Clinical Practice Guideline for Neoadjuvant Therapy in Early Breast Cancer

dr. Een Hendarsih, Sp.PD-KHOM

Abbreviations: eBC, early breast cancer; HER2+, human epidermal growth factor receptor-2 positive.
Reference: 1. BPOM. Product information PERJETA (Pertuzumab). July 2023
2. BPOM. Product Information PHESGO (Pertuzumab and trastuzumab). March 2023
For Healthcare Professionals Only

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Outline

- A Critical Unmet Need in eBC
- HER2+ eBC Treatment for High Risk Patients
- The Role of PHESGO in eBC Treatment
- Assessing Neoadjuvant Outcome
- Asian Real World Evidence Neoadjuvant Experience

Abbreviations: eBC, early breast cancer; HER2+, human epidermal growth factor receptor-2 positive.

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A Critical Unmet Needs in eBC

Abbreviation: eBC, early breast cancer

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Unmet needs of eBC treatment

The goal of eBC therapy is to cure; Therefore patients should be given the most efficacious treatment available[1]

~30% of patients treated for eBC go on to develop mBC[2]

~51% of HER2-positive mBC cases are due to eBC relapse[3]

BC recurrence has a significant impact on the QoL of patients and their families[4-8]

There is currently no cure for HER2-positive mBC,[9] with extended treatment and disease burden having economic implications[4]

BC, breast cancer;
eBC, early breast cancer;
mBC, metastatic breast cancer;
QoL, quality of life.

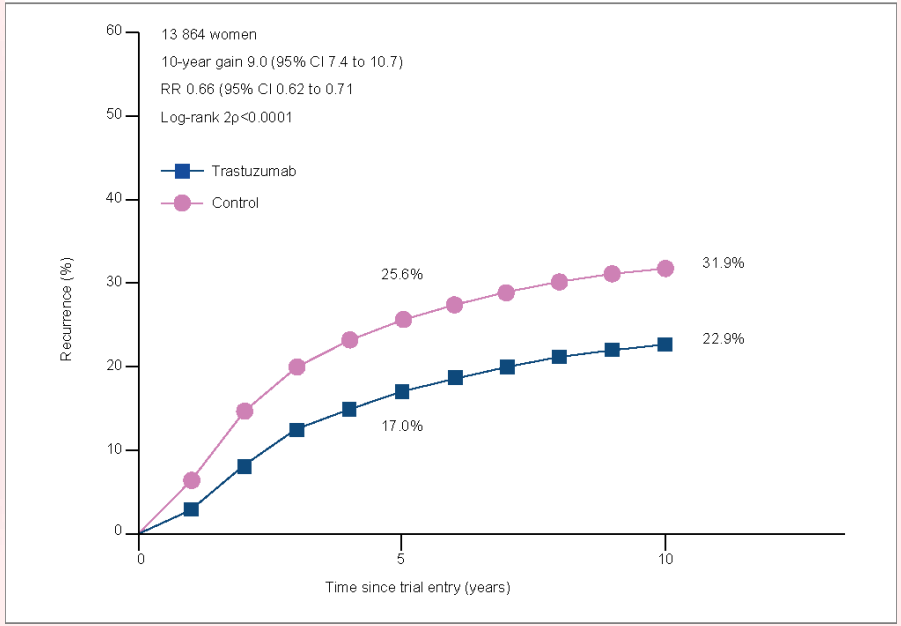
1. Scharl A, *et al. Geburtshilfe Frauenheilkd* 2015; **75**:683–691; 2. O'Shaughnessy J. *Oncologist* 2005; **10 (suppl 3)**:20–29;
3. Tripathy D, *et al.* SABCS 2014 (Abstract P3-07-14; poster presentation); 4. Manders K, *et al. BMC Cancer* 2006; **6**:179;
5. Kwan ML, *et al. Breast Cancer Res* 2009; **11**:R31; 6. Montero AJ, *et al. Breast Cancer Res Treat* 2012; **134**:815–822;
7. Northouse LL, *et al. J Clin Oncol* 2002; **20**:4050–4064; 8. Mayer MS, *et al. Community Oncol* 2010; **7**: 406–412;
9. Savci-Heijink CD, *et al. Breast Cancer Treat* 2015; **150**:547–557.

1 in 4 patients with eBC continue to grapple with unmet needs[1,2]

- Recurrence-free survival is the goal of treatment in eBC.[1]
- **However, 1 in 4 patients** with HER2+ eBC experience **recurrence or death within 10 years** despite trastuzumab-based adjuvant therapy.[2]

67% of first-line HER2+ mBC are recurrent patients after prior treatment in eBC[3]

Effect of trastuzumab versus control on disease recurrence[2]



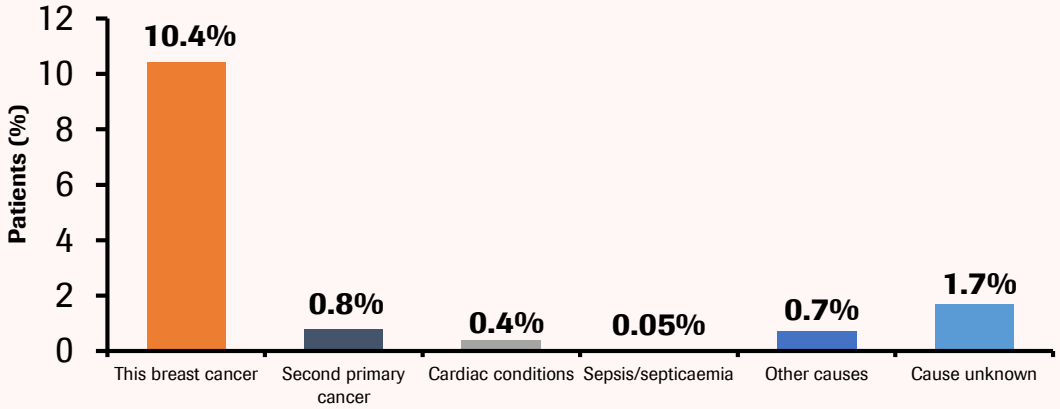
Adapted from Early Breast Cancer Trialists' Collaborative Group. *Lancet Oncol*. 2021.[2]

Abbreviations: eBC, early breast cancer; HER2+, human epidermal growth factor receptor-2 positive; RR, rate ratio; SoC, standard of care.

References: 1. Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer (Review). *Cochrane Database Syst Rev*. 2012;2012:CD006243. 2. Early Breast Cancer Trialists' Collaborative group. Trastuzumab for early-stage, HER2-positive breast cancer: a meta-analysis of 13 864 women in seven randomised trials. *Lancet Oncol*. 2021;22(8):1139-1150. 3. Yardley DA, Kaufman PA, Brufsky A, et al. Treatment patterns and clinical outcomes for patients with de novo versus recurrent HER2-positive metastatic breast cancer. *Breast Cancer Res Treat*. 2014;145(3):725-734.

The majority of deaths following adjuvant trastuzumab are from recurrence of BC

B-31/N9831: 10-year overall survival events and causes of death in patients treated with trastuzumab



Although trastuzumab has revolutionised treatment of women with HER2-positive BC, many patients still die from disease recurrence

Perez EA, *et al. J Clin Oncol* 2014; **32**:3744–3752.

HER2+ eBC Treatment for high risk patients

Abbreviation: eBC, early breast cancer

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HER2 positivity is recognized as high-risk criteria by St Gallen[1]

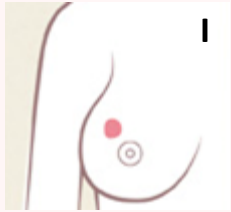
Low risk	Intermediate risk	High risk
• **Node negative** AND **all** of the following features: pT ≤2 cm, AND Grade 1, AND Absence of extensive peritumoral vascular invasion, AND ER and/or PgR expressed, AND HER2/*neu* gene neither overexpressed nor amplified, AND Age ≥35 years	• **Node negative** AND **at least one** of the following features: pT >2 cm, OR Grade 2-3, OR Presence of extensive peritumoral vascular invasion, OR ER and PgR absent, OR HER2/*neu* gene overexpressed or amplified, OR Age <35 years • **Node positive (1-3 involved nodes)** AND ER and/or PgR expressed, AND HER2/*neu* gene neither overexpressed nor amplified	• **Node positive (1-3 involved nodes)** AND ER and PgR absent, OR HER2/*neu* gene overexpressed or amplified • **Node positive (4 or more involved nodes)**

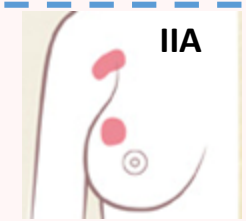
HIGH RISK CRITERIA:

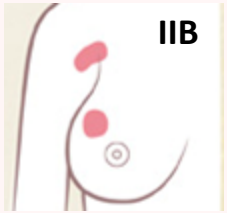
- **Nodal status**
- **ER/PR negative**
- **HER2 overexpression**

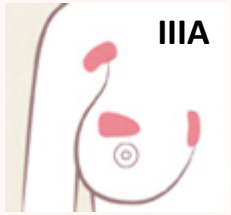
1. Goldhirsch A, et al. Ann Oncol. 2007 Jul;18(7):1133-44.

High-risk HER2-positive disease includes inflammatory, locally advanced and early BC









Early BC[1]
Cancer localised to the breast or lymph nodes in the armpit

Locally advanced BC[1–3]
Cancer has not spread to other parts of the body but may be:
- >5 cm in size
- Present in the lymph nodes in the armpit
- Growing into other tissues around the breast (e.g. skin or muscle of the chest)

Inflammatory[4,5]
- Affects lymphatic vessels in the skin
- Often does not cause a lump
- Subset of locally advanced BC

High-risk disease

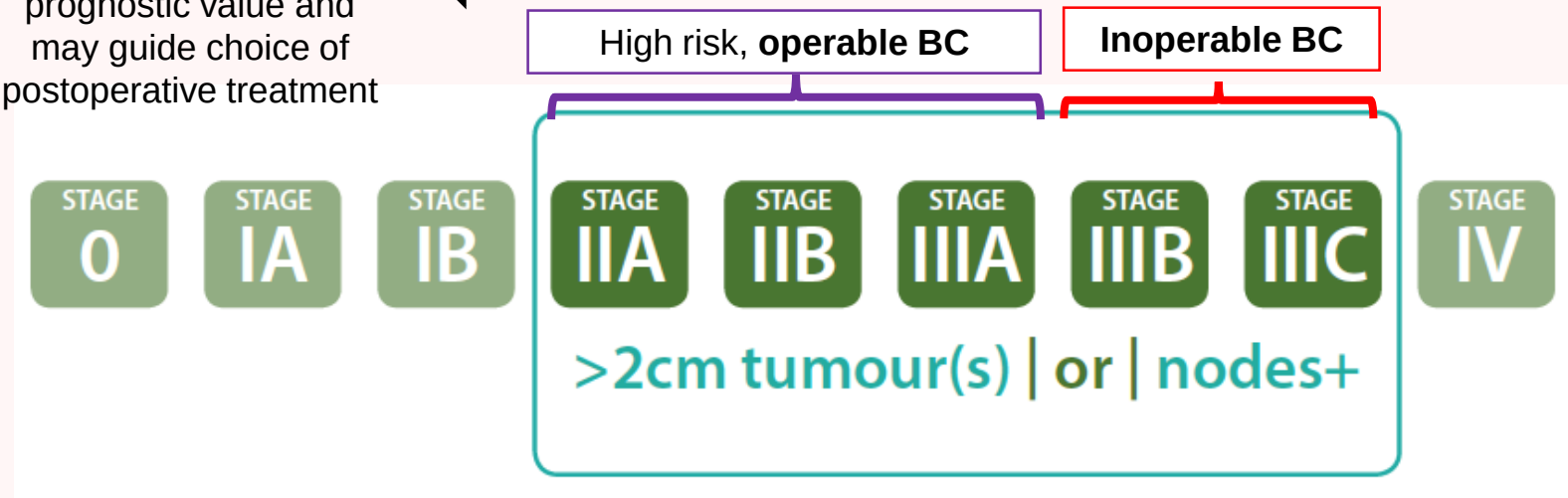
1. TNM Staging. Available on URL http://www.cancerresearchuk.org/about-cancer/type/breast-cancer/treatment/tnm-breast-cancer-staging Accessed on June 15th, 2020
2. Mandilaras V, *et al Curr Oncol* 2015; **22:**25–32;
3. Garg PK & Prakash G. *Curr Oncol* 2015; **22:**e409–e410;
4. Inflammatory Breast Cancer. Available on URL http://www.cancer.org/cancer/breastcancer/moreinformation/inflammatorybreastcancer/ Accessed on June 15th, 2020
5. Inflammatory Breast Cancer. Available on URL https://www.cancer.gov/types/breast/ibc-fact-sheet Accessed on 26 December 2019

