1):71-77.
2. Reimer T et al. Avoiding axillary sentinel node biopsy after neoadjuvant systemic therapy in breast cancer: rationale for the prospective, multicentric EUBREAST-01 trial. Cancers 2020:3698; doi:10.3390/cancers12123698

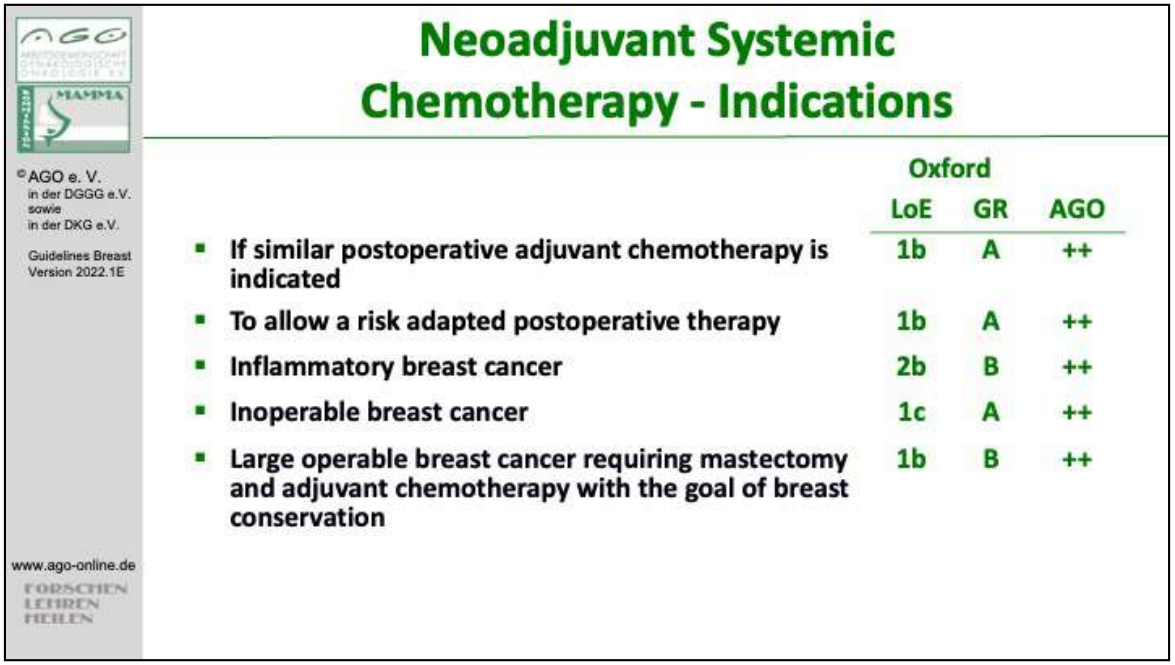
Allows individualization of therapy according to mid-course treatment effect

1. Von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in

various intrinsic breast cancer subtypes. J Clin Oncol 2012: 30; 1796

Allows individualization of post-neoadjuvant treatment

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





Inflammatory breast cancer

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011: 22; 515

Inoperable breast cancer

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011: 22; 515

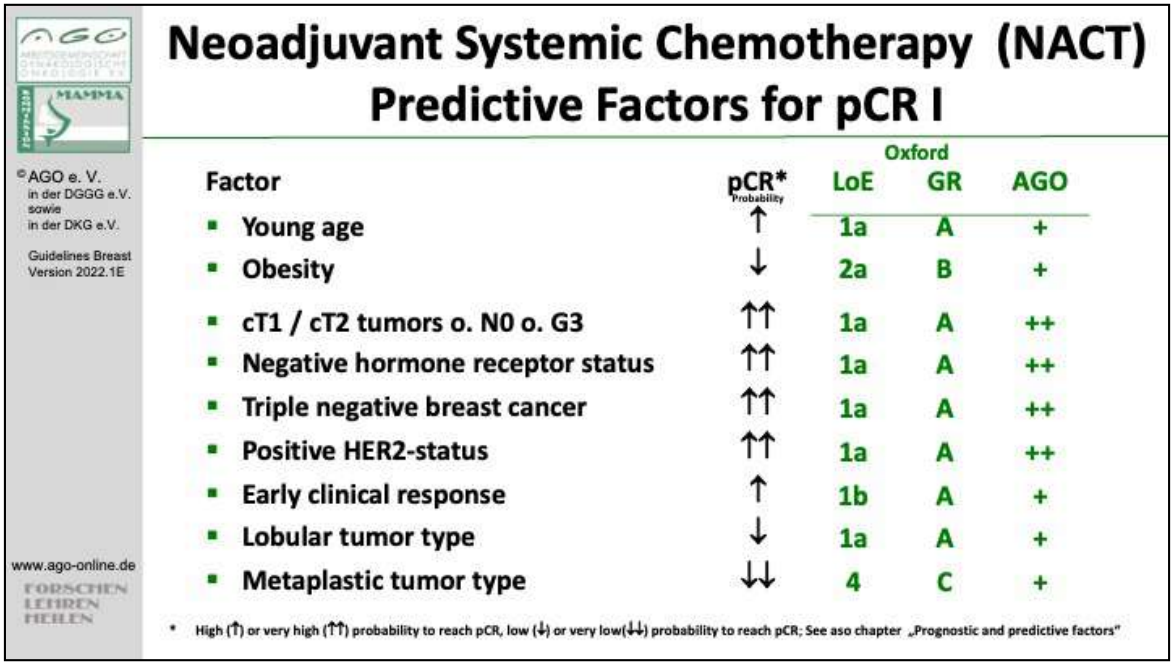
Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant

systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508
3. EBCTCG. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol 2018 Jan;19(1):27-39.

<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

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

Body mass index

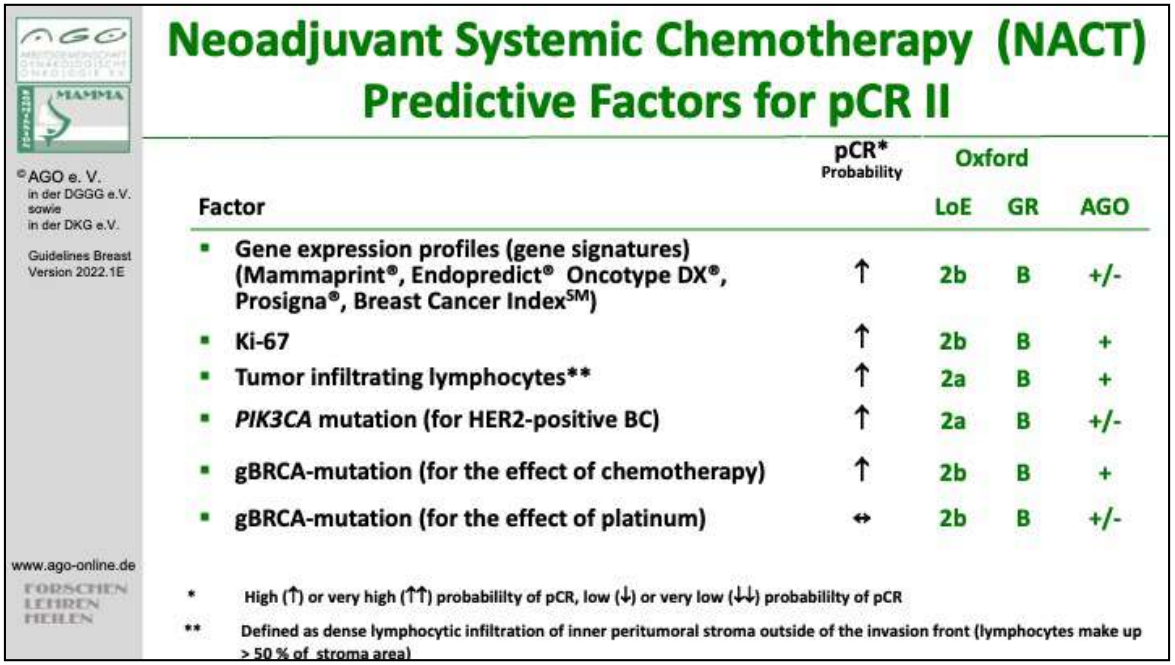
1. Wang H, Zhang S, Yee D, et al. Impact of body mass index on pathological complete response following neoadjuvant chemotherapy in operable breast cancer: a meta analysis. Breast Cancer 2021;28(3):616-629

Lobular cancer

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

Metaplastic breast cancer

1. McMullen ER, 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.



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Guidelines Breast
Version 2022.1E

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FORSCHEN
LEHREN
HEILEN

## Neoadjuvant Systemic Chemotherapy (NACT)
## Predictive Factors for pCR II

| Factor | pCR* Probability | Oxford LoE | Oxford GR | Oxford AGO |
|---|---|---|---|---|
| Gene expression profiles (gene signatures) (Mammaprint®, Endopredict® Oncotype DX®, Prosigna®, Breast Cancer Index$^{SM}$) | ↑ | 2b | B | +/- |
| Ki-67 | ↑ | 2b | B | + |
| Tumor infiltrating lymphocytes** | ↑ | 2a | B | + |
| *PIK3CA* mutation (for HER2-positive BC) | ↑ | 2a | B | +/- |
| gBRCA-mutation (for the effect of chemotherapy) | ↑ | 2b | B | + |
| gBRCA-mutation (for the effect of platinum) | ↔ | 2b | B | +/- |

