Clinical Practice Guideline for Adjuvant Therapy in HER2+ Early Breast Cancer

Abbreviations: 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

Outline

- A CRITICAL UNMET NEED IN EBC
- IMPORTANCE OF CHOOSING THE RIGHT PATIENTS
- PERTUZUMAB-TRASTUZUMAB IN EBC
- CONTINUITY OF CARE WITH PERTUZUMAB-TRASTUZUMAB
- OPTIMISING DURATION OF TREATMENT
- The role Kadcyla in residual disease

Abbreviations: eBC, early breast cancer

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PERTUZUMAB-TRASTUZUMAB

A critical unmet need in eBC

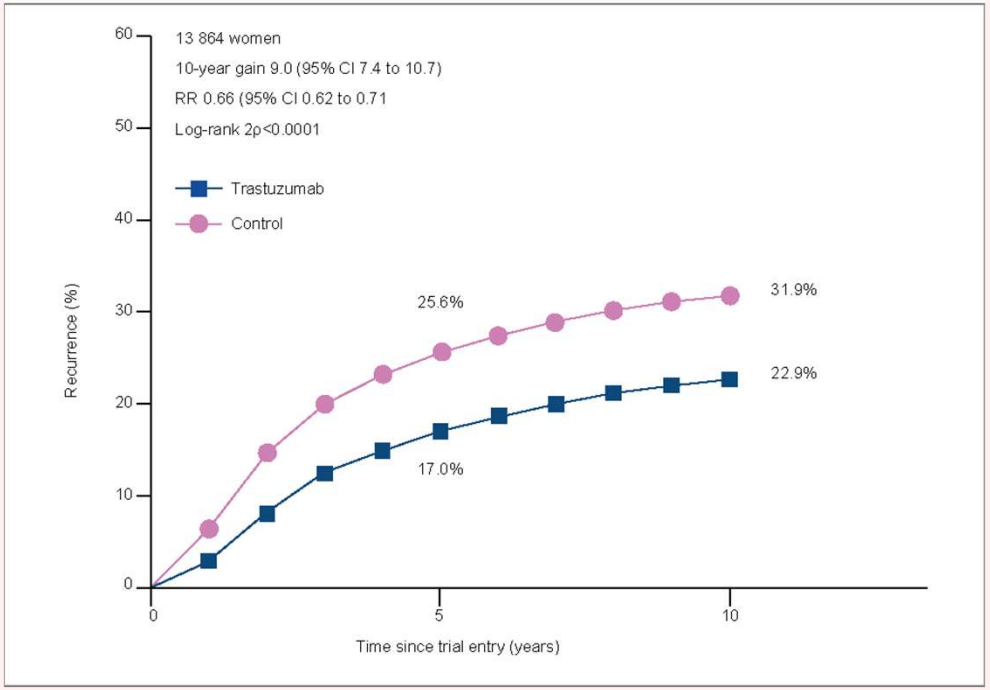
Abbreviation: eBC, early breast cancer

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]

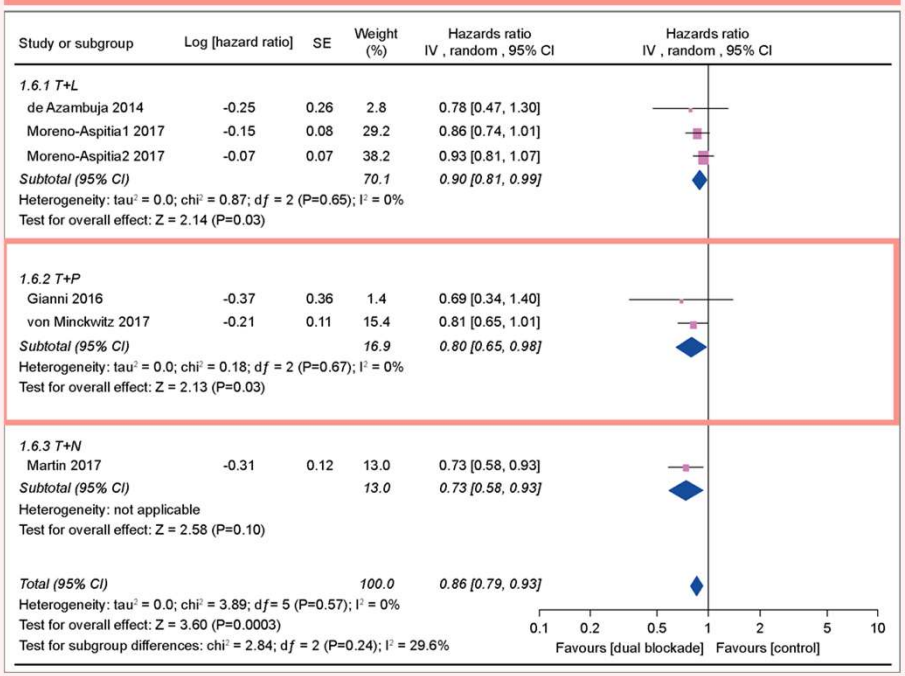
Abbreviations: eBC, early breast cancer; HER2+, human epidermal growth factor receptor-2 positive; RR, rate ratio; SoC, standard of care.