The Shifting Paradigm in Neoadjuvant from Inoperable to High Risk

Treatment guidelines define high risk in the context of neoadjuvant treatment:[1,2,3]

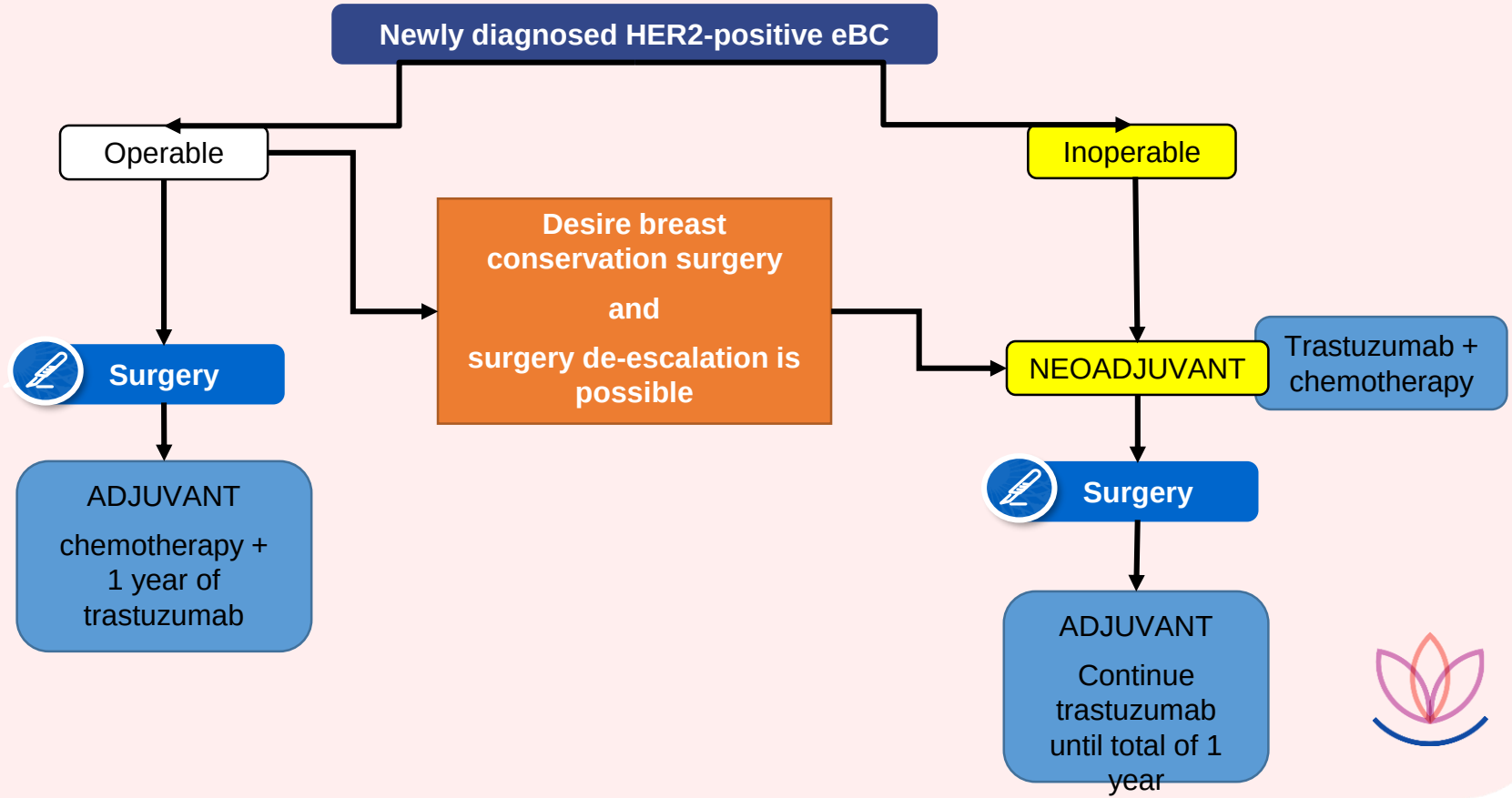
Allows for assessment of therapy response, which is of well-established prognostic value and may guide choice of postoperative treatment

International guidelines recommend neoadjuvant for triple-negative and HER2-positive disease with **tumor size > 2 cm or nodes (+)**



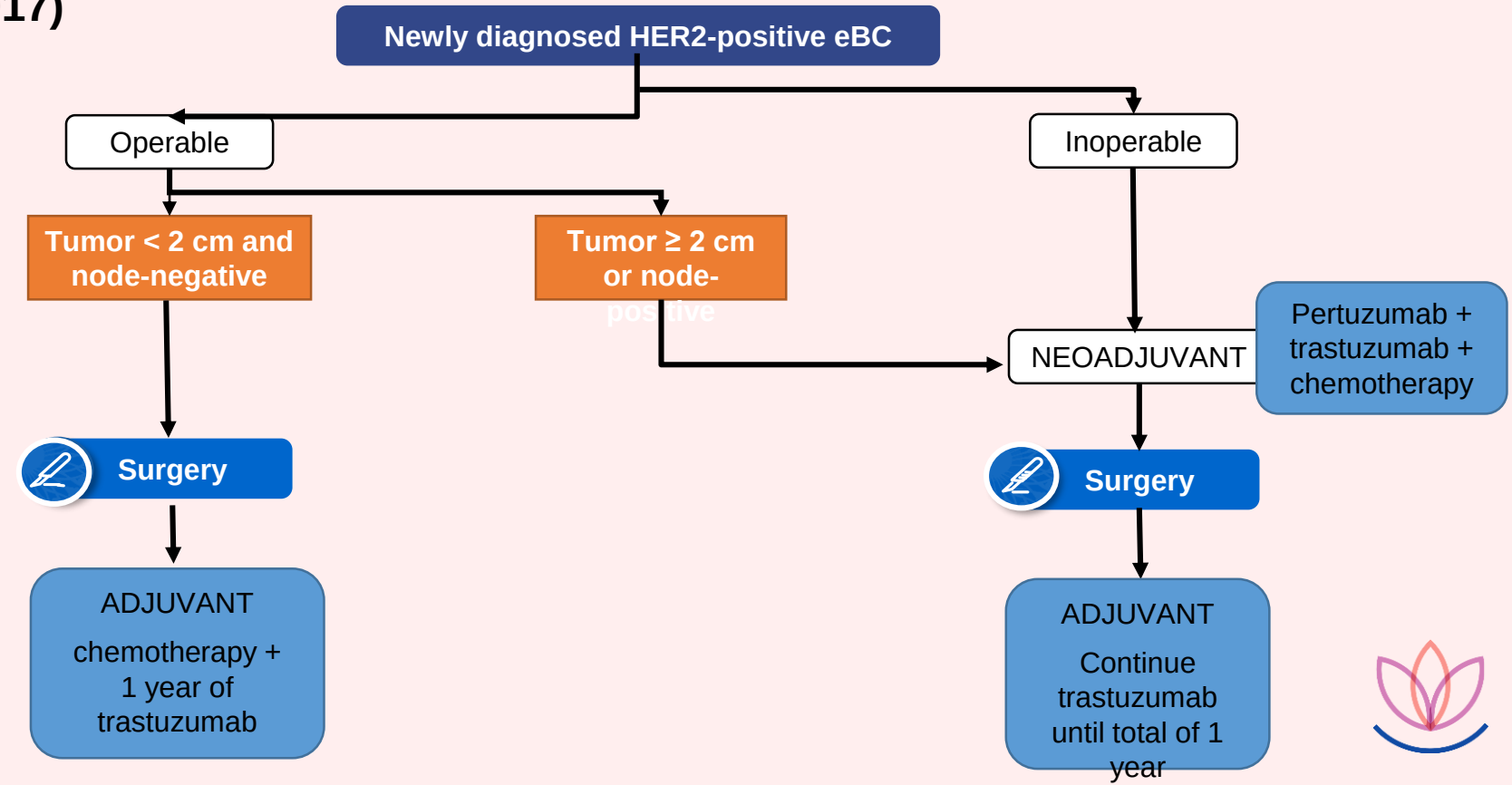
1. Cardoso. Ann Oncol 2019;30:1194-1220. 2. Curigliano G, et al. Ann Oncol. 2017 Aug 1;28(8):1700-1712. 3. NCCN. Breast Cancer V4.2024

HER2-Positive Treatment Algorithm (2015)



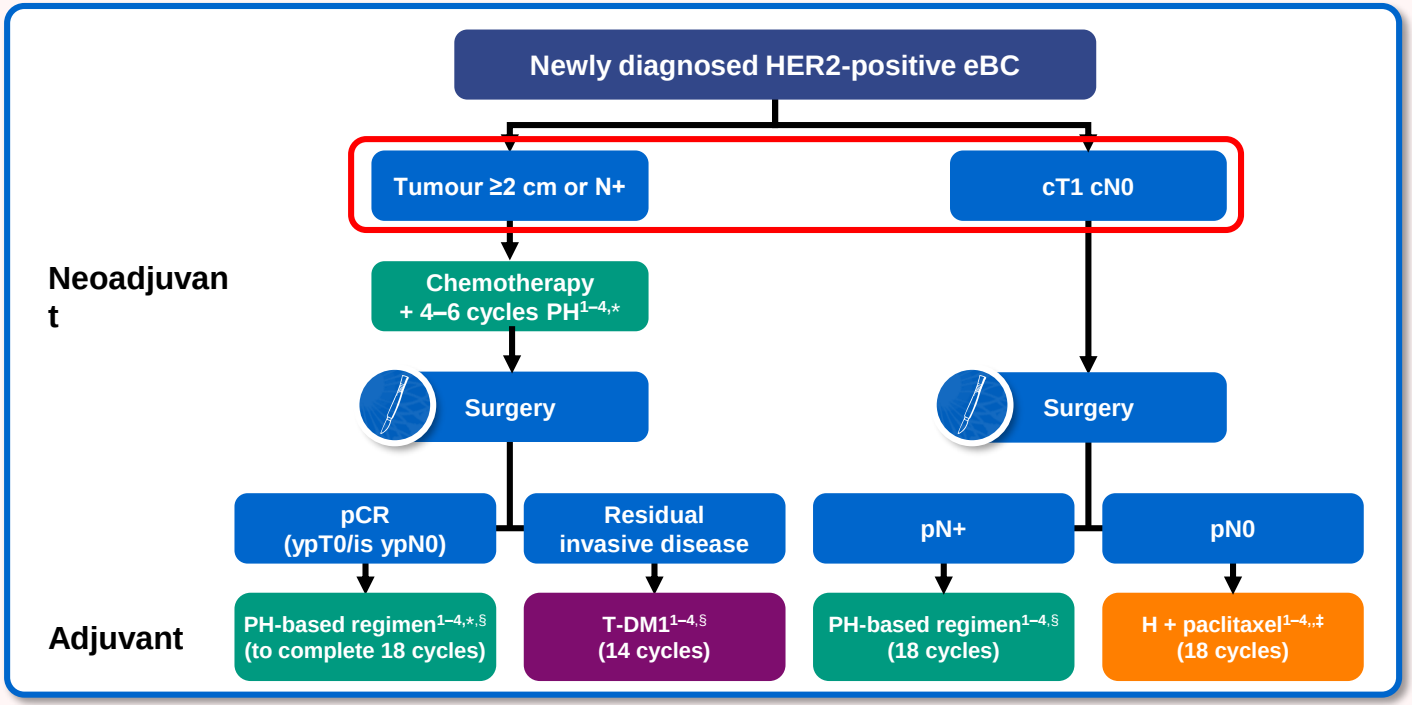
1. Senkus E, et al. Ann Oncol. 2015 Sep;26 Suppl 5:v8-30