* High (↑) or very high (↑↑) probabililty of pCR, low (↓) or very low (↓↓) probabililty of pCR

** Defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (lymphocytes make up > 50 % of stroma area)

TIL


1. Denkert, C., Loibl, S., Noske, A., et al. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. 2010. J. Clin. Oncol. 28, 105–113. doi:10.1200/JCO.2009.23.7370.
2. Denkert C, von Minckwitz G, Brase JC, et al. Tumor-Infiltrating Lymphocytes and Response to Neoadjuvant Chemotherapy With or Without Carboplatin in Human Epidermal Growth Factor Receptor 2-Positive and Triple-Negative Primary Breast Cancers. J Clin Oncol. 2014 Dec 22. pii: JCO.2014.58.1967.
3. Ibrahim EM, Al-Foheidi ME, Al-Mansour MM, et al. The prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancer: a meta-analysis. Breast Cancer Res Treat. 2014 Dec;148(3):467-76
4. Loi S, Michiels S, Salgado R, et al. Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial. Ann Oncol. 2014 Aug;25(8):1544-50. Doi
5. Mao Y, Qu Q, Zhang Y, et al. The Value of Tumor Infiltrating Lymphocytes (TILs) for Predicting Response to Neoadjuvant Chemotherapy in Breast Cancer: A Systematic Review and Meta-Analysis. PLoS One. 2014 Dec 12;9(12)
6. Tung NM, Winer EP. Tumor-Infiltrating Lymphocytes and Response to Platinum in Triple-Negative Breast Cancer. J Clin Oncol. 2015 Jan 5. pii: JCO.2014.59.6031.

7. Denkert C, von Minckwitz G, Darb—Esfahani S et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvanttherapy. Lancet Oncol 2018;19(1):40-50.

PIK3CA

1. Loibl S, von Minckwitz G, Schneeweiss A, et al. PIK3CA mutations are associated with lower rates of pathologic complete response to anti-human epidermal growth factor receptor 2 (her2) therapy in primary HER2-overexpressing breast cancer. J Clin Oncol. 2014 Oct
2. Nuciforo PG, Aura C, Holmes E, et al: Benefit to neoadjuvant anti–Human Epidermal Growth Factor Receptor 2 (HER2)-targeted therapies in HER2-positive primary breast cancer is independent of Phosphatase and tensin homolog deleted from chromosome 10 (PTEN) status. Ann Oncol. 2015 Jul;26(7):1494-500. doi: 10.1093/annonc/mdv175. Epub 2015 Apr 7.
3. Pogue-Geile KL, Song N, Jeong JH, et al: Intrinsic Subtypes, PIK3CA Mutation, and the Degree of Benefit From Adjuvant Trastuzumab in the NSABP B-31 Trial. Clin Oncol. 2015 Jan 5. pii: JCO.2014.56.2439
4. Sueta A, Yamamoto Y, Yamamoto-Ibusuki M, et al. An Integrative Analysis of PIK3CA Mutation, PTEN, and INPP4B Expression in Terms of Trastuzumab Efficacy in HER2-Positive Breast Cancer. PLoS One. 2014 Dec 26;9(12):e116054.
5. Loibl S, Majewski I, Guarneri V, et al. PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol. 2016 Aug;27(8):1519-25.
6. Loibl S, Majewski I, Guarneri V, et al. PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol. 2019 Jan 9. doi: 10.1093/annonc/mdy536. [Epub ahead of print]
7. Fan H, Li C, Xiang Q, et al. PIK3CA mutations and their response to neoadjuvant treatment in early breast cancer: A systematic review and meta-analysis. Thorac Cancer. 2018 May;9(5):571-579.
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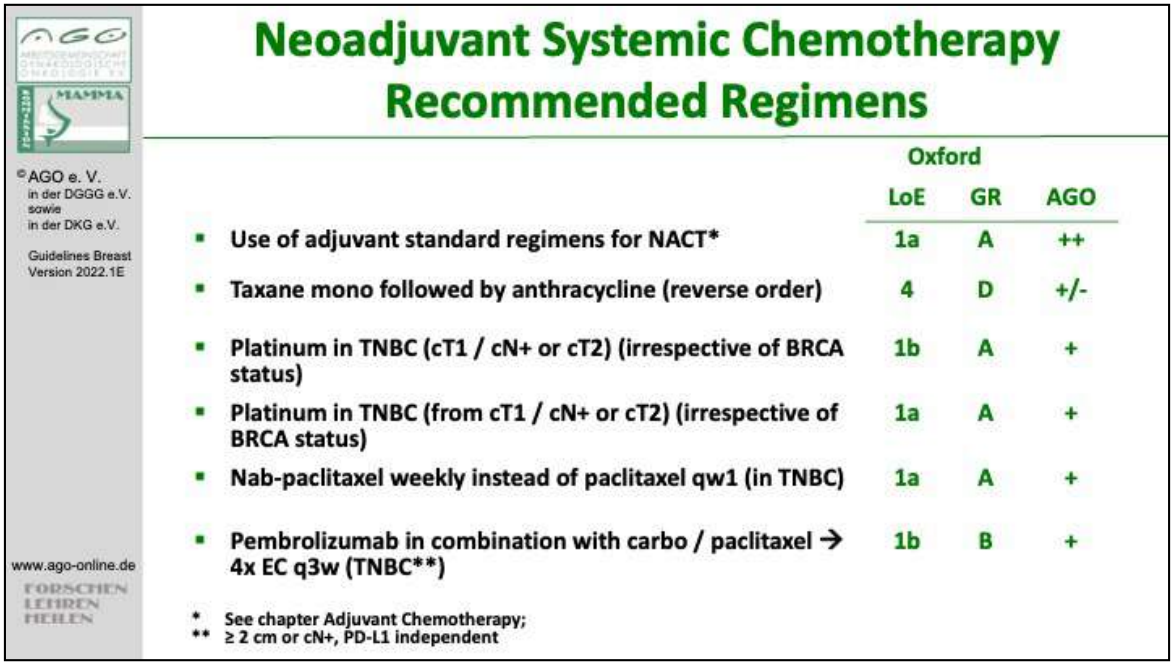
gBRCA bei TNBC

1. Loibl S, Weber KE, Timms KM et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. Ann Oncol. 2018 Dec 1;29(12):2341-2347.





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)

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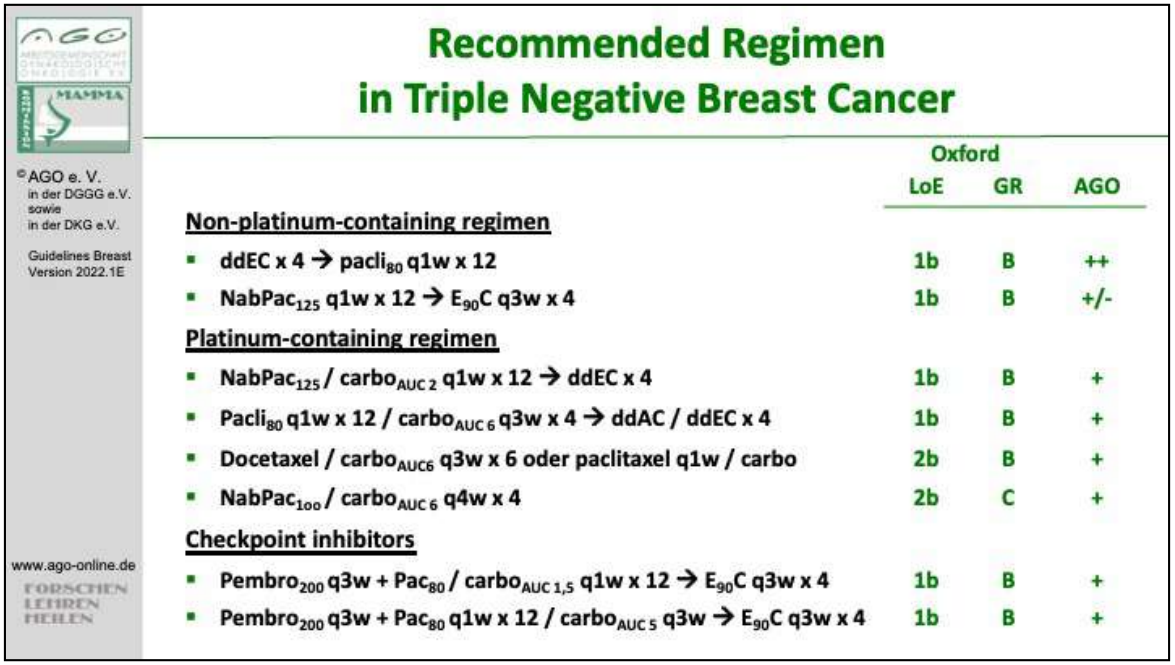