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 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]

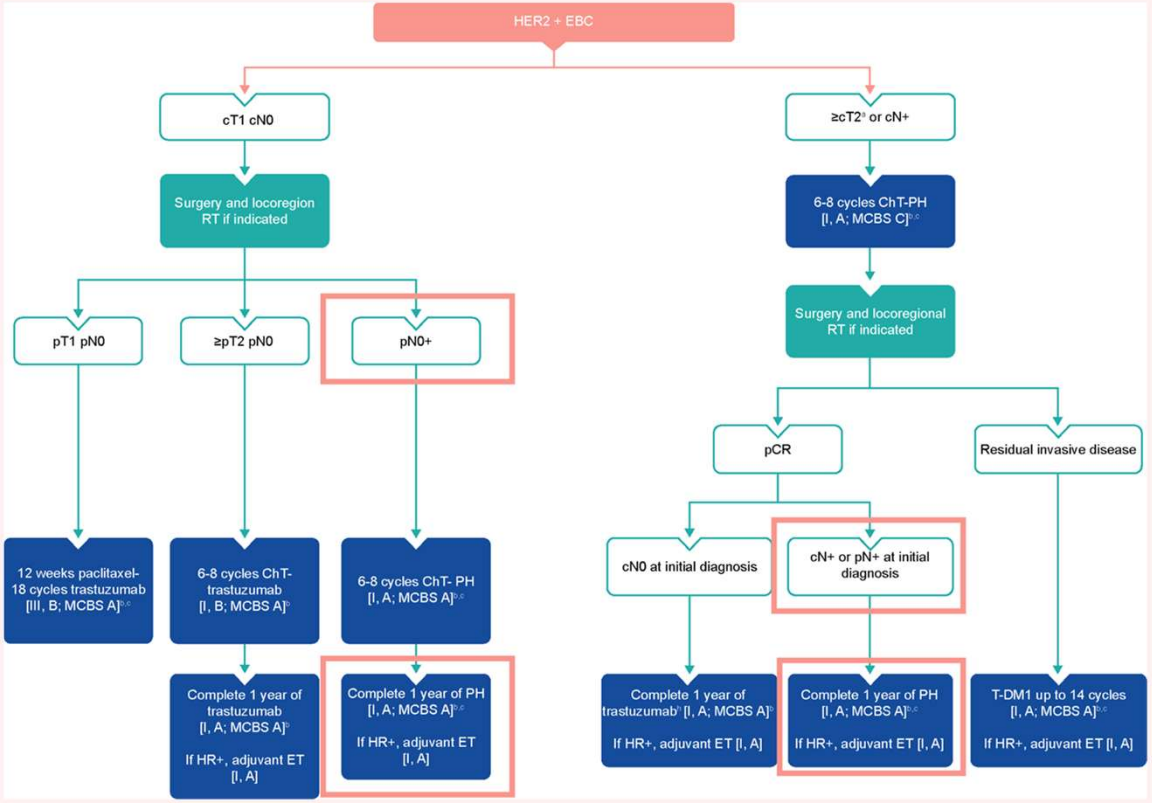


Adapted from Yu L, et al. *J Oncol* 2020.[1]

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 ESMO Clinical Practice Guideline for the management of HER2+ eBC[1]



Turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy.
c, clinical; CISH, chromogenic in situ hybridisation; ChT, chemotherapy; EBC, early breast cancer; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; PH, pertuzumab-trastuzumab; HR, hormone receptor; MCBS, ESMO-Magnitude of Clinical Benefit Scale; N, node; p, pathological; pCR, pathological complete response; RT, radiotherapy; T, tumour; T-DM1, trastuzumab emtansine.
[a]Tumours <2 cm can be considered for neoadjuvant therapy.
[b]ESMO-MCBS v1.1 was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[c]ESCAT score I-A if HER2 gene amplification by FISH/CISH. ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and assisted as needed by the ESMO Translational Research and Precision Medicine Working Group. See Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2023.11.016, for more information on ESCAT scores.

Pertuzumab is approved for 3-6 cycles in neoadjuvant setting for early breast cancer treatment.[2]

Reference: 1. Loibl S, Andre F, Bachelot T, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2024;35(2):159-182. 2. BPOM. Product Information PHESGO. Feb 2025. 3. BPOM. Product Information Perjeta. 2024

Give HER every chance possible. Continue the fight[1,2]

- Trastuzumab-based adjuvant therapy alone is **not enough** to prevent eBC from recurring.[1]
- A **dual blockade** of HER2 with pertuzumab-trastuzumab can significantly improve your patient's odds of IDFS.[2]

Abbreviations: eBC, early breast cancer; EFS, event-free survival; HER2, human epidermal growth factor receptor 2; iDFS, invasive disease-free survival.

References: 1. 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. 2. 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.

Importance of choosing the right patients

Optimise HER outcome. Identify the ideal candidate for pertuzumab-trastuzumab[1]

- Identifying the right candidate for pertuzumab-trastuzumab **maximises treatment efficacy**[1]
- **Minimises the potential risks** of over- or under-treatment[1]

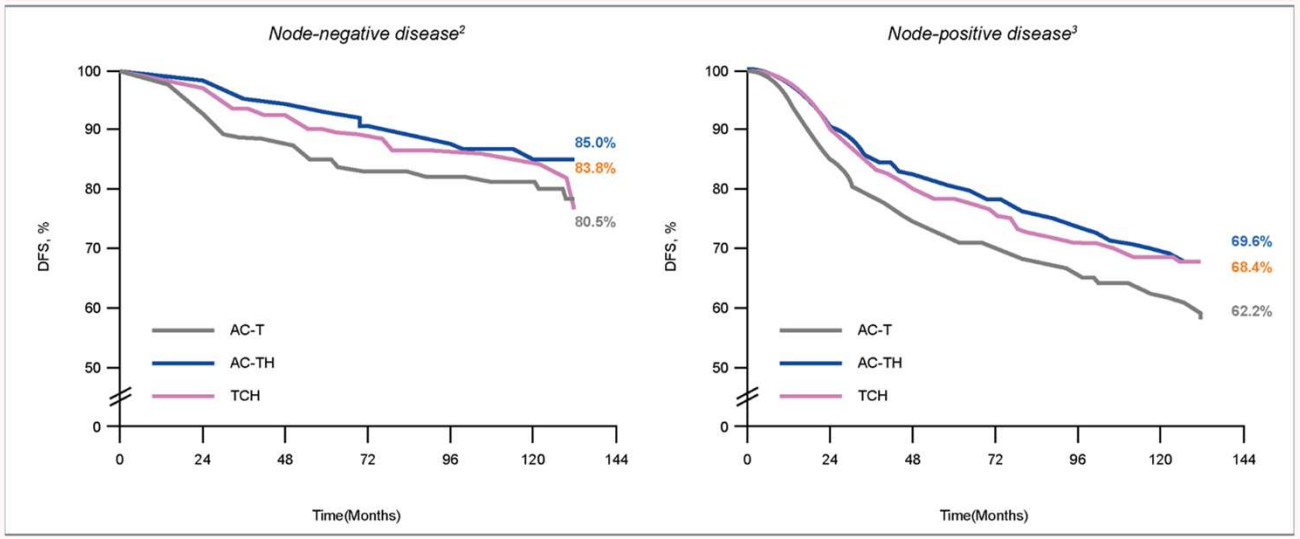
So, who would benefit most from pertuzumab-trastuzumab?

