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Guidelines Breast  
Version 2025.1E

FORSCHEN  
LEHREN  
HEILEN

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

## Systemic therapy of primary early breast cancer - HER2+

# Neoadjuvant Systemic Therapy



- **Versions 2002–2024:**

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

- **Version 2025:**

Blohmer / Huober

## Systematic review of published evidence

PUBMED 1999-2024

ASCO 1999-2024

SABCS 1999-2024

ECCO/ESMO 1999-2024

## Strategies for Differentiated Systemic Treatment in the Curative Situation

|  | AGO |
|--|-----|
| <b>If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred; study participation recommended</b> |     |
| ▪ HR+ / HER2- and „low recurrence-risk“  |     |
| ▪ Endocrine therapy without chemotherapy   | ++  |
| ▪ HR+ / HER2- and „high recurrence-risk“   |     |
| ▪ endocrine therapy  | ++  |
| ▪ endocrine-based therapy (abemaciclib or ribociclib)  | +   |
| ▪ Patients with indication for chemo-endocrine therapy*  |     |
| ▪ Conventionally dosed AT-based chemotherapy (q3w)   | +   |
| ▪ Dose dense chemotherapy (including weekly schedule)  | ++  |
| ▪ gBRCA1/2mut (HR+ / HER2- or TNBC respectively)   |     |
| ▪ Olaparib +/- endocrine therapy   | ++  |
| ▪ Triple-negative (TNBC)   |     |
| ▪ Conventional dosed AT-based chemotherapy (q3w)   | +   |
| ▪ Sequential AT-based chemotherapy (incl. weekly schedule)   | ++  |
| ▪ Neoadjuvant platinum-containing chemotherapy   | +   |
| ▪ Neoadjuvant platinum-containing chemotherapy with ICPI (Pembrolizumab)   | ++  |
| ▪ HER2+  |     |
| ▪ Trastuzumab (plus Pertuzumab in N+ or NACT)  | ++  |
| ▪ Sequential AT-based chemotherapy with concurrent T + anti-HER2 therapy   | ++  |
| ▪ Anthracycline-free, chemotherapy + anti-HER2 therapy   | ++  |

\*see prognosis chapter

### Systematic review of published evidence

PUBMED 1999-2024

ASCO 1999-2024

SABCS 1999-2024

ECCO/ESMO 1999-2024

### Trastuzumab in combination with chemotherapy

1. Gianni L, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet 2010: 375; 377
2. Untch M, et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. J Clin Oncol 2011: 29; 3351
3. Gianni L, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet Oncol 2014: 15; 640
4. Jackisch C, et al. HannaH phase III randomised study: Association of total pathological complete response with event-free survival in

HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. Eur J Cancer. 2016 Jul;62:62-

#### 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.
2. Johnston SRD, Toi M, O'Shaughnessy J et al.; monarchE Committee Members. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2023 Jan;24(1):77-90.

#### 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.
2. Geyer CE Jr, Garber JE, Gelber RD et al.; OlympiA Clinical Trial Steering Committee and Investigators. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in *BRCA1/2* and high-risk, early breast

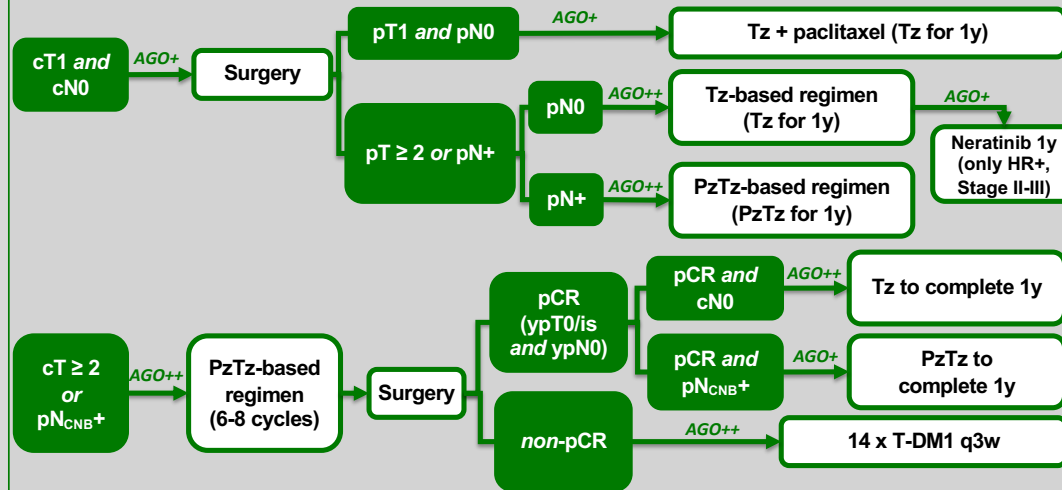
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Platin salts:

1. Geyer CE, Sikov WM, Huober J et al. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. Ann Oncol. 2022 Apr;33(4):384-394.
2. van Mackelenbergh MT, Seither F, Möbus V et al. Effects of capecitabine as part of neo-/adjuvant chemotherapy - A meta-analysis of individual breast cancer patient data from 13 randomised trials including 15,993 patients. Eur J Cancer 2022; 166: 185-201
3. Gupta S, Nair NS, Hawaldar RW et al., Addition of platinum to sequential taxan-anthracycline neoadjuvant chemotherapy in patients with triple-negative breast cancer: a phase III randomized controlled trial SABCS 2022, GS5-01
4. III randomized controlled trial SABCS 2022, GS5-01

# Therapy of HER2-positive Early Breast Cancer

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CNB, core needle biopsy; HR, hormone receptor; pCR, pathological complete response; Pz, Pertuzumab; q3w, every 3 weeks; T-DM1, Trastuzumab emtansine; Tz, Trastuzumab; y, year; if HR+ additional adjuvant endocrine therapy.



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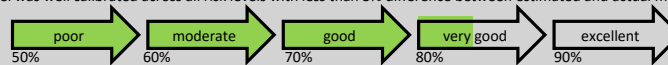
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## Lee-Schonberg Index

<https://eprognosis.ucsf.edu/leeschonberg-result.php>

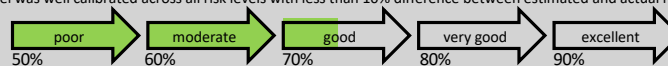
### Lee Index

- This index was developed in 11,701 community-dwelling adults from the eastern, western and central United States who were interviewed in the Health Retirement Survey in 1998 (mean age 67, 57% female, 81% white, 12% 4-year mortality).
- The index was internally validated in 8009 Health Retirement Survey interviewees from the southern United States (mean age 67, 57% female, 71% white, 13% 4-year mortality) and externally validated in 7042 English Longitudinal Study on Ageing interviewees.
- Discrimination: This risk calculator sorts patients who died from patients who lived correctly 82% of the time (c-statistic). The life expectancy calculator sorts patients who lived longer from patients who lived shorter correctly 78-80% of the time in the validation studies
- Calibration: The model was well calibrated across all risk levels with less than 3% difference between estimated and actual mortality rates.



### Schonberg Index

- This index was developed in 16,077 community dwelling older adults who responded to the 1997-2000 National Health Interview (NHIS) (27% >80 years old, 60% female, 85% white, 17% 5-year mortality)
- The index was internally validated in a random sample of 8038 from respondents from the same data source from 2001-2004 and followed through 2006 (27% >80 years old, 60% female, 85% white, 17% 5-year mortality). The index was internally validated in 16,063 respondents from the original development cohort and 8,027 respondents from the original validation cohort from 1997-2000 and followed through 2011 (10 and 14-year mortality).
- Discrimination: This risk calculator sorts patients who died within 5 years from patients who lived correctly 75% of the time (c-statistic). The discrimination was the same in the independent validation study. For 10 year and 14 year mortality the calculator sorts patients correctly 73% and 72% of the time.
- Calibration: The model was well calibrated across all risk levels with less than 10% difference between estimated and actual mortality.



1. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA. 2006 Feb 15;295(7):801-808.
2. Schonberg MA, Davis RB, McCarthy EP, and Marcantonio ER. Index to predict 5-year mortality of community dwelling adults aged 65 and older using data from the National Health Interview Survey. J Gen Intern Med. 2009;24(10):1115-1022.
3. Lee SJ, Boscardin WJ, Kirby KA, Covinsky KE. Individualizing life expectancy estimates for older adults using the Gompertz Law of Human Mortality. Plos One. 2014;9(9):3108540.