HER2-Positive Treatment Algorithm (2017)



1. Curigliano G, et al. Ann Oncol. 2017 Aug 1;28(8):1700-1712.

Treatment decisions in HER2-positive eBC are based on the assessment of multiple risk factors



* AGO and ESMO guidelines: (neo)adjuvant PH is only recommended for the treatment of patients with node-positive disease.
‡ AGO and ESMO guidelines do not recommend the use of trastuzumab + paclitaxel for the treatment of patients with Stage T1mic or T1a disease.[2,3] St. Gallen guidelines state that the use of trastuzumab + paclitaxel can be considered in patients with Stage T1a disease only on a case-by-case basis, and do not recommend its use in patients with Stage T1mic disease.[4]
§ Post-adjuvant therapy with neratinib following adjuvant trastuzumab-based treatment can be considered in high-risk patients with HER2-positive, hormone receptor-positive disease. It is not known if patients who have previously received pertuzumab–trastuzumab or T-DM1 will benefit from post-adjuvant therapy with neratinib.[1–3]

1. NCCN Breast Cancer Guidelines. Version 4, 2024;
2. . AGO. Breast Cancer Guidelines. 2023;
3. Cardoso F, *et al. Ann Oncol* 2019;
4. Burstein HJ, *et al. Ann Oncol* 2021;
5. BPOM. Product Information PHESGO. Mar 2023.

In which case will you consider neoadjuvant first?

High risk patient with T>2 cm or node positive should received neoadjuvant first[1-3]

NEOADJUVANT FIRST	SURGERY FIRST
In HER2-positive or TNBC: **Stage II and III regardless of surgery plan** (mastectomy or BCT)	In **Stage I** disease (tumour < 2 cm AND node-negative) and optimal surgery feasible
In **HER2-negative HR-positive**: with tumour >2 cm or optimal surgery not feasible and **wish for breast conservation** and breast conservation potentially feasible after downstaging	In **HER2-negative HR-positive**: if patient **not wish for breast conservation** or breast conservation not possible
Inflammatory or other **inoperable** locally advanced breast cancer	

1. Burstein HJ, et al. Ann Oncol. 2021 Oct;32(10):1216-1235. 2. Cardoso F, et al. Ann Oncol. 2019 Oct 1;30(10):1674. 3. NCCN Breast Cancer version 4. 2024

Prognostic significance of achieving pCR in neoadjuvant therapy (NAT)[6]

In the case of **HER2+** cancer, achieving **pCR after NAT is significantly linked with a better prognosis of the disease (relapse rate and overall survival)**

HER2+ EFS: HR 0.32; (95% CI, 0.21–0.47); **HER2+ OS:** HR 0.22; (95% CI, 0.15-0.30)[6]

Benefits of neoadjuvant therapy

Enables evaluation of response to treatment [1–3]

- Evaluation of *in vivo* response to treatment, **pCR is associated with improved long-term outcomes**
- Provides **an opportunity to adjust adjuvant therapy** based on the outcome of neoadjuvant therapy (pCR or residual disease)

Early systemic therapy[5]

- Early treatment of micro metastases

Makes time for genetic testing[1]

Improves surgical treatment options [1,4]

- By downstaging of the tumor, NACT can convert patients who are candidates for mastectomy to breast-conserving surgery (BCS) candidates[4]
- May lead to **a reduction in surgical morbidity[4]**
- Reduce excision volumes in patients with large tumors who are already candidates for BCS[4].
- Downstaging of the axilla so that axillary lymph node dissection can be avoided[4].

References: **1.** Cain H, et al. Neoadjuvant Therapy in Early Breast Cancer: Treatment Considerations and Common Debates in Practice. Clin Oncol 29. 642-652. 2017. **2**. Swain SM, et al. Event Free Survival in Patients with Early HER2 Positive Breast Cancer with a Pathological Complete Response after HER2 Targeted Therapy: A Pooled Analysis. Cancers 2022, 14, 5051. **3**. Loibl S, et al. SABCS 2019 (Abstract P5-06-02 and poster presentation). **4**. Volders JH, et al. Breast-conserving surgery following neoadjuvant therapy-a systematic review on surgical outcomes. Breast Cancer Res Treat. 168:1-12. 2018**. 5.** Pernaut C, et al. Standard Neoadjuvant Treatment in Early/Locally Advanced Breast Cancer. Breast Care (Basel) 2018. **6**. Spring L.M., Pathological complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival. a comprehensive meta analysis. Clin Cancer Res. 2020 June 15; 26(12): 2838–2848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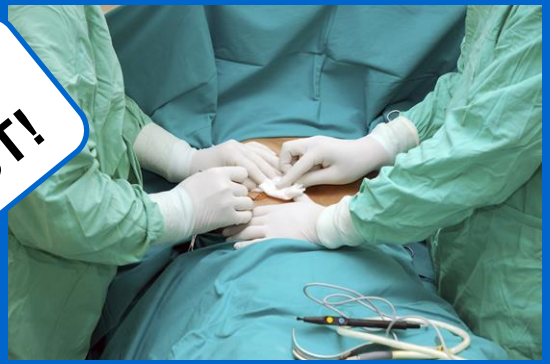
Evaluating response to neoadjuvant therapy[1]

pCR (pathological complete response)

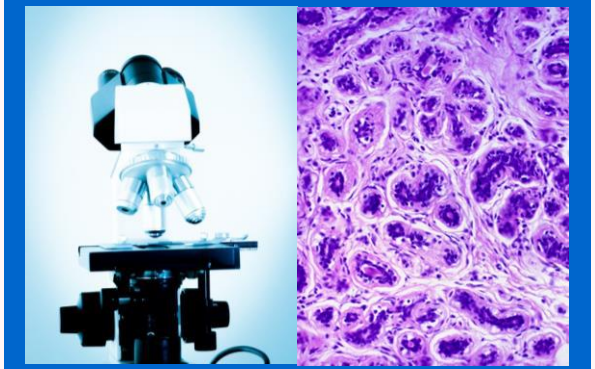
the absence of residual cancer cells on pathologic assessment of tumour resection widely used to evaluate response to neoadjuvant therapy

Assessed on **resected tumour specimens**



SURGERY = A MUST!

No residual cancer on surgical specimen = pCR*



*there are various parameters of pCR, including breast pCR, total pCR, and GBG pCR

1. Graham LJ, *et al*. *J Cancer* 2014; 5:58–68.

pCR is associated with improved long-term clinical outcomes[1-4]

pCR allows early assessment of tumour response[1]

Why pCR?

Systemic therapy → *Average of 12–24 weeks* → **Surgery** → **pCR**

Efficacy evaluation within weeks versus years with time-related endpoints (EFS, OS)

Faster response assessment

pCR is associated with improved long-term clinical outcomes[1-4]

pCR is associated with improved long-term clinical outcomes (EFS, OS)

Association in all breast cancer subtypes, but varies across sub-groups

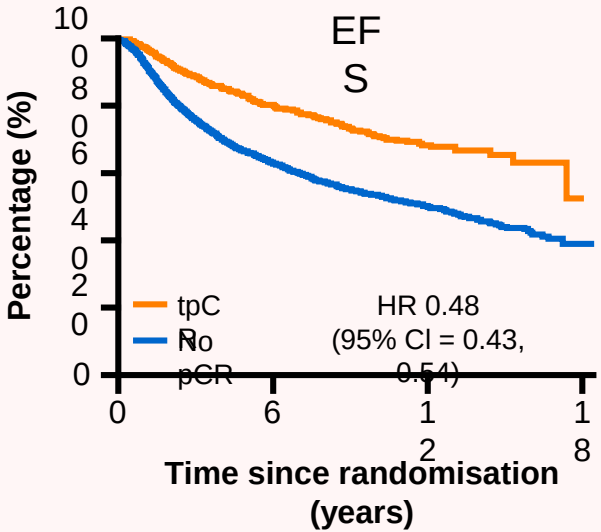
Strongest in HER2-positive and HR-negative[1]

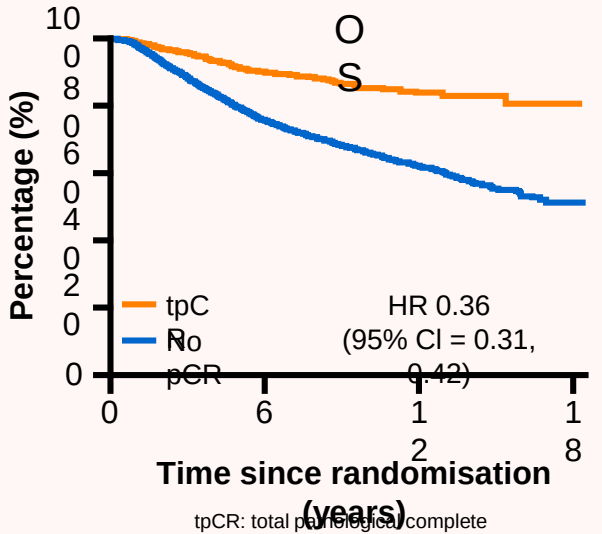
1.Cortazar, *et al. Lancet* 2014;2. Gianni L, *et al. Lancet Oncol* 2012; 3.Gianni L, *et al. Lancet* 2010; 4.Ismael G, *et al. Lancet Oncol* 2012

(EFS, event free survival; OS, overall survival; pCR: pathological complete response)

Achieving pCR improves long-term efficacy

- Patients who achieved tpCR had longer EFS and OS than patients with residual cancer





tpCR: total pathological complete response

Cortazar, *et al. Lancet* 2014

Meta-analysis: Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

- 4756 women in ten randomized trials (median follow-up = 9 years)
- Neoadjuvant chemotherapy results in **higher rates of breast-conserving therapy** than does adjuvant chemotherapy (rate ratio 1·28 [95% CI 1·22–1·34]), **without compromising on distant recurrence, breast cancer survival, or overall survival.**