Reference: 1. Scharl A, Kuhn T, Papathemelis T, et al. The right treatment for the right patient – personalised treatment of breast cancer. *Geburtshilfe Frauenheilkd*. 2015;75(7):683-691.

Node-positivity increases the risk of disease recurrence in eBC[1-3]

- Node involvement is directly related to the risk of breast cancer recurrence.[1]
- After 10 years, patients with node-positive HER2+ eBC have a **15% higher risk of recurrence** versus patients with node-negative disease (30% vs 15%, respectively), despite trastuzumab-based adjuvant therapy.[2,3]

BCIRG-006 (10-year FU): Recurrence rate for patients with node-negative and node-positive disease[3]



Adapted from Slamon DJ, et al. SABCS 2015. Oral Presentation.[3]

Node-positive HER2+ eBC warrants a more aggressive therapeutic approach.[1-3]

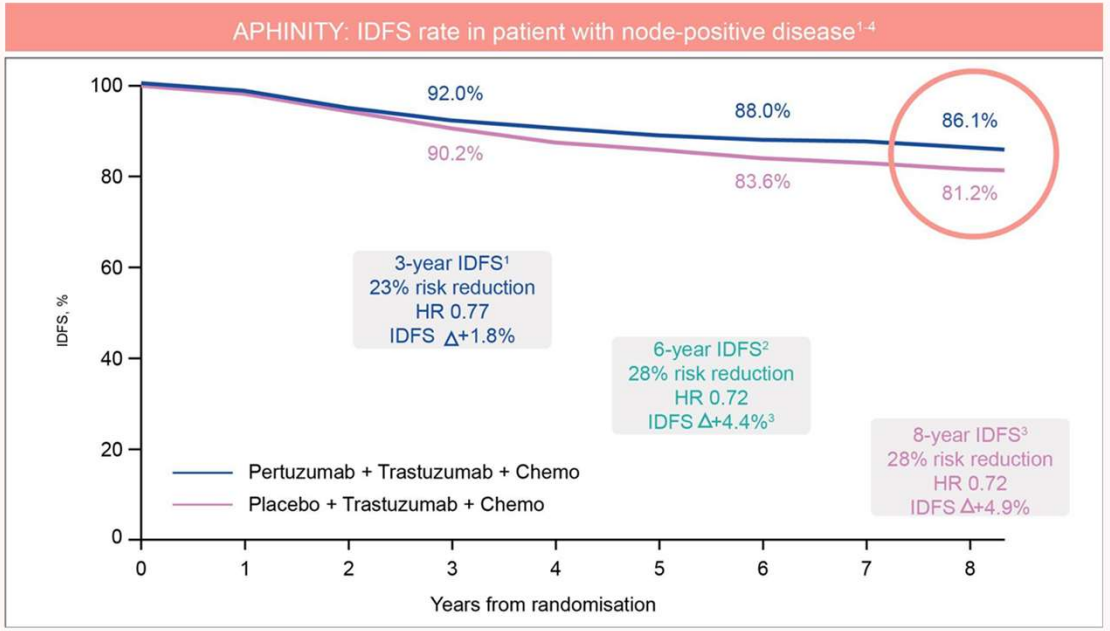
Abbreviations: AC, doxorubicin/cyclophosphamide; C, carboplatin; DFS, disease free survival; eBC, early breast cancer; FU, follow-up; H, trastuzumab; T, docetaxel.

References: 1. Cianfrocca M, Goldstein LJ. Prognostic and predictive factors in early-stage breast cancer. *Oncologist.* 2004;9(6):606-616. 2. Roche, data on file. 3. Slamon DJ, Eiermann W, Robert NJ, et al. Ten year follow-up of BCIRG-006 comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC→T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer. Presented at the San Antonio Breast Cancer Symposium in San Antonio, TX; December 8–12, 2015. SABCS Oral Presentation.