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## Lee-Schonberg Index

<https://eprognosis.ucsf.edu/leeschonberg-result.php>

### Risk Calculator questions

1. How old is your patient?
2. What is the sex of your patient?
3. What is your patient's BMI?
4. Which best describes your patient's health in general?
5. Does your patient have chronic lung disease, such as emphysema or chronic bronchitis?
6. Has your patient ever had cancer (excluding minor skin cancers)?
7. Does your patient have congestive heart failure?
8. Does your patient have diabetes or high blood sugar?
9. Which best describes your patient's cigarette use?
10. Does your patient have difficulty walking 1/4 mile (several city blocks) without help from other people or special equipment?
11. During the past 12 months, how many times was your patient hospitalized overnight?
12. Because of a physical, mental or emotional problem, does your patient need the help of others in handling routine needs such as everyday household chores, doing necessary business, shopping, or getting around for other purposes?
13. Because of a health or memory problem, does your patient have difficulty managing money - such as paying bills and keeping track of expenses?
14. Because of a health or memory problem, does your patient have difficulty with bathing or showering?
15. Because of a health problem, does your patient have difficulty pushing or pulling large objects like a living room chair?

1. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA. 2006 Feb 15;295(7):801-808.
2. Schonberg MA, Davis RB, McCarthy EP, and Marcantonio ER. Index to predict 5-year mortality of community dwelling adults aged 65 and older using data from the National Health Interview Survey. J Gen Intern Med. 2009;24(10):1115-1022.
3. Lee SJ, Boscardin WJ, Kirby KA, Covinsky KE. Individualizing life expectancy estimates for older adults using the Gompertz Law of Human Mortality. Plos One. 2014;9(9):3108540.



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## 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: 93.6% |

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

1. Hurvitz SA, Miller JM, Dichmann R et al. Final analysis of a phase II 3 arm randomized trial of neoadjuvant trastuzumab or lapatinib or th combination of trastuzumab and lapatinib, followed by six cycles 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 randomized phase 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 deprivation: 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. *JAMA Oncol* 2021 Jul 1;7(7):978-984.

## Neoadjuvant Systemic Chemotherapy Clinical Benefit

|   | Oxford |    |
|---|--------|----|
|   | LoE    | 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  |
| ▪ The RCB Score and the class of RCB are subtype independent prognostic factors   | 2a     | B  |
| ▪ 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.

#### RCB Score and RCB class as prognostic factors

1. Yau C, Osdoit M, van der Noordaa Metz al. Residual cancer burden after neoadjuvant chemotherapy and long term survival outcome in breast cancer: a multicentre pooled analysis of 5161 patients. Lancet Oncol. 2022 Jan;23(1):149-160. doi: 10.1016/S1470-2045(21)00589-1. Epub 2021 Dec 11. PMID: 34902335

## Neoadjuvant Systemic Chemotherapy - Indications

|   | Oxford    |          |           |
|---|-----------|----------|-----------|
|   | LoE       | GR       | AGO       |
| ▪ <b>If similar postoperative adjuvant chemotherapy is indicated</b>  | <b>1b</b> | <b>A</b> | <b>++</b> |
| ▪ <b>To allow a risk adapted postoperative therapy</b>  | <b>1b</b> | <b>A</b> | <b>++</b> |
| ▪ <b>Inflammatory breast cancer</b>   | <b>2b</b> | <b>B</b> | <b>++</b> |
| ▪ <b>Primary inoperable breast cancer</b>   | <b>1c</b> | <b>A</b> | <b>++</b> |
| ▪ <b>Large operable breast cancer requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation</b> | <b>1b</b> | <b>B</b> | <b>++</b> |

### 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.

If similar postoperative adjuvant chemotherapy is indicated

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

## Neoadjuvant Systemic Therapy

### Timing of Diagnosis, Surgery and Radiotherapy

|   | Oxford    |          |           |
|---|-----------|----------|-----------|
|   | LoE       | GR       | AGO       |
| <b>Timing of surgery</b><br>4-8 weeks after last course of chemotherapy | <b>2a</b> | <b>B</b> | <b>++</b> |
| <b>Radiotherapy within 2 months after surgery</b>                       | <b>2b</b> | <b>B</b> | <b>++</b> |

#### 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.
2. Hanna TP, King WD, Thibodeau S, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. *BMJ* 2020 Nov 4;371:m4087.doi:10.1136/bmj.m4087

#### Time between surgery and last chemotherapy

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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.
3. Grubstein A, Rapson Y, Stemmer SM et al. Timing to imaging and surgery after neoadjuvant therapy for breast cancer. *Clin Imaging*. 2020;71:24-28..
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.