THE LANCET
Oncology
Volume 19, Issue 1, January 2018, Pages 27-39

Articles

Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials

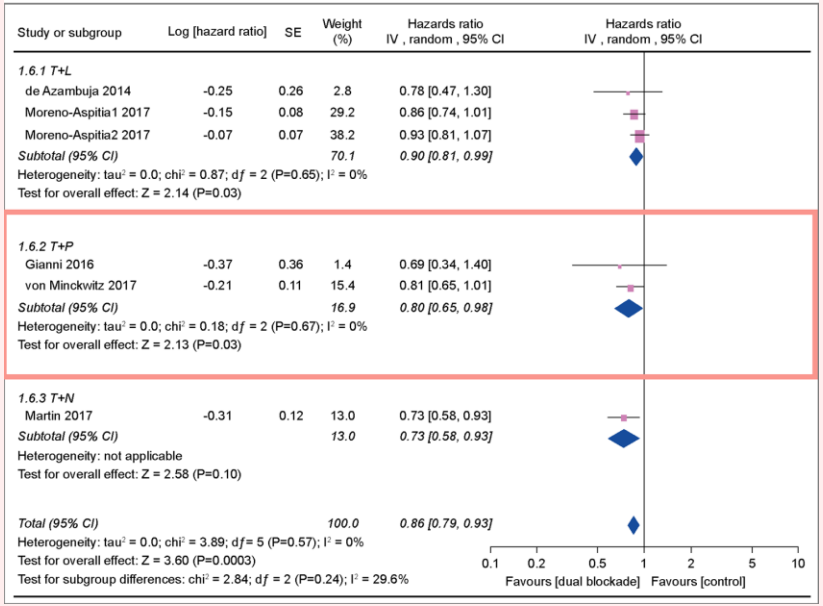
Early Breast Cancer Trialists' Collaborative Group (EBCTCG)†

The Role Pertuzumab-Trastuzumab (PHESGO) in eBC

The pertuzumab-trastuzumab dual-action reduces the risk of eBC recurrence[1]

- **Dual blockade** of HER2 **improves outcomes** than a single anti-HER2 agent alone.[1]
- **Pertuzumab-trastuzumab** reduced the risk of recurrence by **20%** when compared with **trastuzumab alone** in a recent meta-analysis of 10 RCTs investigating 15,284 patients.[1]

IDFS survival stratified by type of dual HER2 blockade regimen[1]

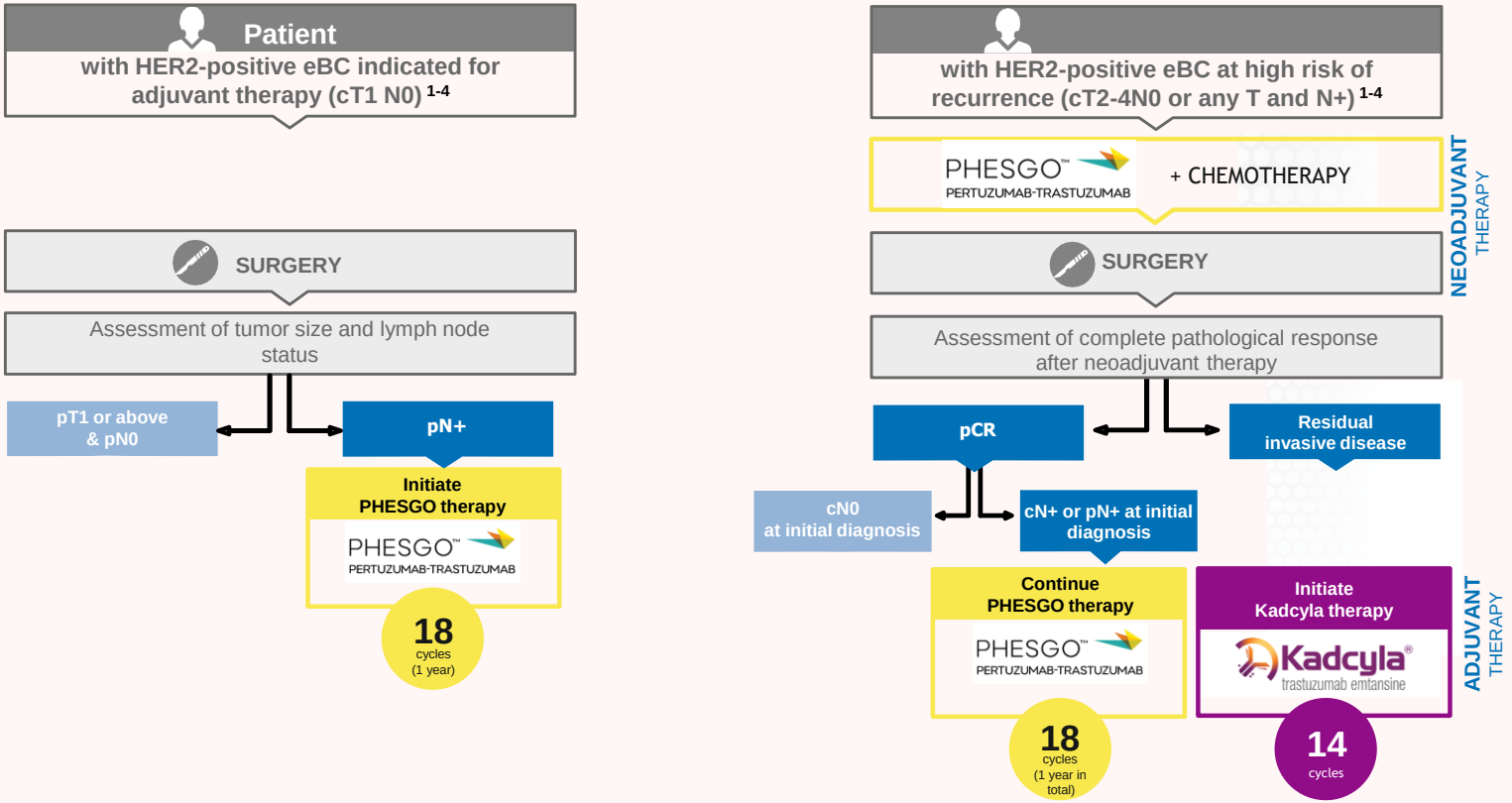


Adapted from Yu L, et al. *J Oncol* 2020.[1]

Abbreviations: CI, confidence interval; eBC, early breast cancer; HER2, human epidermal growth factor receptor 2; IDFS, invasive disease-free survival; IV, inverse-variance method; L, lapatinib; N, neratinib; P, pertuzumab; RCT, randomised controlled trial; SE, standard error; T, trastuzumab.

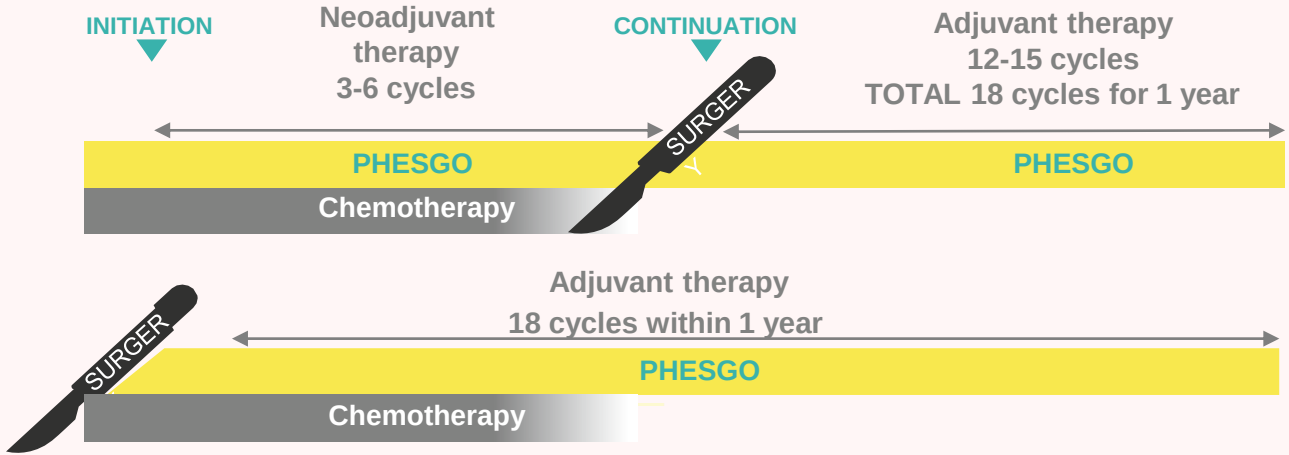
Reference: 1. Yu L, Fu F, Li J, et al. Dual HER2 blockade versus a single agent in trastuzumab-containing regimens for HER2-positive early breast cancer: A systematic review and meta-analysis of randomized controlled trials. *J Oncol.* 2020;2020:5169278.

The role of PHESGO and Kadcyla in the treatment of HER2+ eBC[1-4]



(N+ – positive lymph nodes, pCR – pathological complete response, eBC – early breast cancer)

References:
1. NCCN Clinical Practice Guidelines: Breast Cancer. Version 4.2024. Available at https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (accessed 4 July 2024)
2. Ditsch N, et al. AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2022. Breast Care (Basel). 2022 Aug;17(4):403-420. doi: 10.1159/000524879. ;
3. Loibl S, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2024 Feb;35(2):159-182. doi: 10.1016/j.annonc.2023.11.016. ;
4. Curigliano G, et al. Understanding breast cancer complexity to improve patient outcomes: The St Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023. Ann Oncol. 2023 Nov;34(11):970-986.



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NEOADJUVANT THERAPY

Eligible patients with HER2+ breast cancer (any parameter)

- **Positive lymph nodes**
- **Tumor size greater than or equal to 2 cm**
- **Locally advanced breast cancer**
- **Inflammatory breast cancer**

Patients continue treatment after neoadjuvant therapy:
A total of 18 cycles for 1 year

PHESGO™ PERTUZUMAB-TRASTUZUMAB

ADJUVANT THERAPY

Eligible patients with HER2+ breast cancer

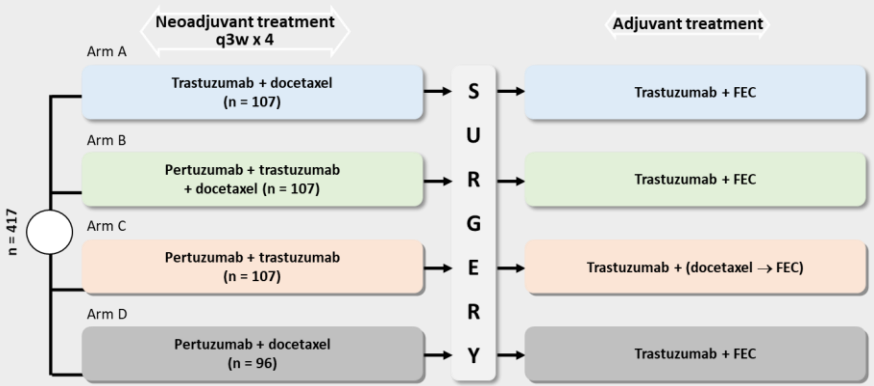
- **High risk of recurrence (e.g. lymph node involvement)**

Patients who begin treatment after surgery:
18 cycles for 1 year

References:
1. BPOM. PHESGO Product Information. Mar 2023.
2. NCCN Clinical Practice Guidelines: Breast Cancer. Version 4.2024. Available at https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (accessed 4 July 2024)

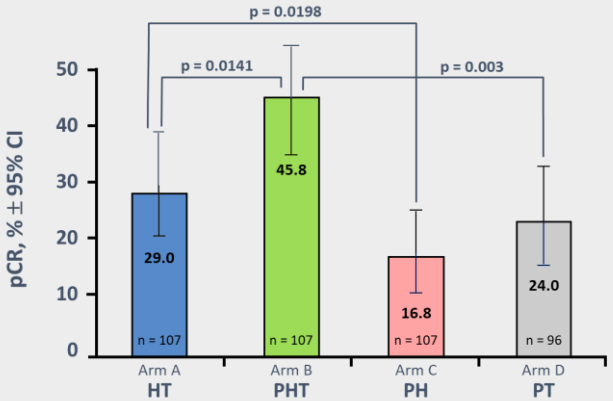
Pertuzumab - NeoSphere Study 2012

Phase II study of Pertuzumab in neoadjuvant setting



Neoadjuvant treatment: trastuzumab 8→6 mg/m^2;
Pertuzumab 840→420 mg/m^2; docetaxel 75→100 mg/m^2
Adjuvant treatment: FEC, 5-fluorouracil, epirubicin and cyclophosphamide q3w x 3;
Docetaxel q3w x 4; Trastuzumab; q3w cycles 5–17 except arm D q3w cycles 5–21.