Patients with node-positive eBC are the ideal candidates for pertuzumab-trastuzumab[1-4]

- Subgroup analysis from the 8.4-year follow-up of the APHINITY trial* demonstrated:

Patients with node-positive eBC continued to derive benefit, with a 28% reduction in the risk of recurrence or death with pertuzumab + trastuzumab + chemo compared to placebo + trastuzumab + chemo.[3,4]



Adapted from Loibl S, et al. ESMO Virtual Plenary. July 2022.[3]

*Refer to the appendix for the APHINITY trial design.

Abbreviations: chemo, chemotherapy; eBC, early breast cancer; HR, hazard ratio; IDFS, invasive disease-free survival

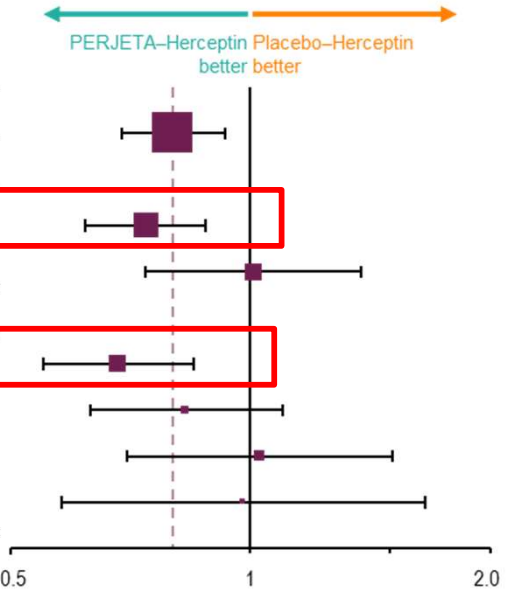
References: 1. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med*. 2017;377(2):122-131. 2. Piccart M, Procter M, Fumagalli D, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. J Clin Oncol. 2021;39(13):1448-1457. 3. Loibl S, Jassem J, Sonnenblick A, et al. Updated results of APHINITY at 8.4 years median follow up. Presented at ESMO Virtual Plenary. July 14–15, 2022. 4. Loibl S, Jassem J, Sonnenblick A, et al. VP6-2022: Adjuvant pertuzumab and trastuzumab in patients with early HER-2 positive breast cancer in APHINITY: 8.4 years' follow-up. *Ann Oncol*. 2022;33(9):P986-987.

IDFS benefit of PHESGO in subgroups according to nodal and hormone receptor status

IDFS benefit of PHESGO was seen irrespective of hormone receptor status

FA

Baseline risk factors	Total patients, n	Pertuzumab–trastuzumab (n = 2400) Patients per group, n	Events, n	Placebo–trastuzumab (n = 2404) Patients per group, n	Events, n	HR (95% CI)
All patients*	4804	2400	303	2404	379	0.80 (0.69, 0.93)
Nodal status						
Node-positive	3005	1503	224	1502	299	0.74 (0.62, 0.88)
Node-negative	1799	897	79	902	80	1.01 (0.74, 1.38)
Nodal and hormone receptor status						
Node-positive, hormone receptor-positive	1912	947	131	965	193	0.68 (0.55, 0.85)
Node-positive, hormone receptor-negative	1093	556	93	537	106	0.83 (0.63, 1.10)
Node-negative, hormone receptor-positive	1170	589	52	581	52	1.03 (0.70, 1.51)
Node-negative, hormone receptor-negative	629	308	27	321	28	0.98 (0.58, 1.66)



- **The clinically meaningful IDFS benefit in the node-positive subgroup was maintained after a median 11.3 years of follow-up; no additional benefit of pertuzumab was seen in the node-negative subgroup**

* Unadjusted analysis of the ITT population.
CI, confidence interval; FA, final analysis; HR, hazard ratio; IDFS, invasive disease-free survival; ITT, intention-to-treat.

Loibl S, *et al*. ESMO BC 2025 (LBA1; oral presentation).