## Neoadjuvant Targeted Therapy in HER2 Positive Tumors

|  | Oxford    |          |            |
|--|-----------|----------|------------|
|  | LoE       | GR       | AGO        |
| ▪ <b>Pertuzumab + trastuzumab in combination with chemotherapy (high-risk defined as cT2-4 and / or cN+)</b> | <b>2b</b> | <b>B</b> | <b>++</b>  |
| ▪ <b>Trastuzumab in combination with stand polychemotherapy (low-risk)*</b>                                  | <b>1b</b> | <b>A</b> | <b>+</b>   |
| ▪ <b>Anti-HER2 agents without chemotherapy</b>   | <b>2b</b> | <b>B</b> | <b>+/-</b> |

\* Single agent chemotherapy combined with trastuzumab should preferably be used in the adjuvant setting

### Review

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2. Pernas S, Tolaney SM. Management of Early-Stage Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer. *JCO Oncol Pract.* 2021 Jun;17(6):320-330.

### 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. Clark A, et al. Neoadjuvant T-DM1/pertuzumab and paclitaxel/trastuzumab/pertuzumab for HER2<sup>+</sup> breast cancer in the adaptively randomized I-SPY2 trial. *Nat Commun.* 2021 Nov 5;12(1):6428.
3. Hatschek T et al. Neoadjuvant Trastuzumab, Pertuzumab, and Docetaxel vs Trastuzumab Emtansine in Patients With ERBB2-Positive Breast Cancer: A Phase 2 Randomized Clinical Trial. *JAMA Oncol.* 2021 Sep 1;7(9):1360-1367.
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5. 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

6. 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
7. Gianni L et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol*. 2016 Jun;17(6):791-800.
8. 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
9. 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
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11. 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]
12. 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.
13. Loibl et al: VP6-2022: Adjuvant pertuzumab and trastuzumab in patients with early HER-2 positive breast cancer in APHINITY: 8.4 years' follow-up; ESMO Virtual Plenary DOI: <https://doi.org/10.1016/j.annonc.2022.06.009>

#### Trastuzumab in combination with chemotherapy

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2. Untch M, et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study

groups. J Clin Oncol 2011; 29; 3351

3. Gianni L, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet Oncol 2014; 15; 640
4. De Azambuja E, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. Lancet Oncol 2014; 15; 1137
5. Jackisch C, et al. HannaH phase III randomised study: Association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. Eur J Cancer. 2016 Jul;62:62
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#### Anti-HER2 agents without chemotherapy

1. Gianni L et al. Effects of neoadjuvant trastuzumab, pertuzumab and palbociclib on Ki67 in HER2 and ER-positive breast cancer. NPJ Breast Cancer. 2022 Jan 10;8(1):1.
2. Pérez-García JM et al; PHERGain steering committee and trial investigators. Chemotherapy de-escalation using an 18F-FDG-PET-based pathological response-adapted strategy in patients with HER2-positive early breast cancer (PHERGain): a multicentre, randomised, open-label, non-comparative, phase 2 trial. Lancet Oncol. 2021 Jun;22(6):858-871.
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5. Rimawi M, et al. Multicenter phase II study of neoadjuvant lapatinib and trastuzumab with hormonal therapy and without chemotherapy in patients with human epidermal growth factor receptor 2-overexpressing breast cancer: TBCRC 006. J Clin Oncol 2013; 31; 1726.
6. Gianni L et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016

Jun;17(6):791-800.

7. 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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#### Anti-HER2 and Immunecheckpoint inhibitors

1. Huober et al. Atezolizumab With Neoadjuvant Anti-Human Epidermal Growth Factor Receptor 2 Therapy and Chemotherapy in Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer: Primary Results of the Randomized Phase III IMpassion050 Trial; *J Clin Oncol* 2022 Pages JCO2102772.