Pertuzumab/Trastuzumab/Docetaxel (PHT) provided the highest pCR rate vs. other treatment strategies.



- pCR rate of 45.8% vs 29.0% with PHT vs HT, respectively.
- No meaningful increase in cardiac risk with pertuzumab over a short course of 4 cycles of neoadjuvant therapy.

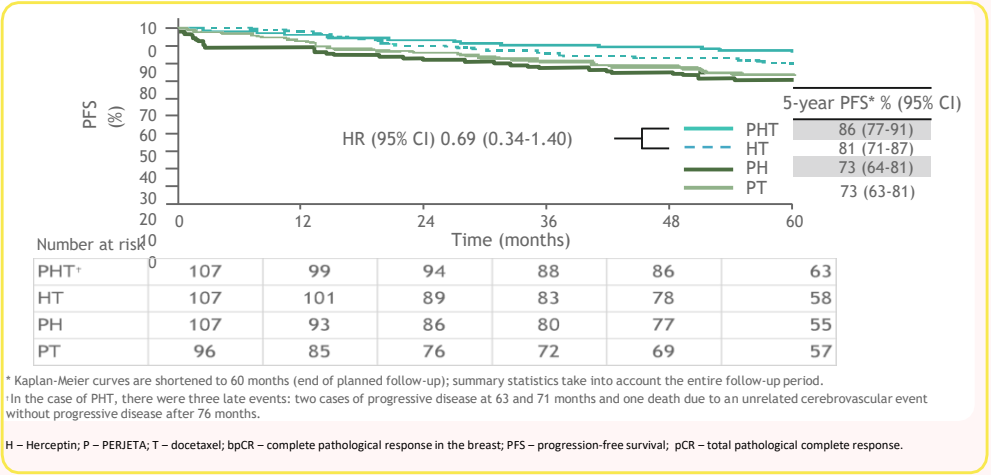
H, trastuzumab; P, pertuzumab; T, docetaxel
EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; pCR, pathological complete response

- These findings support further exploration of more comprehensive HER2 blockade in adjuvant trials and the neoadjuvant approach for pertuzumab evaluation in EBC

1. 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 randomized trial. Lancet Oncol 2016; 17: 791–800

NeoSphere study[1]

Secondary endpoint: PFS



* Kaplan-Meier curves are shortened to 60 months (end of planned follow-up); summary statistics take into account the entire follow-up period.

† In the case of PHT, there were three late events: two cases of progressive disease at 63 and 71 months and one death due to an unrelated cerebrovascular event without progressive disease after 76 months.

H – Herceptin; P – PERJETA; T – docetaxel; bpCR – complete pathological response in the breast; PFS – progression-free survival; pCR – total pathological complete response.

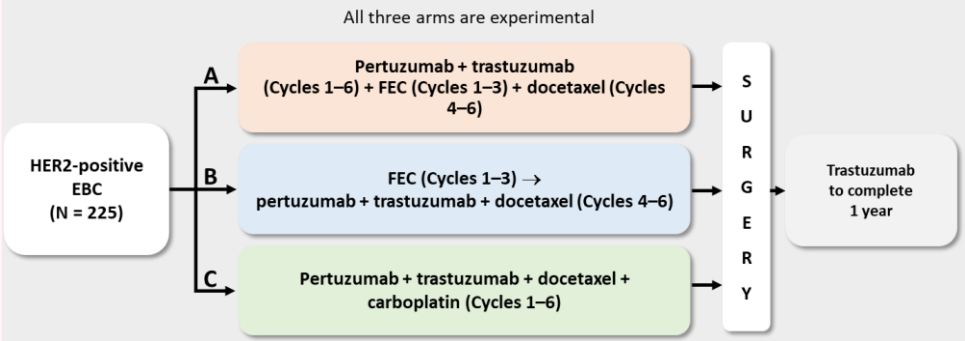
Summary of the results of the NeoSphere study

- In the NeoSphere study, the treatment combination trastuzumab + pertuzumab + docetaxel **achieved the highest PFS rate** compared to other therapeutic combinations in the study[1].
- **86% of patients in this arm remained free of disease progression at 5-year follow-up.** This represents a **31% reduction in the risk of disease progression or death** compared to the trastuzumab + docetaxel treatment combination[1].
- **All patients who achieved tpCR in the NeoSphere study, regardless of which combination they were treated with, lived longer without progression or relapse than patients with residual disease[1].**

References: 1. 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 randomized trial. Lancet Oncol 2016; 17: 791–800

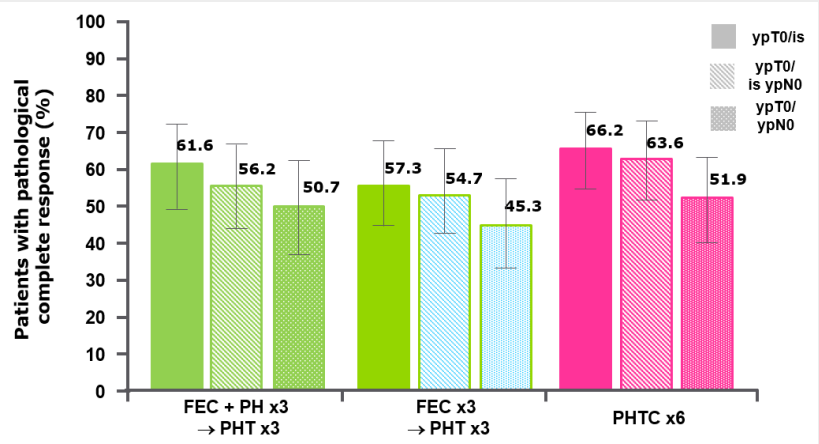
Pertuzumab - TRYPHAENA Study 2013

Phase II study of Pertuzumab with or without anthracycline therapy in neoadjuvant setting



EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; FEC, 5-fluorouracil, epirubicin, cyclophosphamide

High pCR rates were achieved in all arms, PHTC*6 provided the highest pCR rate numerically regardless pCR definition



C, carboplatin; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel
DCIS, ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*; pCR, pathological complete response

ypT0/is, no invasive tumor residues in the breast, DCIS/LCIS in the breast at surgery allowed
ypT0/is ypN0, no invasive tumor residues in the breast and lymph nodes, DCIS/LCIS in the breast at surgery allowed
ypT0/ypN0, no invasive and noninvasive tumor residues in the breast and lymph nodes at surgery

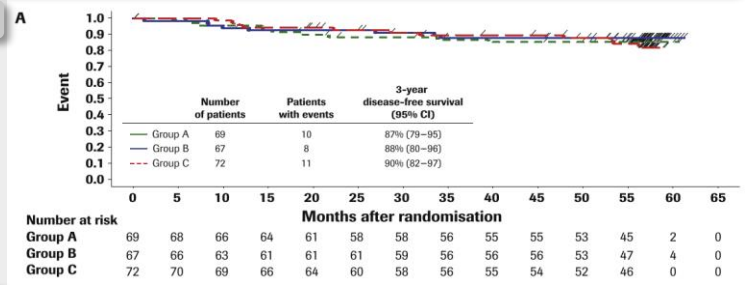
- **Across all treatment arms, the combination of pertuzumab with trastuzumab in the neoadjuvant setting resulted in high pCR rates (57–66%)**

Schneeweiss A, et al. Ann Oncol. 2013;24(9):2278-84.

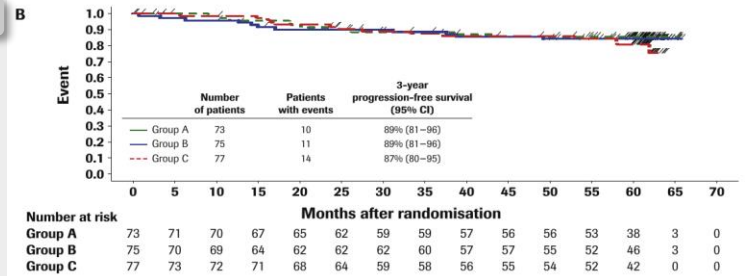
Pertuzumab - TRYPHAENA Long-term Efficacy Analysis 2018

Long-term DFS, PFS and OS were similar between treatment groups

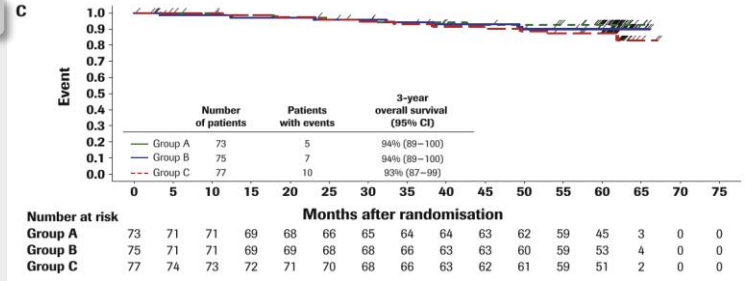
EFS



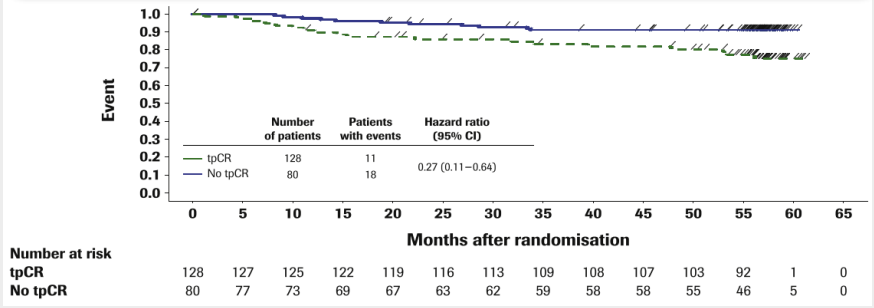
PFS



OS



Patients who achieved tpCR has improved disease-free survival



- The TRYPHAENA study demonstrated that Pertuzumab and Trastuzumab in combination with or without anthracycline therapy in the neoadjuvant setting is well tolerated.
- The results indicated that tpCR is indeed associated with improved long-term outcomes in HER2-positive eBC, 73% risk reduction for DFS (HR=0.27).

Schneeweiss A, et al. Eur J Cancer. 2018 Jan;89:27-35.