Longer recurrence-free interval in patients of Chinese origin[1]

- **A higher proportion of nodal involvement was observed in Chinese patients** in a subgroup analysis of the APHINITY* trial.[1]

Numerical improvement in IDFS was observed with the **addition of pertuzumab to trastuzumab in Chinese patients**

- A meaningful benefit was shown in the node-positive subgroup when compared with the node-negative subgroup (**IDFS event-free rates at 3 years: 91.4% vs 89.4%; HR, 0.65**; 95% CI, 0.36–1.16)

Summary of key efficacy end points in the Chinese population and the global population of the APHINITY study[1]

	Chinese population		Global population (10)	
	Pertuzumab arm (n=275)	Placebo arm (n=283)	Pertuzumab arm (n=2400)	Placebo arm (n=2404)
IDFS				
Patients with event, n (%)	21 (7.6)	31 (11.0)	171 (7.1)	210 (8.7)
HR, (95% CI)	0.69 (0.39-1.19)		0.81 (0.66 - 1.00)	
IDFS including SPNBC				
Patients with event, n (%)	24 (8.7)	33 (11.7)	189 (7.9)	230 (9.6)
HR, (95% CI)	0.74 (0.44-1.25)		0.82 (0.68-0.99)	
DRFI				
Patients with event, n (%)	16 (5.8)	23 (8.1)	119 (5.0)	145 (6.0)
HR, (95% CI)	0.70 (0.37-1.33)		0.82 (0.64-1.04)	
OS				
Patients with event, n (%)	8 (2.9)	12 (4.2)	80 (3.3)	89 (3.7)
HR, (95% CI)	0.67 (0.28-1.65)		0.89 (0.66-1.21)	

HRs for the global population were estimated by Cox regression, stratified by nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen. HRs presented for the Chinese population were estimated by unstratified Cox regression.

Adapted from Shao Z, et al. *Jpn J Clin Oncol*. 2021.[1]

Pertuzumab arm = pertuzumab + trastuzumab + chemo; placebo arm = placebo + pertuzumab + chemo
*Refer to the appendix for the APHINITY trial design.
Abbreviations: chemo, chemotherapy; CI, confidence interval; DRFI, distant recurrence-free interval; HR, hazard ratio; IDFS, invasive disease-free survival; OS, overall survival; SPNBC, second primary non-breast cancer.
Reference: 1. Shao Z, Tseng L, Huang C, et al. Pertuzumab and trastuzumab as adjuvant treatment for HER2-positive early breast cancer: outcomes in Chinese patients in the APHINITY study. *Jpn J Clin Oncol*. 2021;51(3):345-353.

Continue the fight for your patients with pertuzumab-trastuzumab[1,2]

- **Patients with node-positive disease** continue to derive clear benefit from addition of pertuzumab to trastuzumab and chemo.[1]
- Pertuzumab + trastuzumab + chemo demonstrates a **35% reduction in the risk of recurrence or death (at 3 years) in Chinese patients with node-positive disease** compared to placebo + trastuzumab + chemo.[2]

Abbreviations: chemo, cheomtherapy; eBC, early breast cancer.

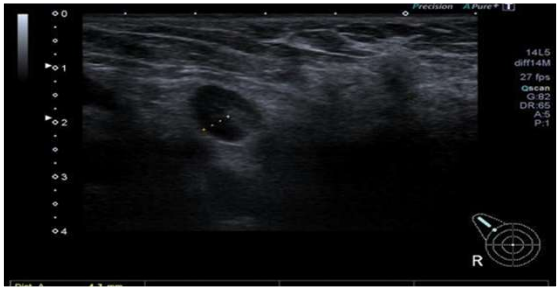
References: 1. Loibl S, Jassem J, Sonnenblick A, et al. VP6-2022: Adjuvant pertuzumab and trastuzumab in patients with early HER-2 positive breast cancer in APHINITY: 8.4 years' follow-up. *Ann Oncol*. 2022;33(9):P986-987. 2. Shao Z, Tseng L, Huang C, et al. Pertuzumab and trastuzumab as adjuvant treatment for HER2-positive early breast cancer: outcomes in Chinese patients in the APHINITY study. *Jpn J Clin Oncol*. 2021;51(3):345-353.

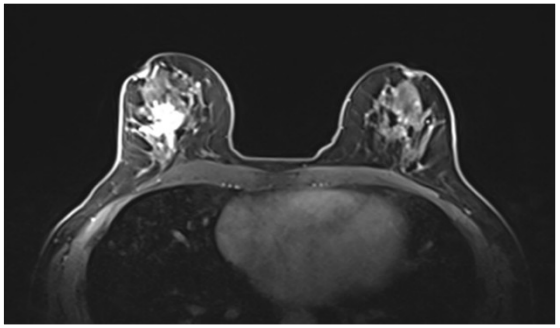
PHESGO®
PERTUZUMAB-TRASTUZUMAB

Mrs M, 48-year-old, premenopausal lady, presented with a lump in her right breast for 1 month

Diagnosis and Staging

Relevant information
Corporate executive
Married with 2 children
No known medical illness/ prior surgeries
Declined gBRCA test
Notes: She wishes to avoid mastectomy if possible.