## Neoadjuvant Chemotherapy Treatment Strategies Based on Clinical Response

|   | Oxford |    |     |
|---|--------|----|-----|
|   | LoE    | GR | AGO |
| <b>In case of early response</b>                                    |        |    |     |
| ▪ Completion of neoadjuvant chemotherapy                            | 1b     | A  | ++  |
| <b>In case of no change:</b>  |        |    |     |
| ▪ Completion of neoadjuvant chemotherapy (NACT) followed by surgery | 2b     | C  | ++  |
| <b>In case of disease progression</b>                               |        |    |     |
| ▪ 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  | +/- |

### Completion of neoadjuvant chemotherapy

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

### In case of no change:

#### Completion of NACT, followed by surgery

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

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

#### Continuation of NST with non-cross-resistant regimen

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

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

##### DAC2x -> NX x 4

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

#### In case of progressive disease:

##### Stop of NACT and immediate surgery or radiotherapy

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

Additional adjuvant chemotherapy with non-cross-resistant regimen

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

## Postneoadjuvant Therapy HER2-positive

|  | Oxford |    |     |
|--|--------|----|-----|
|  | LoE    | GR | AGO |
| <b>pCR</b>   |        |    |     |
| ▪ Low risk: Trastuzumab (to complete 12 mths)                                | 2a     | C  | ++  |
| ▪ High risk (cN+): Trastuzumab + Pertuzumab (to complete 12 mths)            | 2b     | C  | +   |
| ▪ Neratinib after 1 year Trastuzumab (HR-positive, stage II-III)*            | 2b     | B  | +/- |
| <b>non-pCR</b>   |        |    |     |
| ▪ T-DM1  | 1b     | B  | ++  |
| ▪ Trastuzumab + Pertuzumab (to complete 12 mths)                             | 2b     | C  | +   |
| ▪ Additional HER2-directed therapy after 1 yr (extended adjuvant th.)        |        |    |     |
| ▪ Neratinib after Trastuzumab (HR-positive, stage II-III)*                   | 2b     | B  | +   |
| ▪ Neratinib after other HER2-directed therapies (HR-positive, stage II-III)* | 5      | D  | +/- |

\* In combination with standard endocrine treatment

### Statement HER2 positiv (pCR):

1. Piccart M et al.; APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. J Clin Oncol. 2021 May 1;39(13):1448-1457.
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.
3. Martin M et al.; ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(12):1688-1700
4. 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.
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.
6. Swain S, Macharia H, Cortes J et al. Event-free survival in patients with early HER2-positive breast cancer with a pathologic complete response after HER2-targeted therapy: A pooled analysis. Cancers 2022;14(20):5051. doi: 10.3390/cancers14205051.

### 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.
2. 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.
3. Martin M et al.; ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18(12):1688-1700

Statement rastuzumab + Pertuzumab in N+:

1. Gelber RD, Wang XV, Cole BF et al.; APHINITY Steering Committee and Investigators. Six-year absolute invasive disease-free survival benefit of adding adjuvant pertuzumab to trastuzumab and chemotherapy for patients with early HER2-positive breast cancer: A Subpopulation Treatment Effect Pattern Plot (STEPP) analysis of the APHINITY (BIG 4-11) Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. *Eur J Cancer* 2022;166:219-228.
2. Piccart M, Procter M, Fumagalli D et al.; APHINITY Steering Committee and Investigators. *J Clin Oncol* 2021;39(13):1448-1457.
3. Loibl S, Jassem J, Sonnenblick A, Viale G, Bines J, Piccart M. Adjuvant pertuzumab and trastuzumab in patients with early HER-2 positive breast cancer in APHINITY: 8.4 years' follow-up. ESMO Virtual Plenary, 15.07.2022, # VP6-2022, *Annals of Oncology* 33(9): 986-987.