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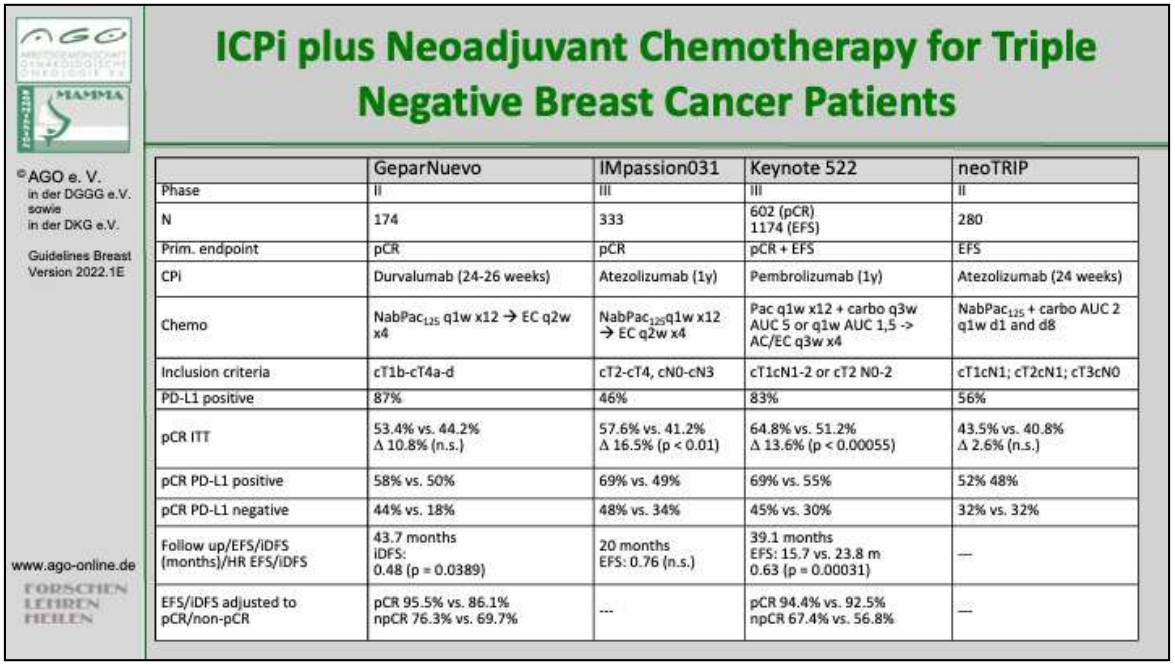

## ICPi plus Neoadjuvant Chemotherapy for Triple Negative Breast Cancer Patients

| | GeparNuevo | IMpassion031 | Keynote 522 | neoTRIP |
|---|---|---|---|---|
| Phase | II | III | III | II |
| N | 174 | 333 | 602 (pCR)<br>1174 (EFS) | 280 |
| Prim. endpoint | pCR | pCR | pCR + EFS | EFS |
| CPi | Durvalumab (24-26 weeks) | Atezolizumab (1y) | Pembrolizumab (1y) | Atezolizumab (24 weeks) |
| Chemo | $NabPac_{125}$ q1w x12 → EC q2w x4 | $NabPac_{125}$q1w x12 → EC q2w x4 | Pac q1w x12 + carbo q3w AUC 5 or q1w AUC 1,5 -> AC/EC q3w x4 | $NabPac_{125}$ + carbo AUC 2 q1w d1 and d8 |
| Inclusion criteria | cT1b-cT4a-d | cT2-cT4, cN0-cN3 | cT1cN1-2 or cT2 N0-2 | cT1cN1; cT2cN1; cT3cN0 |
| PD-L1 positive | 87% | 46% | 83% | 56% |
| pCR ITT | 53.4% vs. 44.2%<br>Δ 10.8% (n.s.) | 57.6% vs. 41.2%<br>Δ 16.5% (p < 0.01) | 64.8% vs. 51.2%<br>Δ 13.6% (p < 0.00055) | 43.5% vs. 40.8%<br>Δ 2.6% (n.s.) |
| pCR PD-L1 positive | 58% vs. 50% | 69% vs. 49% | 69% vs. 55% | 52% 48% |
| pCR PD-L1 negative | 44% vs. 18% | 48% vs. 34% | 45% vs. 30% | 32% vs. 32% |
| Follow up/EFS/iDFS (months)/HR EFS/iDFS | 43.7 months<br>iDFS:<br>0.48 (p = 0.0389) | 20 months<br>EFS: 0.76 (n.s.) | 39.1 months<br>EFS: 15.7 vs. 23.8 m<br>0.63 (p = 0.00031) | — |
| EFS/iDFS adjusted to pCR/non-pCR | pCR 95.5% vs. 86.1%<br>npCR 76.3% vs. 69.7% | — | pCR 94.4% vs. 92.5%<br>npCR 67.4% vs. 56.8% | — |




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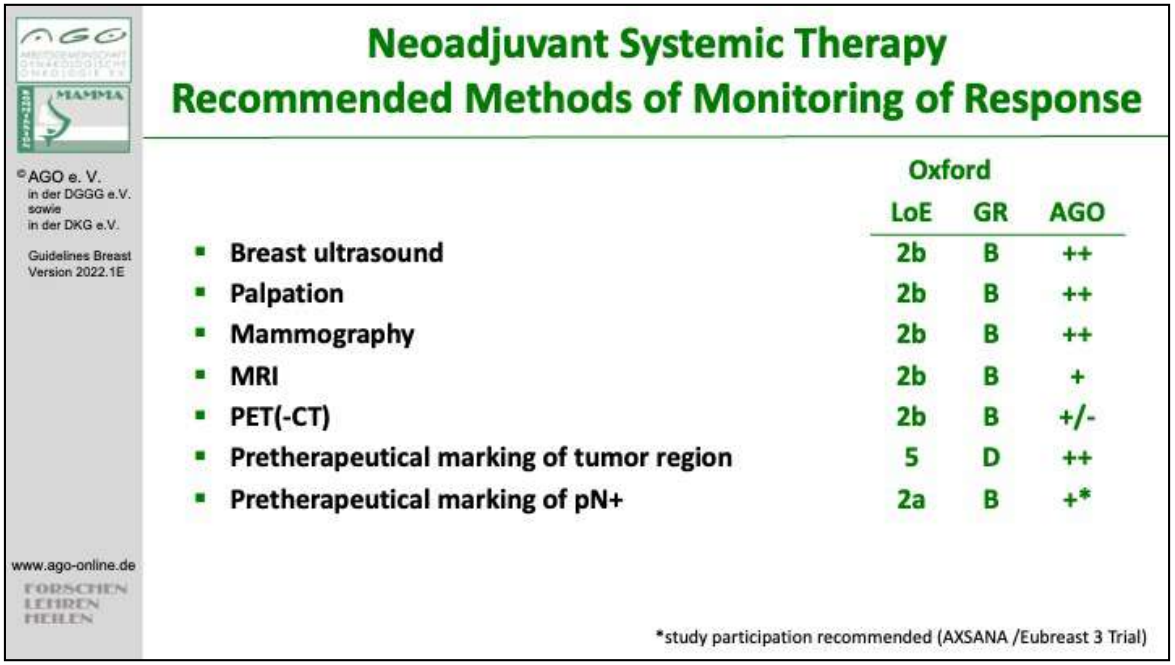



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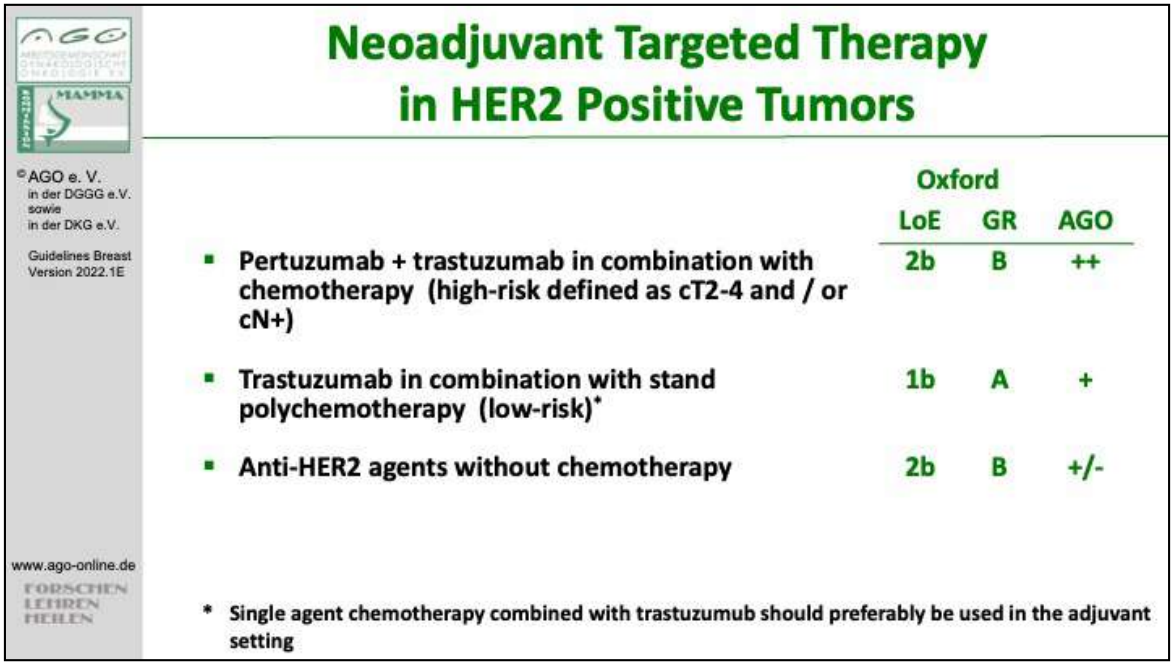