PEONY Primary Endpoint (ITT): PERJETA+Herceptin+chemo nearly doubled pCR rate vs Herceptin+chemo

Key eligibility criteria:
- ≥ 18 years
- Centrally confirmed HER2 positive (IHC 3+ or ISH positive) early (T2-3, N0-1, M0) locally advance (T2-3, N2 or N3, M0; T4, any N, M0) breast cancer
- Tumor>2cm
- Known HR status
- ECOG performance status of 0 or 1
- Baseline LVEF ≥55%

2:1

RANDOMIZATION

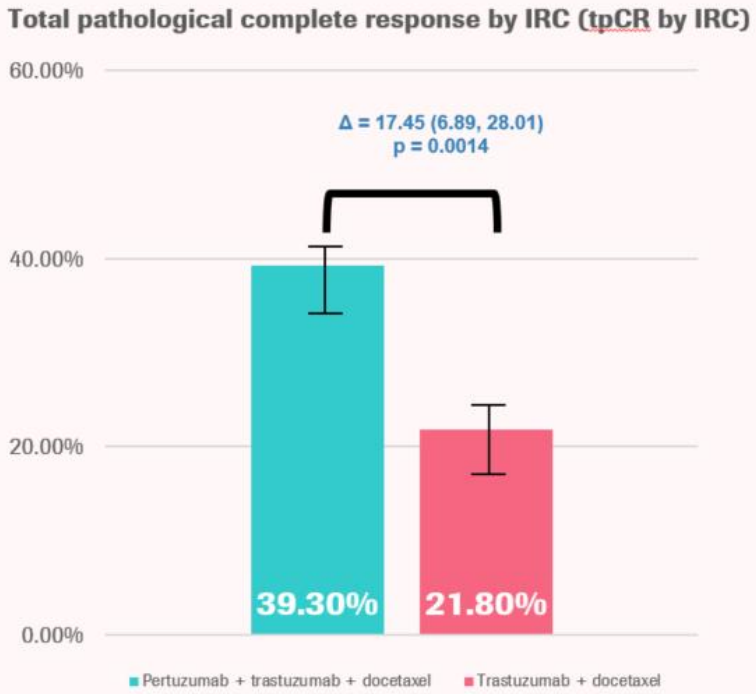
Pertuzumab
(840 mg loading/420 mg q3w)
+
Trastuzumab
(8mg/kg loading 6mg/kg q3w)
+
Docetaxel (75mg/m^2 q3w)

Placebo (q3w)
+
Trastuzumab
(8mg/kg loading 6mg/kg q3w)
+
Docetaxel (75 mg/m2 q3w)

SURGERY

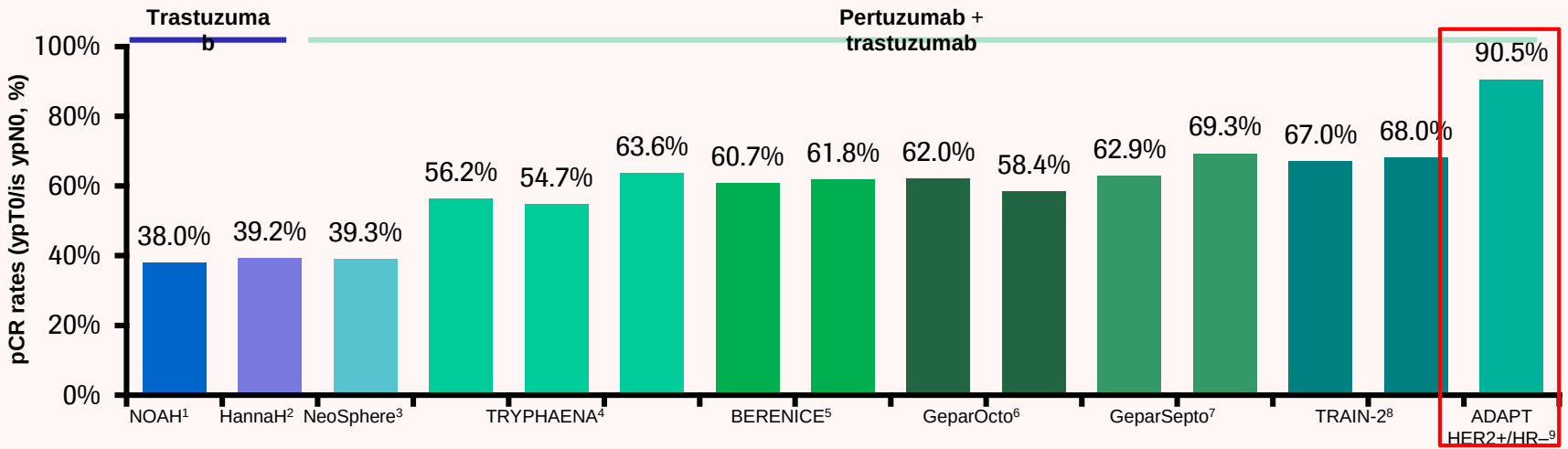
Primary endpoint: tpCR rate assessed by IRC

Secondary endpoints: tpCR rate assessed by local pathologist, bpCR rate assessed by IRC and by local pathologist, clinical response rates, safety and tolerability



Shao Z.,MD, et al. JAMA Oncol. doi:10.1001/jamaoncol.2019.3692

Studies show that neoadjuvant treatment with pertuzumab + trastuzumab + chemotherapy results in higher pCR rates vs. trastuzumab + chemotherapy



Phase	III[1]	III[2]	II[3]	II[4]			II[5]		III[6]		III[7]		III[8]		II[9]
n*	117	260	107	73	75	77	201	199	192	190	197	199	212	206	42
Regimen	AT+H – T+H – CMF+H	Doc+H – FEC+H	Doc/PH	FEC-Doc/PH	FEC-Doc/PH	Cb/Doc/PH	FEC-Doc/PH	ddAC-Pac/PH	E-TC/PH	Pac/NPLD / Cb/PH	Pac-EC/PH	nabPac-EC/PH	FEC-Pac/Cb/PH	Pac/Cb/PH	Pac weekly/PH
Duration of anti-HER2 therapy	33 weeks	24 weeks	12 weeks	18 weeks	9 weeks	18 weeks	18 weeks	20 weeks	12 weeks	18 weeks	24 weeks		27 weeks		12 weeks

* N values represent number of patients in particular treatment arm.

1. Gianni L, *et al. Lancet Oncol* 2012; 3. Gianni L, *et al. Lancet Oncol* 2012; 4. Schneeweiss A, *et al. Ann Oncol* 2013; G, *et al. Lancet Oncol* 2012; ncol 2018; 6. Schneeweiss A, *et al. Eur J Cancer* 2013 (incl. suppl. info.);
7. Loibl S, *et al. Ann Oncol* 2017; 8. van Ramshorst MS, *et al. Lancet Oncol* 2018; 9. Nitz UA, *et al. Ann Oncol* 2017.

Pertuzumab–trastuzumab is supported by international guidelines for neoadjuvant treatment of patients with high-risk HER2-positive eBC

NCCN Breast Cancer Guidelines[1]

A pertuzumab-containing regimen **may be administered** preoperatively to patients with ≥ T2 or ≥ N1, HER2-positive eBC.

ESMO Guidelines for eBC[3]

Dual blockade with trastuzumab–pertuzumab **can be considered** in high-risk patients (node-positive or ER-negative) for 1 year, starting before or after surgery [I, A; MCBS v1.1 score: B].

Pan-Asian adapted ESMO Guideline for eBC[5]

For patients with clinical **stage II-III HER2-positive breast cancer** (e.g. T >2 cm or node-positive), **neoadjuvant systemic ChT** with anti-HER2 therapy comprising **trastuzumab-pertuzumab is the preferred option [I, A]**

AGO Guidelines[2]

If chemotherapy is indicated, systemic treatment before surgery (neoadjuvant) should be preferred.

Pertuzumab plus trastuzumab in combination with chemotherapy is recommended **for patients at high risk** of recurrence (AGO++).

St. Gallen Guidelines[4]

Neoadjuvant systemic therapy is the preferred initial approach in stage 2 or 3 HER2-overexpressing or triple-negative breast cancer.

Chemotherapy in combination with trastuzumab and pertuzumab is the preferred approach for **stage 2 or 3** HER2-positive tumours in adjuvant and neoadjuvant settings.

1. NCCN Breast Cancer Guidelines. Version 4, 2024 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf; **2**. AGO Diagnosis and Treatment of Patients with early and advanced Breast Cancer Guidelines. 2023; **3**. Cardoso F, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Annals of Oncology. 2019;30(8):1194-1220. doi: https://doi.org/10.1093/annonc/mdz173; **4**. Burstein HJ, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. Ann Oncol.2021;32(10):1216-1235. doi:10.1016/j.annonc.2021.06.023 **5**. K.H Park et al. ESMO Open. Volume 9, Issue 5, May 2024 https://doi.org/10.1016/j.esmoop.2024.102974

Open access Editorial

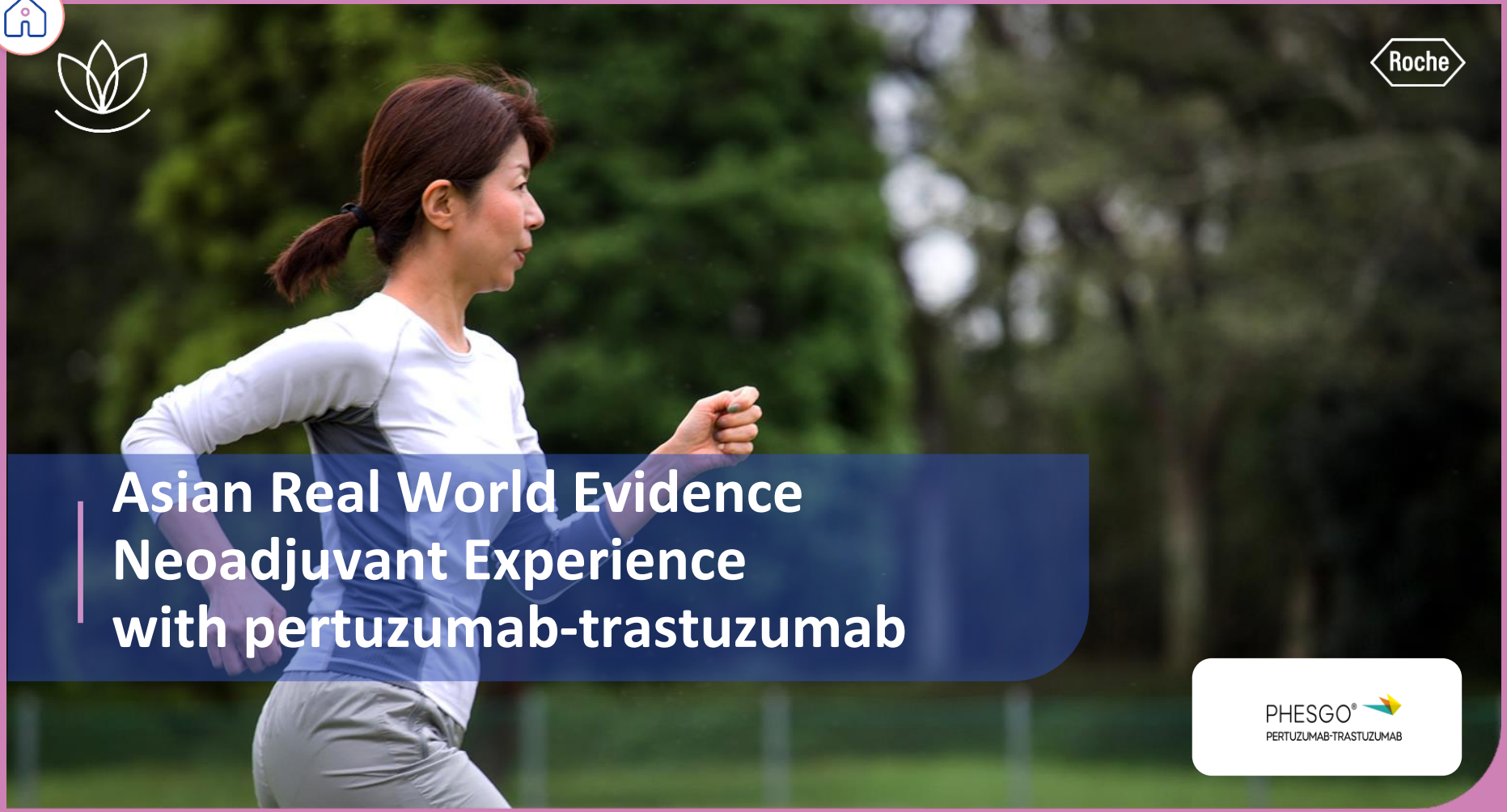
Check for updates

Neoadjuvant treatment for intermediate/high-risk HER2-positive and triple-negative breast cancers: no longer an 'option' but an ethical obligation