## (Neo)Adjuvant Chemotherapy: in Small, Node-Negative Tumors (T1)

### ■ HER2+ in combination with trastuzumab

- > 10 mm neoadjuvant or adjuvant
- > 5-10 mm adjuvant
- ≤ 5 mm adjuvant

| Oxford |    |     |
|--------|----|-----|
| LoE    | GR | AGO |
| 1a     | A  | ++  |
| 2b     | B  | +   |
| 2b     | B  | +/- |

### TNBC

1. Gamucci T, Vaccaro A, Ciancola F et. al. Recurrence risk in small, node-negative, early breast cancer: a multicenter retrospective analysis. J Cancer Res Clin Oncol. 2013;139(5):853-60. doi: 10.1007/s00432-013-1388-2. Epub 2013 Feb 15.
2. Kolben T, Harbeck N, Wuerstlein R et al. Endocrine sensitivity is decisive for patient outcome in small node-negative breast cancers (BC) (pT1a,b) - results from the Munich Cancer Registry. Breast. 2015;24(1):24-31. doi: 10.1016/j.breast.2014.10.007. Epub 2014 Nov 8.
3. Nonneville A, Goncalves C, Zemmour M et al. Adjuvant chemotherapy in pT1ab node-negative triple-negative breast carcinomas: Results of a national multi-institutional retrospective study . European J Cancer. 2017; (84):34-43.
4. Oladeru OT, Singh AK, Ma SJ. Association of Adjuvant Chemotherapy With Overall Survival Among Women With Small, Node-Negative, Triple-Negative Breast Cancer. JAMA Netw Open. 2020 Sep 1;3(9):e2016247.
5. Steenbruggen TG, van Werkhoven E, van Ramshorst MS, et al.. Adjuvant chemotherapy in small node-negative triple-negative breast cancer. Eur J Cancer. 2020 Aug;135:66-74. doi: 10.1016/j.ejca.2020.04.033. Epub 2020 Jun 14. PMID: 32554215.

### HER2

1. Denduluri N, Somerfield MR, Eisen A et al. Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor (Her2)- negative and adjuvant targeted therapy for Her2-positive breast cancers: an American Society of Clinical

- Oncology Guideline adaptation of the Cancer Care Ontario Clinical Practice Guideline. *J Clin Oncol* 2016;34(20):2416-27.
2. O'Sullivan CC, Bradbury I, Campbell C et al. Efficacy of Adjuvant Trastuzumab for Patients With Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer and Tumors  $\leq 2$  cm: A Meta-Analysis of the Randomized Trastuzumab. *J Clin Oncol*. 2015;33(24):2600-8.
  3. de Nonneville A, Gonçalves A, Zemmour C, et al. Benefit of adjuvant chemotherapy with or without trastuzumab in pT1ab node-negative human epidermal growth factor receptor 2-positive breast carcinomas: results of a national multi-institutional study. *Breast Cancer Res Treat*. 2017;162(2):307-316.

#### HR+/HER2-

1. Sparano JA, Crager MR, Tang G et al. Development and Validation of a Tool Integrating the 21-Gene Recurrence Score and Clinical-Pathological Features to Individualize Prognosis and Prediction of Chemotherapy Benefit in Early Breast Cancer. *Journal of Clinical Oncology* 2021; 39: 557-564.
2. Shen K, Yao L, Zhu J et al. Impact of adjuvant chemotherapy on T1N0M0 breast cancer patients: a propensity score matching study based on SEER database and external cohort. *BMC Cancer* 2022; 22: 863.
3. Nguyen TTA, Postlewait LM, Zhang C et al. Utility of Oncotype DX score in clinical management for T1 estrogen receptor positive, HER2 negative, and lymph node negative breast cancer. *Breast Cancer Res Treat* 2022; 192: 509-516.

## Adjuvant HER2-directed Treatment

|  | Oxford          |    |     |
|--|-----------------|----|-----|
|  | LoE             | GR | AGO |
| <ul style="list-style-type: none"> <li>■ <b>Trastuzumab + Pertuzumab</b> <ul style="list-style-type: none"> <li>■ pN+</li> <li>■ pN-</li> </ul> </li> </ul>  | 1b <sup>a</sup> | B  | ++  |
|  | 1b <sup>a</sup> | B  | +/- |
| <ul style="list-style-type: none"> <li>■ <b>Neratinib</b> <ul style="list-style-type: none"> <li>■ 1 year after 1 year trastuzumab (HR-positive, stage II-III)</li> <li>■ 1 year after trastuzumab / pertuzumab / T-DM1 (HR-positive, stage II-III)</li> </ul> </li> </ul> | 1b              | B  | +   |
|  | 5               | D  | +/- |