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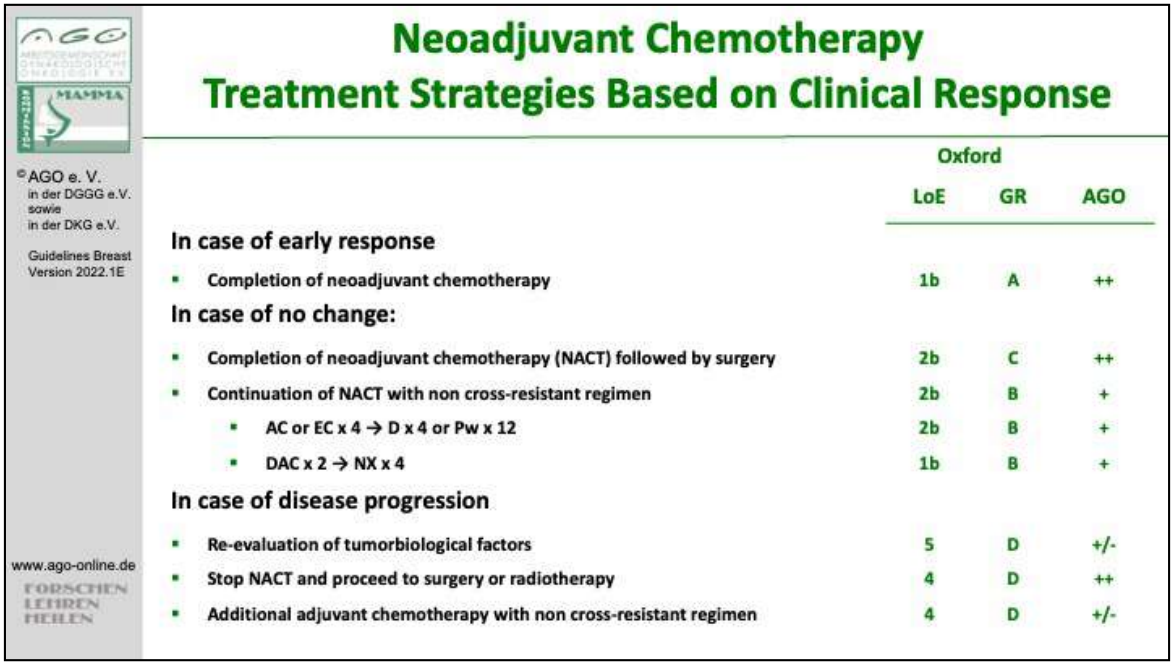


## Neoadjuvant Chemotherapy
## Treatment Strategies Based on Clinical Response

| | Oxford LoE | Oxford GR | Oxford AGO |
|---|---|---|---|
| **In case of early response** | | | |
| ▪ Completion of neoadjuvant chemotherapy | 1b | A | ++ |
| **In case of no change:** | | | |
| ▪ Completion of neoadjuvant chemotherapy (NACT) followed by surgery | 2b | C | ++ |
| ▪ Continuation of NACT with non cross-resistant regimen | 2b | B | + |
| ▪ AC or EC x 4 → D x 4 or Pw x 12 | 2b | B | + |
| ▪ DAC x 2 → NX x 4 | 1b | B | + |
| **In case of disease progression** | | | |
| ▪ Re-evaluation of tumorbiological factors | 5 | D | +/- |
| ▪ Stop NACT and proceed to surgery or radiotherapy | 4 | D | ++ |
| ▪ Additional adjuvant chemotherapy with non cross-resistant regimen | 4 | D | +/- |


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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
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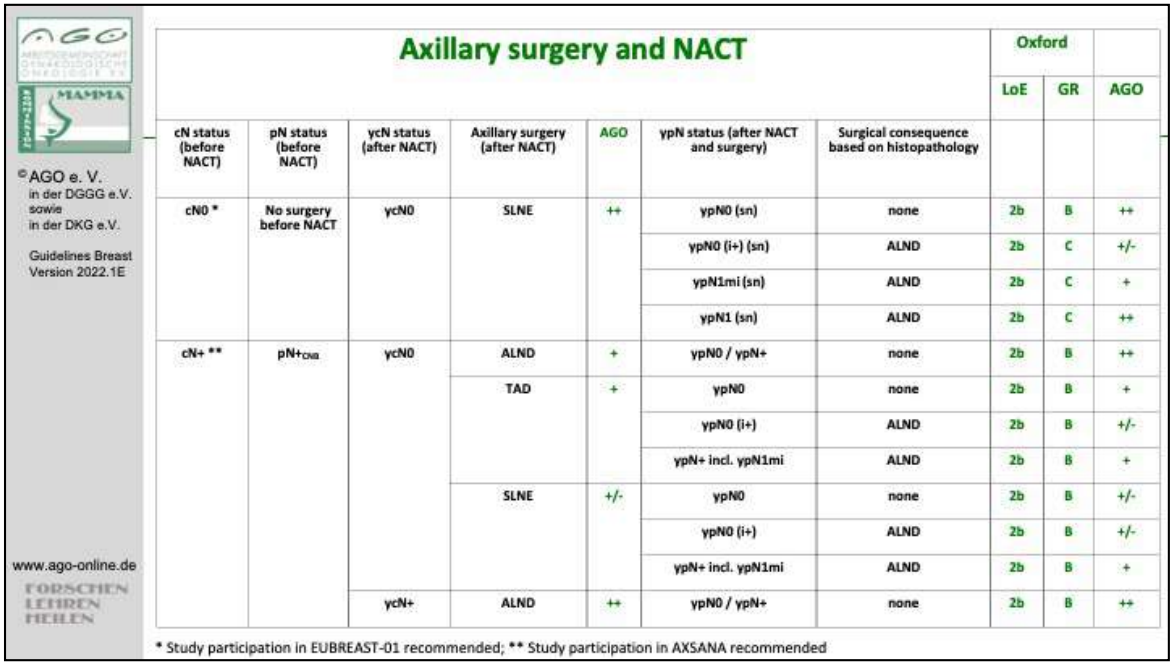
3. Colleoni M, Gray KP, Gelber S et al. Low-Dose Oral Cyclophosphamide and Methotrexate Maintenance for Hormone Receptor-Negative Early Breast Cancer: International Breast Cancer Study Group Trial 22-00. J Clin Oncol 2016;34(28):3400-8.



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LEHREN
HEILEN

## Axillary surgery and NACT

| cN status (before NACT) | pN status (before NACT) | ycN status (after NACT) | Axillary surgery (after NACT) | AGO | ypN status (after NACT and surgery) | Surgical consequence based on histopathology | Oxford LoE | Oxford GR | AGO |
|---|---|---|---|---|---|---|---|---|---|
| cN0 * | No surgery before NACT | ycN0 | SLNE | ++ | ypN0 (sn) | none | 2b | B | ++ |
| | | | | | ypN0 (i+) (sn) | ALND | 2b | C | +/- |
| | | | | | ypN1mi (sn) | ALND | 2b | C | + |
| | | | | | ypN1 (sn) | ALND | 2b | C | ++ |
| cN+ ** | $pN+_{CNB}$ | ycN0 | ALND | + | ypN0 / ypN+ | none | 2b | B | ++ |
| | | | TAD | + | ypN0 | none | 2b | B | + |
| | | | | | ypN0 (i+) | ALND | 2b | B | +/- |
| | | | | | ypN+ incl. ypN1mi | ALND | 2b | B | + |
| | | | SLNE | +/- | ypN0 | none | 2b | B | +/- |
| | | | | | ypN0 (i+) | ALND | 2b | B | +/- |
| | | | | | ypN+ incl. ypN1mi | ALND | 2b | B | + |
| | | ycN+ | ALND | ++ | ypN0 / ypN+ | none | 2b | B | ++ |

* Study participation in EUBREAST-01 recommended; ** Study participation in AXSANA recommended