Mariana Brandão,[1] Fabien Reyal,[2,3] Anne-Sophie Hamy,[3] Martine Piccart-Gebhart[1]

"…Patients with intermediate to high-risk TNBC or HER2-positive disease (≥T2 and/or lymph-node positive tumours) ***must*** *receive neoadjuvant treatment, as this strategy not only increases the chance of less aggressive surgery, but identifies patients who will benefit from 'salvage' adjuvant therapy with an impact on long-term outcomes."*

Brandão M, Reyal F, Hamy A, et al. ESMO Open 2019;4:e000515. doi: 10.1136/esmoopen-2019-000515


Roche
Asian Real World Evidence
Neoadjuvant Experience
with pertuzumab-trastuzumab
PHESGO®
PERTUZUMAB-TRASTUZUMAB

Hong Kong data from 13,435 women who had been diagnosed with invasive breast cancer during the period of 2006 to 2017, including 1,084 patients who received NAC

CME

ORIGINAL ARTICLE

Preoperative considerations and benefits of neoadjuvant chemotherapy: insights from a 12-year review of the Hong Kong Breast Cancer Registry

Yolanda HY Chan, Carol CH Kwok, Desiree MS Tse, HM Lee, PY Tam, Polly SY Cheung *

https://www.hkmj.org/abstracts/v29n3/198.htm

The use of NAC in Hong Kong increased from 2006 to 2017

- The administration of NAC was positively associated with cancer stage at diagnosis

- The proportion increased from 0.3% in patients with stage I disease to 26.9% among patients with stage III Disease.

- Furthermore, greater proportions of patients with
  - ✓ luminal B (HER2-positive),
  - ✓ HER2-positive (non-luminal), or
  - ✓ triple-negative subtypes of breast cancer received NAC.

Chan Yolanda HY, et al. Preoperative considerations and benefits of neoadjuvant chemotherapy: insights from a 12-year review of the Hong Kong Breast Cancer Registry. Hong Kong Medical Journal 2023.

TABLE 1. Clinical characteristics of non-neoadjuvant chemotherapy and neoadjuvant chemotherapy cases in each cohort*

	Total cases		2006-2011		2012-2017	
	Non-NAC cases n=12 528	NAC cases n=1097	Non-NAC cases n=6151	NAC cases n=363	Non-NAC cases n=6377	NAC cases n=734
Age-group, y						
<40	1040 (8.3%)	164 (14.9%)	597 (9.7%)	53 (14.6%)	443 (6.9%)	111 (15.1%)
40-69	10 423 (83.2%)	907 (82.7%)	5081 (82.6%)	302 (83.2%)	5342 (83.8%)	605 (82.4%)
≥70	942 (7.5%)	18 (1.6%)	412 (6.7%)	7 (1.9%)	530 (8.3%)	11 (1.5%)
Unknown	123 (1.0%)	8 (0.7%)	61 (1.0%)	1 (0.3%)	62 (1.0%)	7 (1.0%)
Histological type						
Invasive ductal NOS	10 703 (85.4%)	932 (85.0%)	5273 (85.7%)	302 (83.2%)	5430 (85.1%)	630 (85.8%)
Invasive lobular	475 (3.8%)	19 (1.7%)	219 (3.6%)	11 (3.0%)	256 (4.0%)	8 (1.1%)
Others	1250 (10.0%)	49 (4.5%)	606 (9.9%)	16 (4.4%)	644 (10.1%)	33 (4.5%)
Unknown	100 (0.8%)	97 (8.8%)	53 (0.9%)	34 (9.4%)	47 (0.7%)	63 (8.6%)
Tumour grade						
1	2212 (17.7%)	24 (2.2%)	1071 (17.4%)	9 (2.5%)	1141 (17.9%)	15 (2.0%)
2	5261 (42.0%)	194 (17.7%)	2554 (41.5%)	60 (16.5%)	2707 (42.4%)	134 (18.3%)
3	4122 (32.9%)	233 (21.2%)	2058 (33.5%)	76 (20.9%)	2064 (32.4%)	157 (21.4%)
Unknown	933 (7.4%)	646 (58.9%)	468 (7.6%)	218 (60.1%)	465 (7.3%)	428 (58.3%)
T stage						
T1	6468 (51.6%)	58 (5.3%)	3189 (51.8%)	18 (5.0%)	3279 (51.4%)	40 (5.4%)
T2	5362 (42.8%)	375 (34.2%)	2655 (43.2%)	105 (28.9%)	2707 (42.4%)	270 (36.8%)
T3	403 (3.2%)	257 (23.4%)	200 (3.3%)	100 (27.5%)	203 (3.2%)	157 (21.4%)
T4	102 (0.8%)	285 (26.0%)	54 (0.9%)	119 (32.8%)	48 (0.8%)	166 (22.6%)
Unknown	193 (1.5%)	122 (11.1%)	53 (0.9%)	21 (5.8%)	140 (2.2%)	101 (13.8%)
N stage						
N0	7636 (61.0%)	229 (20.9%)	3689 (60.0%)	95 (26.2%)	3947 (61.9%)	134 (18.3%)
N1	3205 (25.6%)	391 (35.6%)	1639 (26.6%)	137 (37.7%)	1566 (24.6%)	254 (34.6%)
N2	967 (7.7%)	129 (11.8%)	515 (8.4%)	39 (10.7%)	452 (7.1%)	90 (12.3%)
N3	515 (4.1%)	198 (18.0%)	258 (4.2%)	63 (17.4%)	257 (4.0%)	135 (18.4%)
Unknown	205 (1.6%)	150 (13.7%)	50 (0.8%)	29 (8.0%)	155 (2.4%)	121 (16.5%)
Cancer stage						
I	4987 (39.8%)	13 (1.2%)	2403 (39.1%)	3 (0.8%)	2584 (40.5%)	10 (1.4%)
IIA	3867 (30.9%)	114 (10.4%)	1938 (31.5%)	34 (9.4%)	1929 (30.2%)	80 (10.9%)
IIB	1785 (14.2%)	213 (19.4%)	893 (14.5%)	76 (20.9%)	892 (14.0%)	137 (18.7%)
III	1639 (13.1%)	603 (55.0%)	857 (13.9%)	224 (61.7%)	782 (12.3%)	379 (51.6%)
Unknown	250 (2.0%)	154 (14.0%)	60 (1.0%)	26 (7.2%)	190 (3.0%)	128 (17.4%)
Biological subtype						
HR +ve, HER2 -ve	8227 (65.7%)	440 (40.1%)	3913 (63.6%)	131 (36.1%)	4314 (67.6%)	309 (42.1%)
HER2 +ve (HR +ve)	1496 (11.9%)	223 (20.3%)	859 (14.0%)	75 (20.7%)	637 (10.0%)	148 (20.2%)
HER2 +ve (HR –ve)	1012 (8.1%)	131 (11.9%)	509 (8.3%)	50 (13.8%)	503 (7.9%)	81 (11.0%)
Triple-negative	1347 (10.8%)	158 (14.4%)	678 (11.0%)	46 (12.7%)	669 (10.5%)	112 (15.3%)
Unknown	446 (3.6%)	145 (13.2%)	192 (3.1%)	61 (16.8%)	254 (4.0%)	84 (11.4%)
Median tumour size, cm (range)	2.0 (0.01-19.1)	4.0 (0.55-20.0)	2.0 (0.01-19.1)	4.1 (0.55-20.0)	2.0 (0.01-17.0)	3.8 (0.79-20.0)

Abbreviations: +ve = positive; -ve = negative; HER2 = human epidermal growth factor receptor 2; HR = hormonal receptor; NAC = neoadjuvant chemotherapy; NOS = not otherwise specified

* Data are shown as No. (%) or median (range)

After treatment with NAC, greater proportions of patients with clinical stage IIA or IIB disease underwent breast-conserving surgery

- Patients with clinical stage IIA disease were most likely to switch from mastectomy to BCS after NAC; **53.9% underwent BCS after NAC, compared with 38.2%** of patients with stage IIA disease who did not receive NAC.
- The second highest proportion was observed among patients with clinical stage IIB disease, 38.3% of whom underwent BCS after NAC.
- Even among patients with clinical stage III disease, 14.1% underwent BCS after NAC.
- Significant differences in the rate of BCS were also observed between the NAC and non-NAC groups in patients with stages IIA (P=0.02) and IIB (P=0.031) disease.