### Statement Trastuzumab + Pertuzumab (pN+/-)

1. von Minckwitz G, Procter M, de Azambuja E et al; APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017;377(2):122-131.
2. Piccart M, Procter M, Fumagalli D et al. Interim overall survival analysis of APHINITY (BIG 4-11): A randomized multicenter, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab versus chemotherapy plus trastuzumab plus placebo as adjuvant therapy in patients with operable HER2-positive early breast cancer. SABCS 2019; abstr. GS 01-04
3. Yu L, Fu F, Li J, Huang M, Zeng B, Lin Y, Mei Q, Lv J, Wang C. Dual HER2 Blockade versus a Single Agent in Trastuzumab-Containing Regimens for HER2-Positive Early Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Oncol 2020 <https://doi.org/10.1155/2020/5169278> (accessed 12302020)
4. Loibl, S., et al. (2022). "VP6-2022: Adjuvant pertuzumab and trastuzumab in patients with early HER-2 positive breast cancer in APHINITY: 8.4 years' follow-up." Annals of Oncology 33(9): 986-987.

### Neratinib

1. Chan A, Moy B, Mansi J, Ejlersen B, Holmes FA, Chia S, Iwata H, Gnant M, Loibl S, Barrios CH, Somali I, Smichkoska S, Martinez N, Alonso MG, Link JS, Mayer IA, Cold S, Murillo SM, Senecal F, Inoue K, Ruiz-Borrego M, Hui R, Denduluri N, Patt D, Rugo HS, Johnston SRD, Bryce R, Zhang B, Xu F, Wong A, Martin M; 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. doi: 10.1016/j.clbc.2020.09.014. Epub 2020 Oct 6. PMID: 33183970.

2. Holmes FA, Moy B, Delaloge S, Chia SKL, Ejlersen B, Mansi J, Iwata H, Gnant M, Buyse M, Barrios CH, Silovski T, Šeparović R, Bashford A, Zotano AG, Denduluri N, Patt D, Gokmen E, Gore I, Smith JW 2nd, Loibl S, Masuda N, Tomašević Z, Petráková K, DiPrimeo D, Wong A, Martin M, Chan A; ExteNET Study Group. Overall survival with neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): A randomised, double-blind, placebo-controlled, phase 3 trial. Eur J Cancer. 2023 May;184:48-59. Eur J Cancer. 2023 May;184:48-59.

Statements:Trastuzumab in node-negative disease (if chemotherapy is indicated)

1. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al.; Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353(16):1659-72.
2. Smith I, Procter M, Gelber RD et al.; HERA study team. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet. 2007;369(9555):29-36.
3. Goldhirsch A, Gelber RD, Piccart-Gebhart, MJ et al.; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet. 2013;382(9897):1021-8.
4. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al.; Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017;389(10075):1195-1205.
5. Perez EA, Romond EH, Suman VJ et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol. 2014;32(33):3744-52.
6. Jackisch C, Hegg R, Stroyakovskiy D et al. HannaH phase III randomised study: Association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. Eur J Cancer. 2016;62:62-75.

## (Neo)Adjuvant Treatment with Trastuzumab / Pertuzumab

|  | Oxford |    |     |
|--|--------|----|-----|
|  | LoE    | GR | AGO |
| <b>Start of treatment</b>                        |        |    |     |
| ▪ Simultaneously with taxanes                    | 1a     | A  | ++  |
| ▪ Sequentially up to 3 months after chemotherapy | 1b     | B  | +   |
| <b>Duration</b>                                  |        |    |     |
| ▪ For 1 year                                     | 1a     | A  | ++  |
| ▪ For 0.5 years (Trastuzumab)                    | 1a     | A  | +   |
| ▪ For 2 years                                    | 1b     | A  | -   |

### Statement: Start of treatment simultaneously with taxanes

1. Smith I, Procter M, Gelber RD et al.; HERA study team. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet*. 2007;369(9555):29-36.
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3. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al.; Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet*. 2017;389(10075):1195-1205.
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#### Statement s.c.