1. Giuliano AE, Ballman KV, McCall L et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: The acosog z0011 (alliance) randomized clinical trial. JAMA 2017, 318, 918-926
2. Reimer TS, Nekljudova V, Loibl, S et al. Restricted axillary staging in clinically and sonographically node-negative early invasive breast cancer (c/i t1-2) in the context of breast concerving therapy: First results following commencement of the intergroup-sentinel-mamma (insema) trial. Geburtsh Frauenheilk 2017, 77, 149-157
3. Gion M, Pérez-García JM, Llombart-Cussac A et al. Surrogate endpoints for early-stage breast cancer: a review of the state of the art, controversies, and future prospects. Ther Adv Med Oncol 2021, 13:17588359211059587.
4. Chiec L, Shah AN. Risk-based Approaches for Optimizing Treatment in HER2-Positive Early Stage Breast Cancer. Semin Oncol 2020, 47:249-258.
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Locoregional recurrence risk after neoadjuvant chemotherapy: A pooled analysis of nine prospective neoadjuvant breast cancer trials. Eur J Cancer 2020, 130, 92-101.
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10. 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, 1455-1461.
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12. Simons JM, van Nijnatten TJA, van der Pol CC et al. Diagnostic accuracy of different surgical procedures for axillary staging after neoadjuvant systemic therapy in node-positive breast cancer: A systematic review and meta-analysis. Ann Surg 2019, 269, 432-442.
13. Tee, S.R.; Devane, L.A.; Evoy, D.; et al. E.W. Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. Br J Surg 2018, 105, 1541-1552.
14. Schneeweiss A, Mobus V, Tesch H et al. Intense dose-dense epirubicin, paclitaxel, cyclophosphamide versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer) for neoadjuvant treatment of high-risk early breast cancer (geparocto-gbg 84): A randomised phase iii trial. Eur J Cancer 2019, 106, 181-192.
15. Barron AU, Hoskin TL, Day CN et al. Association of low nodal positivity rate among patients with erbb2-positive or triple-negative breast cancer and breast pathologic complete response to neoadjuvant chemotherapy. JAMA surgery 2018.
16. Samiei, S.; Simons, J.M.; Engelen, S.M.E.; et al. Axillary pathologic complete response after neoadjuvant systemic therapy by breast cancer subtype in patients with initially clinically node-positive disease: A systematic review and meta-analysis. JAMA surgery 2021, e210891.
17. Tadros, A.B.; Yang, W.T.; Krishnamurthy, S.; et al. Identification of patients with documented pathologic complete response in the breast after neoadjuvant chemotherapy for omission of axillary surgery. JAMA surgery 2017, 152, 665-670.
18. Samiei, S.; van Nijnatten, T.J.A.; de Munck, L.; et al. Correlation between pathologic complete response in the breast and absence of axillary lymph node metastases after neoadjuvant systemic therapy. Ann Surg 2018.
19. Kuemmel, S.; Heil, J.; Rueland, A.; et al. A prospective, multicenter registry study to evaluate the clinical feasibility of targeted axillary dissection (tad) in node-positive breast cancer patients. Ann Surg 2020.
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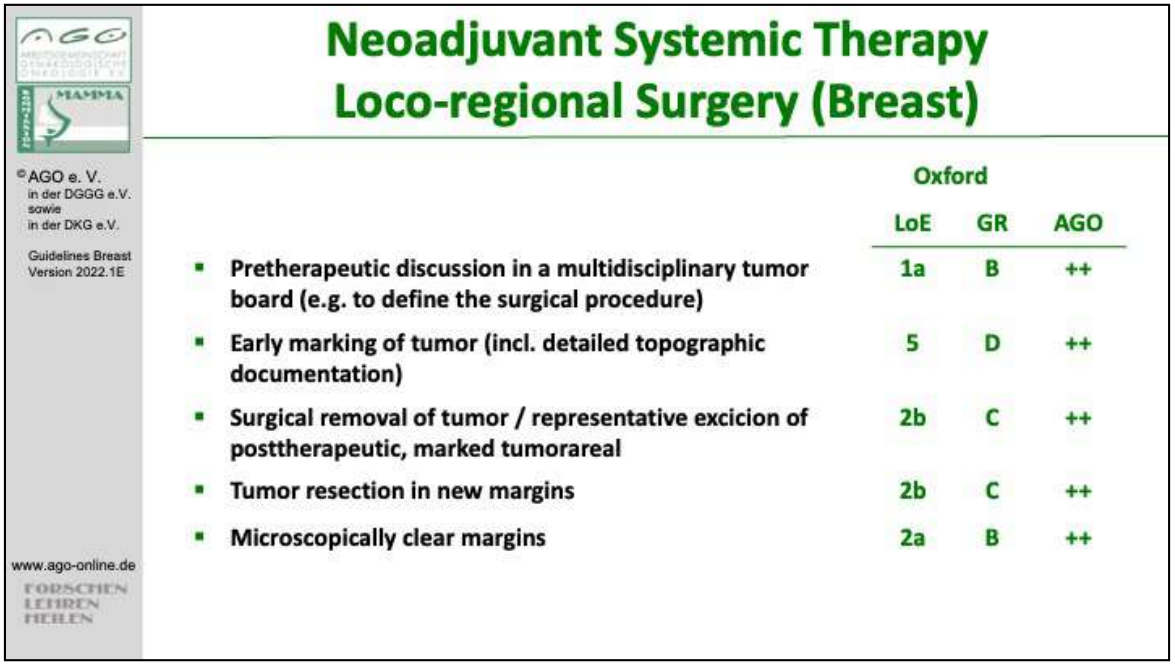




Pretherapeutic definition of the definitive surgical procedure

1. EBCTCG. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol Lancet Oncol. 2018 Jan;19(1):27-39.
2. Bossuyt V, Symmans WF. Standardizing of Pathology in Patients Receiving Neoadjuvant Chemotherapy. Ann Surg Oncol. 2016 Oct;23(10):3153-61.
3. Zdenkowski N et al. A survey of Australian and New Zealand clinical practice with neoadjuvant systemic therapy for breast cancer. Intern Med J. 2016 Jun;46(6):677-83.

Mark previous tumor region

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

Surgery

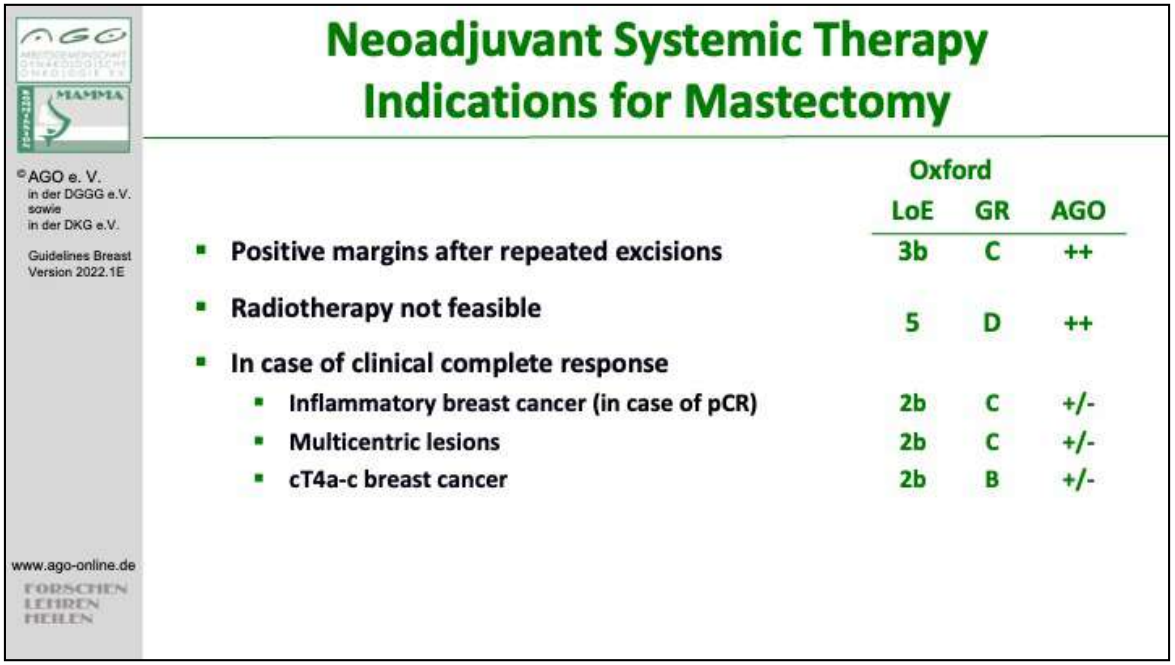
1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