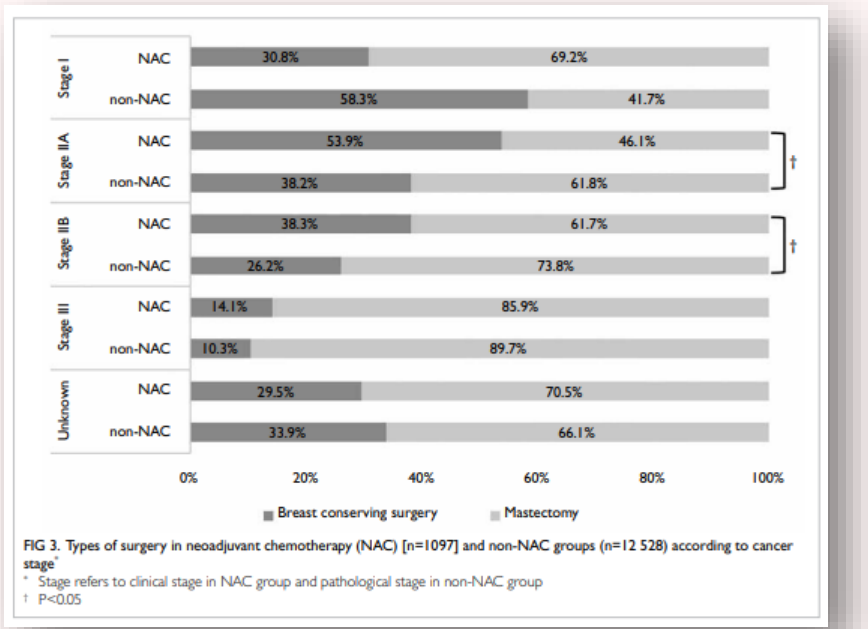


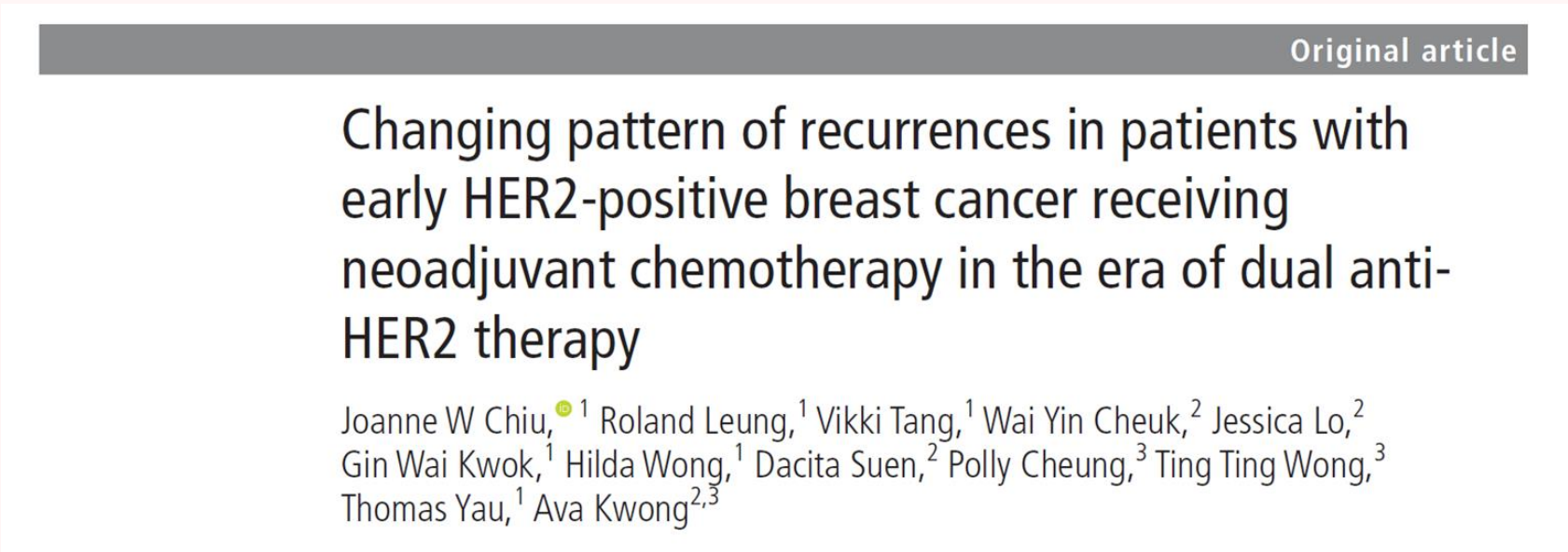
FIG 3. Types of surgery in neoadjuvant chemotherapy (NAC) [n=1097] and non-NAC groups (n=12 528) according to cancer stage*

* Stage refers to clinical stage in NAC group and pathological stage in non-NAC group

† P<0.05

Yolanda HY Chan, et al. Preoperative considerations and benefits of neoadjuvant chemotherapy: insights from a 12-year review of the Hong Kong Breast Cancer Registry. Hong Kong Medical Journal 2023.

Retrospective study analyzed the outcome of neoadjuvant chemotherapy during the period 2005 to 2016



Original article

Changing pattern of recurrences in patients with early HER2-positive breast cancer receiving neoadjuvant chemotherapy in the era of dual anti-HER2 therapy

Joanne W Chiu,[1] Roland Leung,[1] Vikki Tang,[1] Wai Yin Cheuk,[2] Jessica Lo,[2] Gin Wai Kwok,[1] Hilda Wong,[1] Dacita Suen,[2] Polly Cheung,[3] Ting Ting Wong,[3] Thomas Yau,[1] Ava Kwong[2,3]

Chiu JW, et al. Postgrad Med J 2019;0:1–7.

Significant increase in pCR and breast conservation rate in Chemo-DH (chemo plus double anti-HER2) cohort

Table 1 Basic patient demographics and treatment outcome

	Overall	Chemo	Chemo-H	Chemo-DH	P value
No of patients	221*	41	138	43	
No of cases	226	42	141	43	
Ethnicity	206 (93.2%)	36 (87.8%)	128 (92.8%)	43 (100.0%)	0.110
► Chinese	14 (6.3%)	5 (12.2%)	9 (6.5%)	0 (0.0%)	
► Southeast Asian	1 (0.5%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	
► Other					
Median onset age (years)	50	48.5	50	49	0.198
Premenopausal	133 (59.6%)	24 (57.1%)	78 (56.5%)	31 (72.1%)	0.181
Staging					
► IA	2 (0.9%)	0 (0.0%)	2 (1.4%)	0 (0.0%)	0.858†
► IIA	40 (17.7%)	6 (14.3%)	25 (17.7%)	9 (20.9%)	
► IIB	56 (24.8%)	12 (28.6%)	33 (23.4%)	11 (25.6%)	
► IIIA	67 (29.6%)	12 (28.6%)	48 (34.0%)	7 (16.3%)	
► IIIB	17 (7.5%)	5 (11.9%)	10 (7.1%)	2 (4.7%)	
► IIIC	44 (19.5%)	7 (16.7%)	23 (16.3%)	14 (32.6%)	
ER/PR positive	119 (52.7%)	15 (35.7%)	78 (55.3%)	26 (60.5%)	0.045
Anthracycline-containing regimens	58 (26.0%)	40 (95.2%)	16 (11.6%)	2 (4.7%)	<0.0001
Taxane-containing regimens	204 (91.5%)	25 (59.5%)	137 (99.3%)	42 (97.7%)	<0.0001
Median time to surgery (months)	4.7	5.4	4.7	4.6	0.001
Clinical significant anti-HER2-related cardiomyopathy	4	NA	2 (1.4%)	2 (4.7%)	
Breast conservative therapy	74 (32.7%)	13 (31.0%)	39 (28.3%)	21 (48.8%)	0.046
pCR	64 (28.3%)	2 (4.8%)	36 (25.5%)	26 (60.5%)	<0.0001
Additional adjuvant chemotherapy	59 (26.5%)	20 (47.6%)	32 (23.4%)	7 (16.3%)	0.003
► pCR	5	0	5	0	
► Residual disease	54	20	27	7	

*One patient who had received chemotherapy with trastuzumab for first occurrence of breast cancer developed metachronous contralateral breast cancer and received double anti-HER2 targeted therapy in combination with chemotherapy.
†Stage II (IIA and IIB) vs stage III (IIIA, IIIB and IIIC).
ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; NA, not available; PR, progesterone receptor; pCR, pathologic complete response.

Chiu JW, et al. Postgrad Med J 2019;0:1–7.

The outcome and adverse events associated with the trastuzumab+pertuzumab subgroup

	Trastuzumab+pertuzumab		
No of cases	24		
pCR	17 (70.8%)		
Median proportion of cycles with double-HER blockade	100.0%		
Adverse events (%)			
	G1	G2	G3
Anaemia	4 (17%)	0	0
Neutropenia		1 (4%)	4 (17%)
Thrombocytopenia	4 (17%)	0	0
Peripheral neuropathy	7 (29%)	1 (4%)	0
Diarrhoea	9 (38%)	3 (13%)	0
Mucositis	4 (17%)	0	0
Rash	3 (13%)	0	0
Transaminitis	2 (8%)	0	0

HER2, human epidermal growth factor receptor 2; pCR, pathological complete response.

Chiu JW, et al. Postgrad Med J 2019;0:1–7.

Patients with pCR had significantly longer RFS compared with those with residual disease

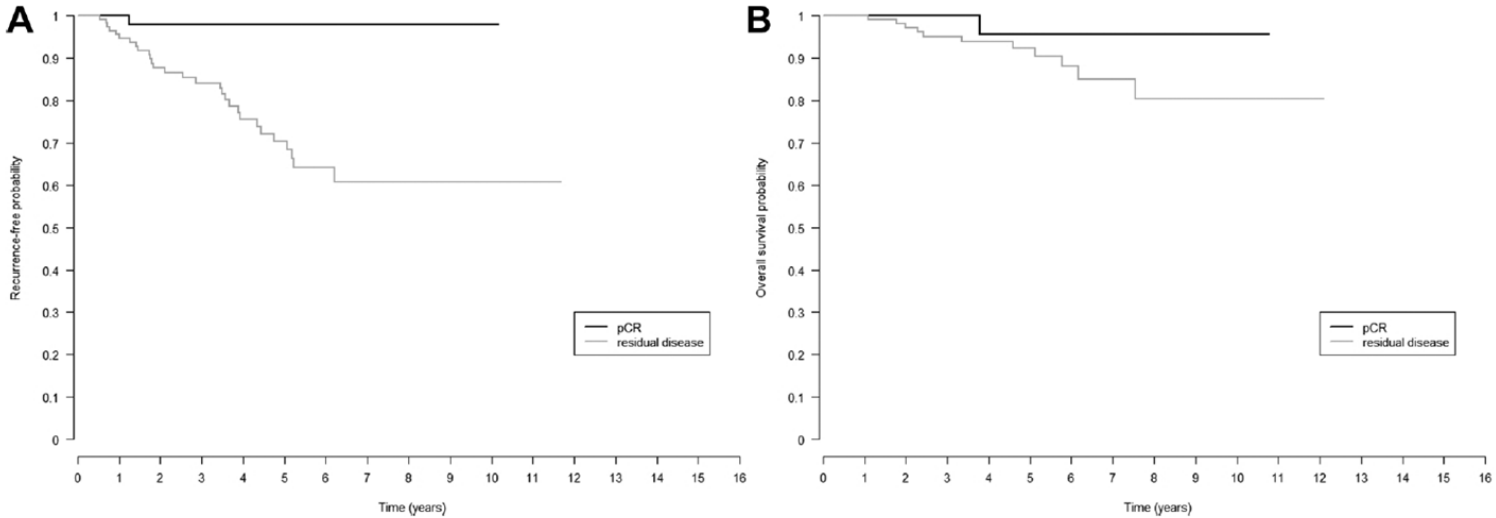


Figure 3 (A) Recurrence-free survival and (B) overall survival according to outcome of neoadjuvant therapy in Chemo-H and Chemo-DH cohorts. Chemo-DH, chemotherapy plus double anti-human epidermal growth factor receptor 2 therapy; Chemo-H, chemotherapy plus trastuzumab; pCR, pathological complete response.

Chiu JW, et al. Postgrad Med J 2019;0:1–7.

Summary

- The incorporation of neoadjuvant anti-HER2 therapy in early breast cancer setting has benefits[1]:
  - reducing tumor size, increasing resectability and breast conservation rate,
  - assess response,
  - correlated with long-term outcome (EFS, OS)
- **Current international guidelines recommend neoadjuvant therapy** for for triple-negative and HER2-positive disease with **tumor size > 2 cm or nodes (+)**[2-5]
- Neoadjuvant Pertuzumab+Trastuzumab (PHESGO) was proven to increase pathological complete response rate, improve EFS, and is recommended by all major international guideline: NCCN, ESMO PAGA, AGO. St Gallen
- Neosphere: **Neoadjuvant PERJETA-Herceptin plus chemotherapy nearly doubled pCR rate across subgroups**[6]
- International guidelines recommend **continuing adjuvant pertuzumab-trastuzumab** treatment in patients with **node-positive eBC even after achieving pCR to complete 18 cycles** in the adjuvant setting[2-5]
- **T-DM1** is currently the main anti-HER2 therapy **endorsed by international treatment guidelines** for treatment of **patients who did not achieve pCR** (non-pCR) post neoadjuvant treatment[2-5]

1. Cain H, et al. Neoadjuvant Therapy in Early Breast Cancer: Treatment Considerations and Common Debates in Practice. Clin Oncol 29. 642-652. 2017. **2.** NCCN clinical practice guidelines in oncology: Breast cancer. V4. 2024; NCCN Breast Cancer Guidelines. Version 4, 2024 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf; 2. AGO Diagnosis and Treatment of Patients with early and advanced Breast Cancer Guidelines. 2023; **3**. Cardoso F, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Annals of Oncology. 2019;30(8):1194-1220. doi: https://doi.org/10.1093/annonc/mdz173; **4**. Burstein HJ, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. Ann Oncol.2021;32(10):1216-1235. doi:10.1016/j.annonc.2021.06.023 **5**. K.H Park et al. ESMO Open. Volume 9, Issue 5, May 2024 https://doi.org/10.1016/j.esmoop.2024.102974. **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 randomized trial. Lancet Oncol 2016; 17: 791–800

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