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3. Jackisch C, Stroyakovskiy D, Pivot X et al. Subcutaneous vs Intravenous Trastuzumab for Patients With ERBB2-Positive Early Breast Cancer: Final Analysis of the HannaH Phase 3 Randomized Clinical Trial. JAMA Oncol. 2019;5(5):e190339. doi: 10.1001/jamaoncol.2019.0339.
4. Federica Tan AR, *et al.* SABCS 2019 (Abstract PD4-07),
5. Phrancesca O'Shaughnessy J *et al.* ESMO 2020, Abstract-Nr. 165MO

#### Statement: Duration

*Duration Trastuzumab 1 year*

*Duration Trastuzumab 2 year*

*Duration Trastuzumab 0.5 years*

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

1. Chen L, Zhou W, Hu X et al. Short-duration versus 1-year adjuvant trastuzumab in early HER2 positive breast cancer: A meta-analysis of randomized controlled trials. *Cancer Treat Rev.* 2019;75:12-19. doi: 10.1016/j.ctrv.2019.02.003.
2. Inno A, Barni S, Ghidini A et al. One year versus a shorter duration of adjuvant trastuzumab for HER2-positive early breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat.* 2019;173(2):247-254. doi: 10.1007/s10549-018-5001-x.
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## (Neo)Adjuvant Treatment with Trastuzumab +/- Pertuzumab: Chemotherapy regimen

|  | Oxford |    |     |
|--|--------|----|-----|
|  | LoE    | GR | AGO |
| <b>Trastuzumab simultaneously with</b>                         |        |    |     |
| ▪ paclitaxel / docetaxel after AC / EC                         | 1a     | A  | ++  |
| ▪ P q1w 12 x in pT < 2 cm, pN0                                 | 2b     | B  | +   |
| ▪ docetaxel and carboplatin                                    | 1b     | A  | +   |
| <b>Trastuzumab + Pertuzumab simultaneously with</b>            |        |    |     |
| ▪ paclitaxel q1w (or docetaxel q3w) after EC / AC              | 1b     | B  | ++  |
| ▪ docetaxel+ carboplatin                                       | 1b     | B  | ++  |
| ▪ taxanes dose-dense   | 2b     | B  | +   |
| <b>Radiotherapy concurrently with Trastuzumab / Pertuzumab</b> | 1a     | A  | ++  |

### Statement: with paclitaxel/docetaxel after AC/EC

1. Perez EA, Suman VJ, Davidson NE et al. Sequential Versus Concurrent Trastuzumab in Adjuvant Chemotherapy for Breast Cancer. J Clin Oncol 2011;29:4491-4497
2. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al.; Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017;389(10075):1195-1205.
3. Papakonstantinou A, Matikas A, Bengtsson NO et al. Efficacy and Safety of Tailored and Dose-Dense Adjuvant Chemotherapy and Trastuzumab for Resected HER2-Positive Breast Cancer: Results From the Phase 3 PANTHER Trial. Cancer 2019 doi: 10.1002/cncr.32653. [Epub ahead of print]

### Statement: P q1w12 in pT < 2 cm pN0

1. Tolaney SM, Barry WT, Dang CT et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med. 2015;372(2):134-41.
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Statement: with docetaxel and carboplatin

1. Valero V, Forbes J, Pegram MD et al. Multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab as first-line chemotherapy for patients with HER2-gene-amplified metastatic breast cancer (BCIRG 007 study): two highly active therapeutic regimens. J Clin Oncol. 2011;29(2):149-56.
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Statement: Trastuzumab + Pertuzumab simultaneously with Paclitaxel q1w or Docetaxel q3w (after EC or AC)

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

Statement: Trastuzumab + Pertuzumab simultaneously with Docetaxel and Carboplatin q3w

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

Statement: Trastuzumab + Pertuzumab simultaneously with taxanes dose-dense

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

Statement: radiotherapy concurrent with trastuzumab

1. M. Y. Halyard, T. M. Pisansky, L. J. Solin et al. Trastuzumab can be administered concurrent to adjuvant radiotherapy of the breast or thoracic wall. Adjuvant radiotherapy (RT) and trastuzumab in stage I-IIA breast cancer: Toxicity data from North Central Cancer Treatment Group Phase III trial N9831 J Clin Oncol. 2009;27(16):2638-44