Microscopically clear margins

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

Tumor resection according to imaging result

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




## Neoadjuvant Systemic Therapy
## Indications for Mastectomy

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


Positive margins after repeated excisions

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

Radiotherapy not feasible

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

In case of clinical complete response:
Inflammatory breast cancer in case of pCR

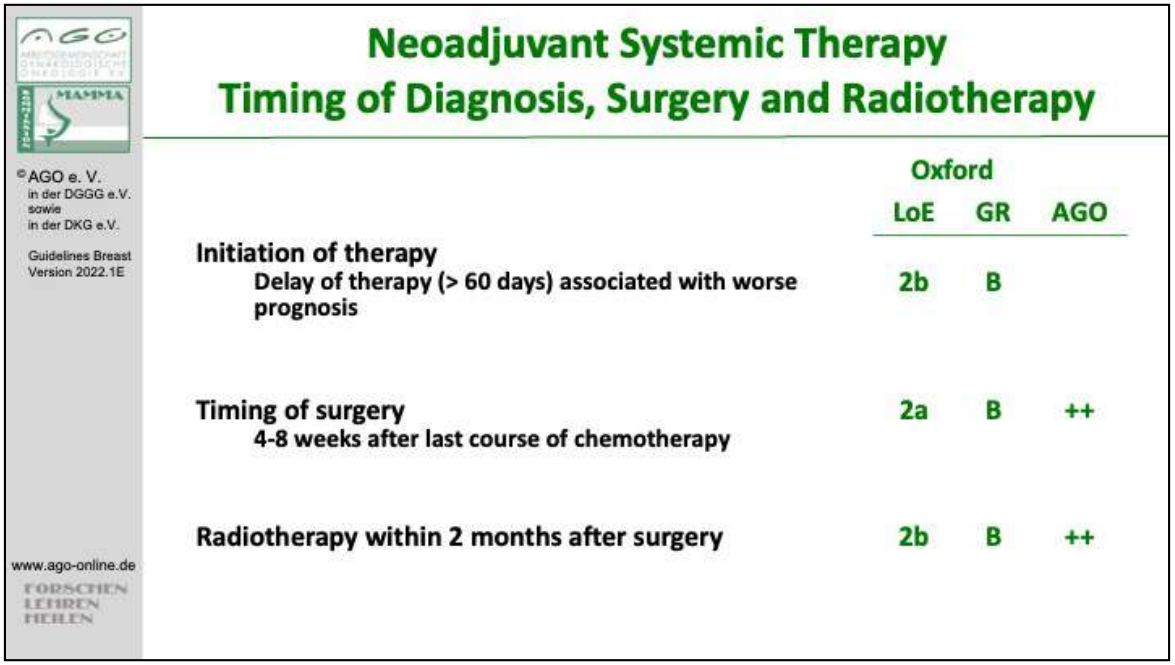
1. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011: 22; 515
2. Brzezinska M, Williams LJ, Thomas J et al.: Outcomes of patients with inflammatory breast cancer treated by breast-conserving surgery.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

Multicentric lesions

1. Ataseven B, et al. Impact of Multifocal or Multicentric Disease on Surgery and Locoregional, Distant and Overall Survival of 6,134 Breast Cancer Patients Treated With Neoadjuvant Chemotherapy. Ann Surg Oncol 2014 [Epub ahead of print]

cT4a-c breast cancer

1. Ataseven B, et al. Impact of Multifocal or Multicentric Disease on Surgery and Locoregional, Distant and Overall Survival of 6,134 Breast Cancer Patients Treated With Neoadjuvant Chemotherapy. Ann Surg Oncol 2014





Initiation of chemotherapy after histologic diagnosis

1. de Melo Gagliato D, Lei X, Giordano SH, et al. Impact of Delayed Neoadjuvant Systemic Chemotherapy on Overall Survival Among Patients with Breast Cancer. Oncologist. 2020;25(9):749-757. doi: 10.1634/theoncologist.2019-0744.

Time between surgery and last chemotherapy

1. Cullinane C, Shrestha A, Al Maksoud A, et al. Optimal timing of surgery following breast cancer neoadjuvant chemotherapy: A systematic review and meta-analysis. J Surg Oncol. 2021 Jul;47(7):1507-1513.
2. Suleman K, Almalik O, Haque E et al. Does the Timing of Surgery after Neoadjuvant Therapy in Breast Cancer Patients Affect the Outcome? Oncology. 2020;98(3):168-173.
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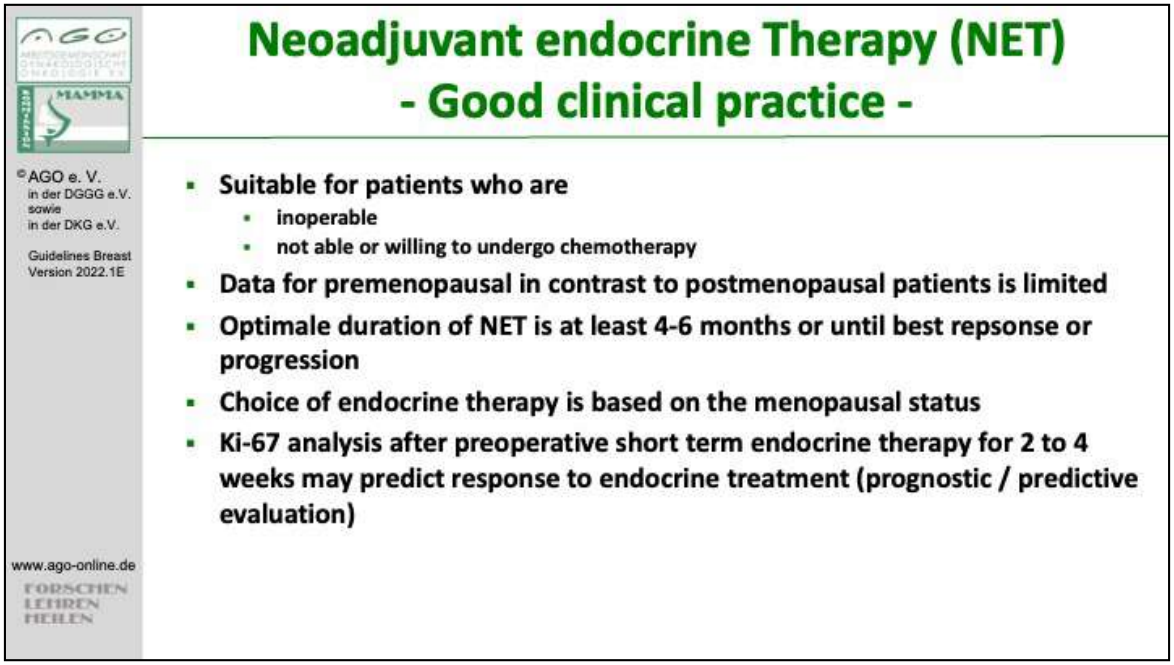
4. Sanford RA, Lei X, Barcenas CH et al. Impact of Time from Completion of Neoadjuvant Chemotherapy to Surgery on Survival Outcomes in Breast Cancer Patients. Ann Surg Oncol 2016;23(5):1515-21.

Radiotherapy 2 mths after surgery BCS

1. Silva SB, Pereira AAL, Marta GN, et al. Clinical impact of adjuvant radiation therapy delay after neoadjuvant chemotherapy in locally advanced breast cancer. Breast. 2018;38:39-44. doi: 10.1016/j.breast.2017.11.012.





1. Lerebours F, Cabel L, Pierga JY. Neoadjuvant Endocrine Therapy in Breast Cancer Management: State of the Art. Cancers (Basel). 2021 Feb 21;13(4):902.
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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.
4. Harbeck N, Gluz O, Kümmel S et al., Endocrine therapy alone in patients with intermediate or high-risk luminal early breast cancer (0-3 lymph nodes), Recurrence Score <26 and Ki67 response after preoperative endocrine therapy: Primary outcome results from the WSG-ADAPT HR+/HER2- trial. SABCS 2020 GS4-04.
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6. Nitz U et al. The run-in phase of the prospective WSG-ADAPT HR+/Her2- trial demonstrates the feasibility of a study design combining static and dynamic biomarker assessments for individualized therapy in early breast cancer. Ther Adv Med Oncol. 2020 Nov23:12:1758835920973130
7. Madigan LI et al. Neoadjuvant endocrine therapy in locally advanced estrogen and progesterone receptor-positive breast cancer: determining the optimal endocrine agent and treatment duration in postmenopausal women-a literature review and proposed

guidelines. Breast Cancer Res. 2020 Jul 20;22(1):77.
8. Kurozumi S et al. Impact of combining the progesterone receptor and preoperative endocrine prognostic index (PEPI) as a prognostic factor after neoadjuvant endocrine therapy using aromatase inhibitors in postmenopausal ER positive and HER2 negative breast cancer. PLoS One. 2018;13(8):e0201846.
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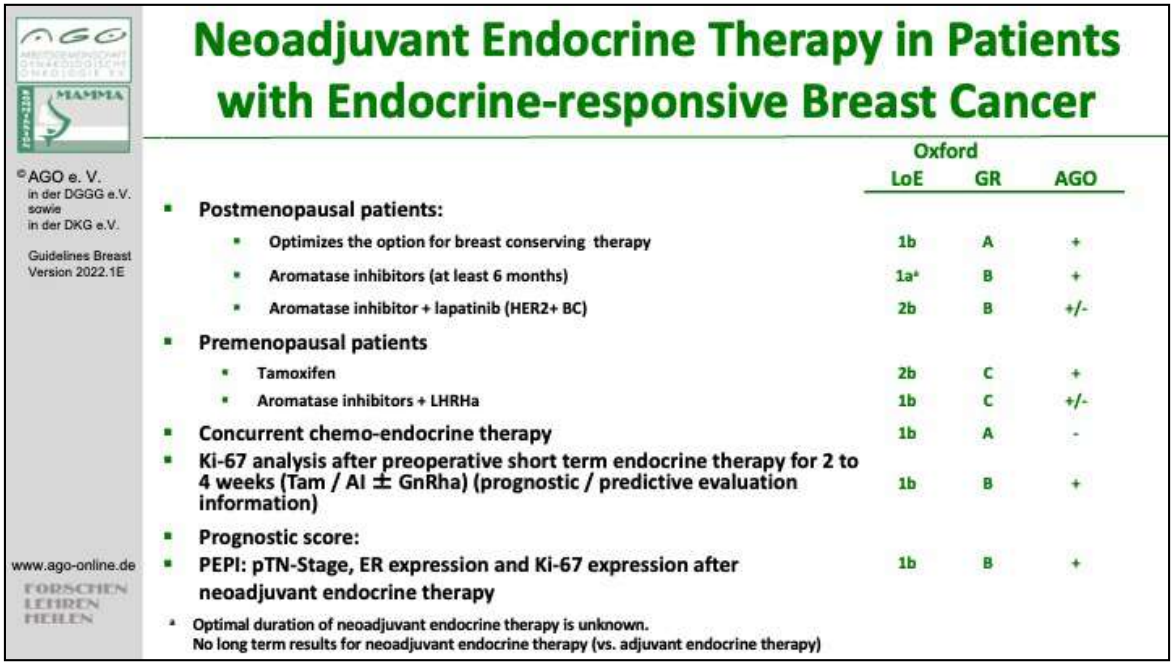
10. Spring LM, et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA Oncol. 2016 Nov 1;2(11):1477-1486.
11. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009: 18; 339




<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
4. Spring LM et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA oncology 2016;2(11):1477-86.
5. Madigan LI et al. Neoadjuvant endocrine therapy in locally advanced estrogen and progesterone receptor-positive breast cancer: determiningthe 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


<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
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, 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. Lerebours F, Cabel L, Pierga JY. Neoadjuvant Endocrine Therapy in Breast Cancer Management: State of the Art. Cancers (Basel). 2021 Feb 21;13(4):902.
2. Sella T, Weiss A, Mittendorf EA, et al. Neoadjuvant Endocrine Therapy in Clinical Practice: A Review. JAMA Oncol. 2021 Nov 1;7(11):1700-1708.
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5. Smith I 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

6. Nitz U et al. The run-in phase of the prospective WSG-ADAPT HR+/Her2- trial demonstrates the feasibility of a study design combining static and dynamic biomarker assessments for individualized therapy in early breast cancer. Ther Adv Med Oncol. 2020 Nov23:12:1758835920973130
7. Madigan LI et al. Neoadjuvant endocrine therapy in locally advanced estrogen and progesterone receptor-positive breast cancer: determining the optimal endocrine agent and treatment duration in postmenopausal women-a literature review and proposed guidelines. Breast Cancer Res. 2020 Jul 20;22(1):77.
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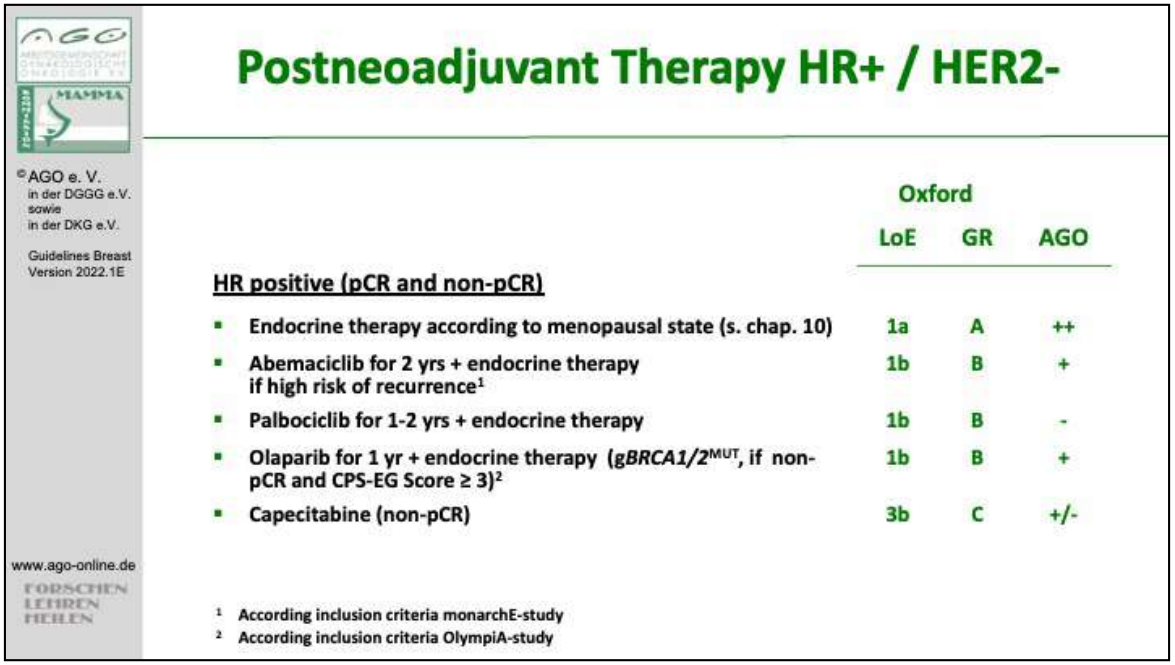
9. Ellis MJ et al. Ki67 proliferation index as a tool for chemotherapy decisions during and after neoadjuvant aromatase inhibitor treatment of breast cancer: results from the American College of Surgeons Oncology Group Z1031 Trial (Alliance). J Clin Oncol. 2017;35(10):1061–9
10. Spring LM, et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA Oncol. 2016 Nov 1;2(11):1477-1486.
11. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009: 18; 339

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.

Statement CDK4/6 inhibitors

1. Harbeck N, Rastogi P, Martin M, et al.; monarchE Committee Members. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol. 2021 Dec;32(12):1571-1581.
2. Martin M, Hegg R, Sung-Bae K, et al., Abemaciclib combined with adjuvant endocrine therapy in patients with high risk early breast cancer who received neoadjuvant chemotherapy (NAC). J Clin Oncol 2021;39(15 suppl): abstract 517
3. Gnant M, Dueck AC, Frantal S, et al.; PALLAS groups and investigators. Adjuvant Palbociclib for Early Breast Cancer: The PALLAS Trial Results (ABCSG-42/AFT-05/BIG-14-03). J Clin Oncol. 2021 Dec 7:JCO2102554.
4. Mayer EL, Dueck AC, Martin M, et al. Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2021 Feb;22(2):212-222.
5. Loibl S, Marmé F, Martin M, et al. Palbociclib for Residual High-Risk Invasive HR-Positive and HER2-Negative Early Breast Cancer-

The Penelope-B Trial. J Clin Oncol. 2021 May 10;39(14):1518-1530.
6. 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.
7. Johnston SRD, Harbeck N, Hegg R et al.; monarchE Committee Members and Investigators Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol. 2020 Dec 1;38(34):3987-3998.

Statement Olaparib gBRCAmt

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Statement Capecitabine (bei non-pCR; 8 Kurse)

1. Joensuu H, Kellokumpu-Lehtinen PL, Huovinen R et al. Adjuvant Capecitabine for Early Breast Cancer: 15-Year Overall Survival Results From a Randomized Trial. J Clin Oncol. 2022 Jan 12:JCO2102054.
2. Lluch A et al. Phase III Trial of adjuvant capecitabine after standard neo-/adjuvant chemotherapy in patients with early triple-negative breast cancer (GEICAM/2003-11_CIBOMA/2004-01). J Clin Oncol. 2020 Jan 20;38(3):203-213.
3. 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.

# How to Calculate CPS+EG Score?

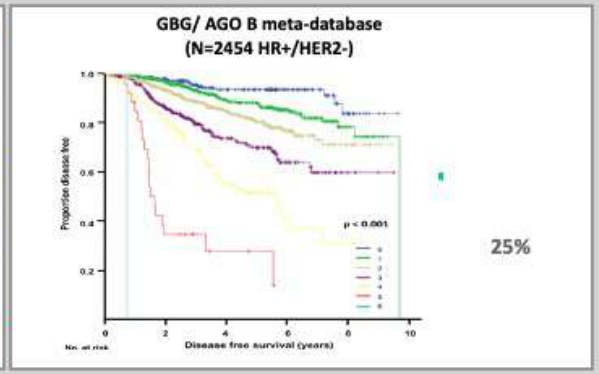


Guidelines Breast
Version 2022.1E



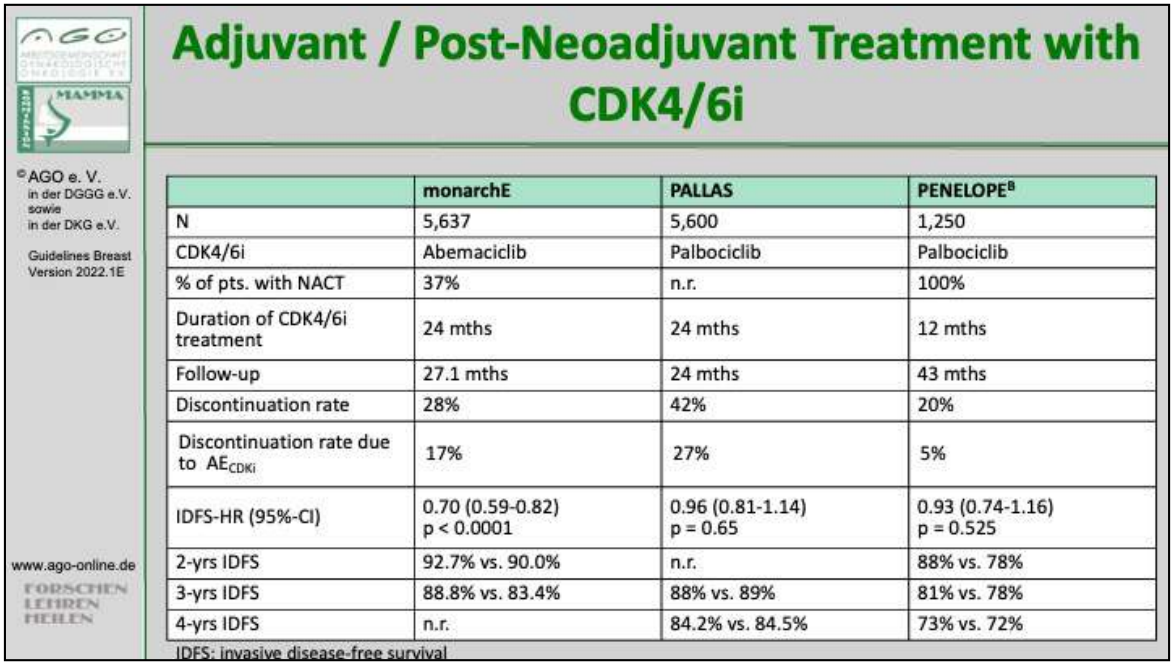
Point assignment for CPS+EG score

| | | |
|---|---|---|
| **Clinical Stage** | | |
| I | 0 | T1N0; T0N1mi; T1N1mi |
| IIA | 0 | T0N1; T1N1; T2N0 |
| IIB | 1 | T2N1; T3N0 |
| IIIA | 1 | T0-2N2 |
| IIIB | 2 | T4N0-2 |
| IIIC | 2 | Any T N3 |
| **Pathologic Stage** | | |
| 0 | 0 | Tis/pN0 |
| I | 0 | T1N0; T0N1mi; T1N1mi |
| IIA | 1 | T0N1; T1N1; T2N0 |
| IIB | 1 | T2N1; T3N0 |
| IIIA | 1 | T0-2 N2 |
| IIIB | 1 | T4 N0-N2 |
| IIIC | 2 | Any T N3 |
| **Tumor Biologic Factors** | | |
| ER negative | 1 | |
| Nuclear grade 3 | 1 | |




25%

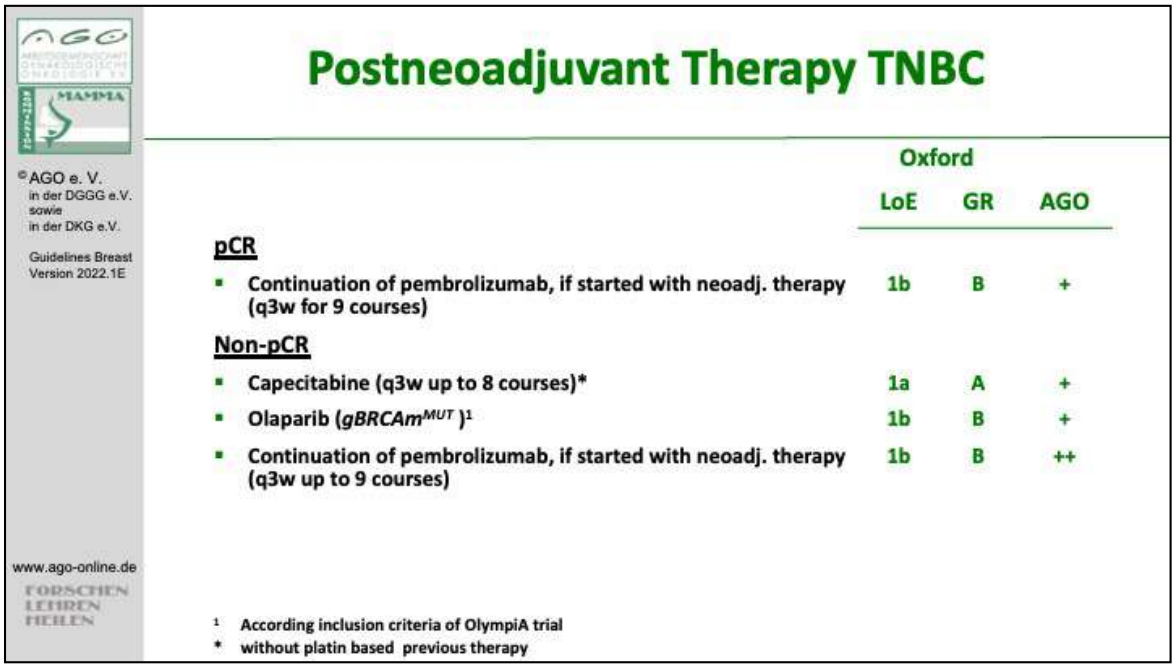
Mittendorf EA, J Clin Oncol 2011;
Marmé F, et al. Eur J Cancer 2016




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

IDFS: invasive disease-free survival


1. 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
2. Loibl S, Marmé F, Martin M, et al. Palbociclib for Residual High-Risk Invasive HR-Positive and HER2-Negative Early Breast Cancer-The Penelope-B Trial. J Clin Oncol. 2021 May 10;39(14):1518-1530. doi: 10.1200/JCO.20.03639. Epub 2021 Apr 1.PMID: 33793299
3. Harbeck N, Rastogi P, Martin M, et al.; monarchE Committee Members. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol. 2021 Dec;32(12):1571-1581. doi: 10.1016/j.annonc.2021.09.015. Epub 2021 Oct 14.PMID: 34656740
4. Gnant M, Dueck AC, Frantal S, et al.; PALLAS groups and investigators. Adjuvant Palbociclib for Early Breast Cancer: The PALLAS Trial Results (ABCSG-42/AFT-05/BIG-14-03). J Clin Oncol. 2021 Dec 7:JCO2102554. doi: 10.1200/JCO.21.02554. Online ahead of print.PMID: 34874182





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

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2. Lluch A et al. Phase III Trial of adjuvant capecitabine after standard neo-/adjuvant chemotherapy in patients with early triple-negative breast cancer (GEICAM/2003-11_CIBOMA/2004-01). J Clin Oncol. 2020 Jan 20;38(3):203-213.
3. 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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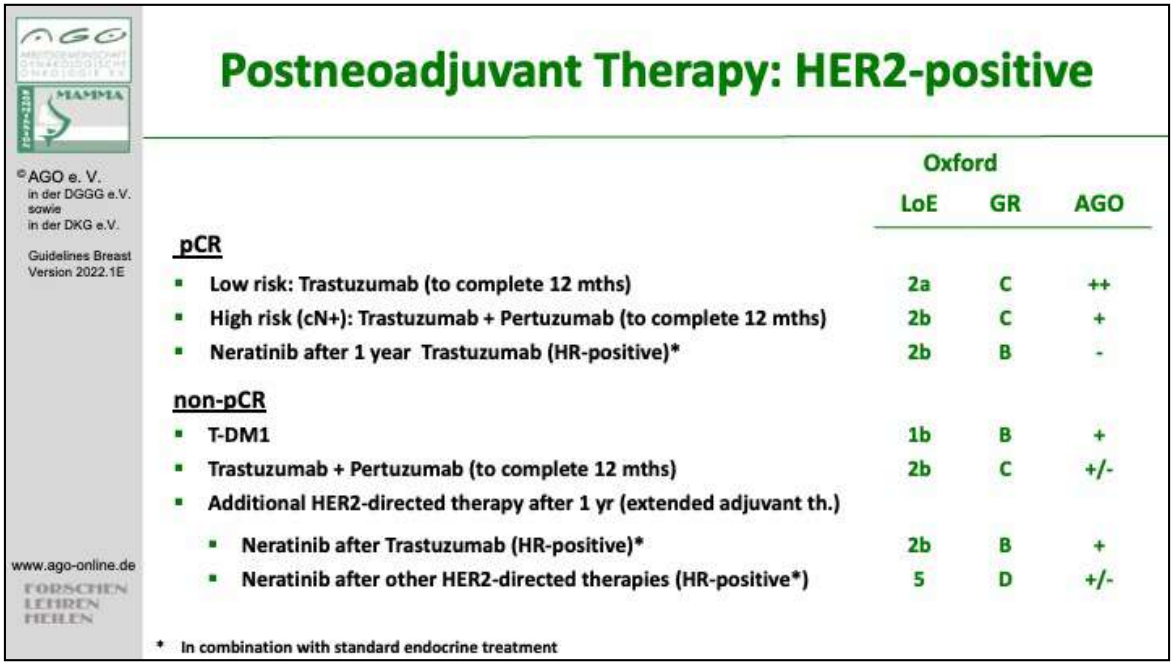
Pembrolizumab in combination with chemotherapy

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


Statement Olaparib gBRCAmut





Statement HER2 positiv (pCR):

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2. 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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5. 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.

Statement HER2 positiv (non-pCR) :

1. Chan A, Moy B, Mansi J, et al.; ExteNET Study Group. Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial. Clin Breast Cancer. 2021 Feb;21(1):80-91.e7.

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