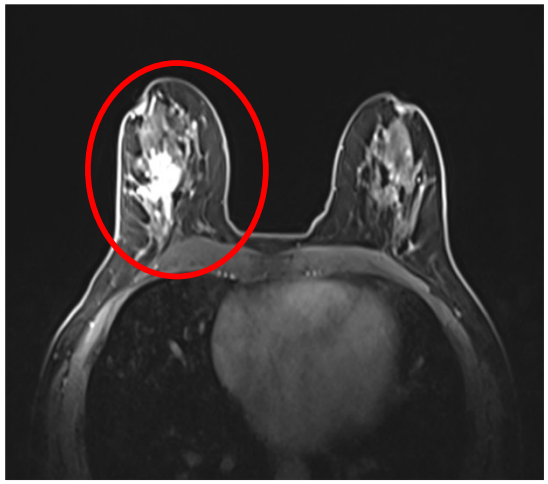
Breast examination:	3-4 cm lump at the right breast. Not fixed, normal overlying skin and nipple No Axillary LN palpable
Ultrasound Breasts	Single 30 mm tumour at right breast, one suspicious axillary LN, 1.2 cm
CN Biopsy	Ductal invasive carcinoma, Grade 3, ER 6/8, PR 4/8, Ki67 50%, HER2 IHC 3+ (Ventana 4B5)
MRI breast	3.1 mm lesion One suspicious lymph node
CT Scan chest/abdomen	No evidence of distant metastases

Clinical stage 2B, cT2 cN1 M0, ER+PR+HER2+

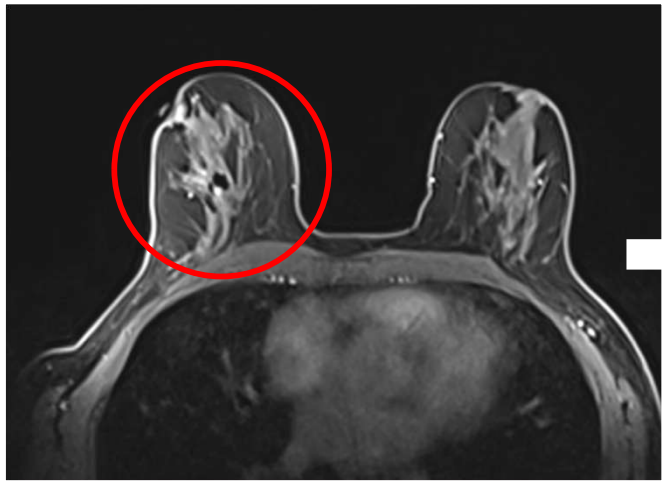
ER, oestrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; LN, lymph node; MRI, magnetic resonance imaging; R: Right; Ki67, Antigen Kiel 67; c, clinical; T, tumour; N, node, M, metastasis. Note: Images courtesy of Mr Henry Cain

Treatment Journey

- Started on 6 cycles of neoadjuvant: docetaxel + carboplatin + PHESGO (TCHP)
- Continue with surgery & evaluate neoadjuvant response



Before neoadjuvant therapy



After neoadjuvant therapy

ypT0 ypN0

Histopathological examination:
Pathological Complete Response (pCR)

Images courtesy of Mr Henry Cain.

If Mrs M's neoadjuvant therapy resulted in pCR (ypT0N0M0), what optimal adjuvant treatment regimen would you choose for the best outcome?

Roche

- Continue pertuzumab + trastuzumab SC (PHESGO) to complete 18 cycles
- Continue trastuzumab to complete 18 cycles

Pertuzumab-trastuzumab in eBC

Abbreviation: eBC, early breast cancer

Ensuring continuity in care: transition from neoadjuvant to adjuvant treatment phases[1-4]

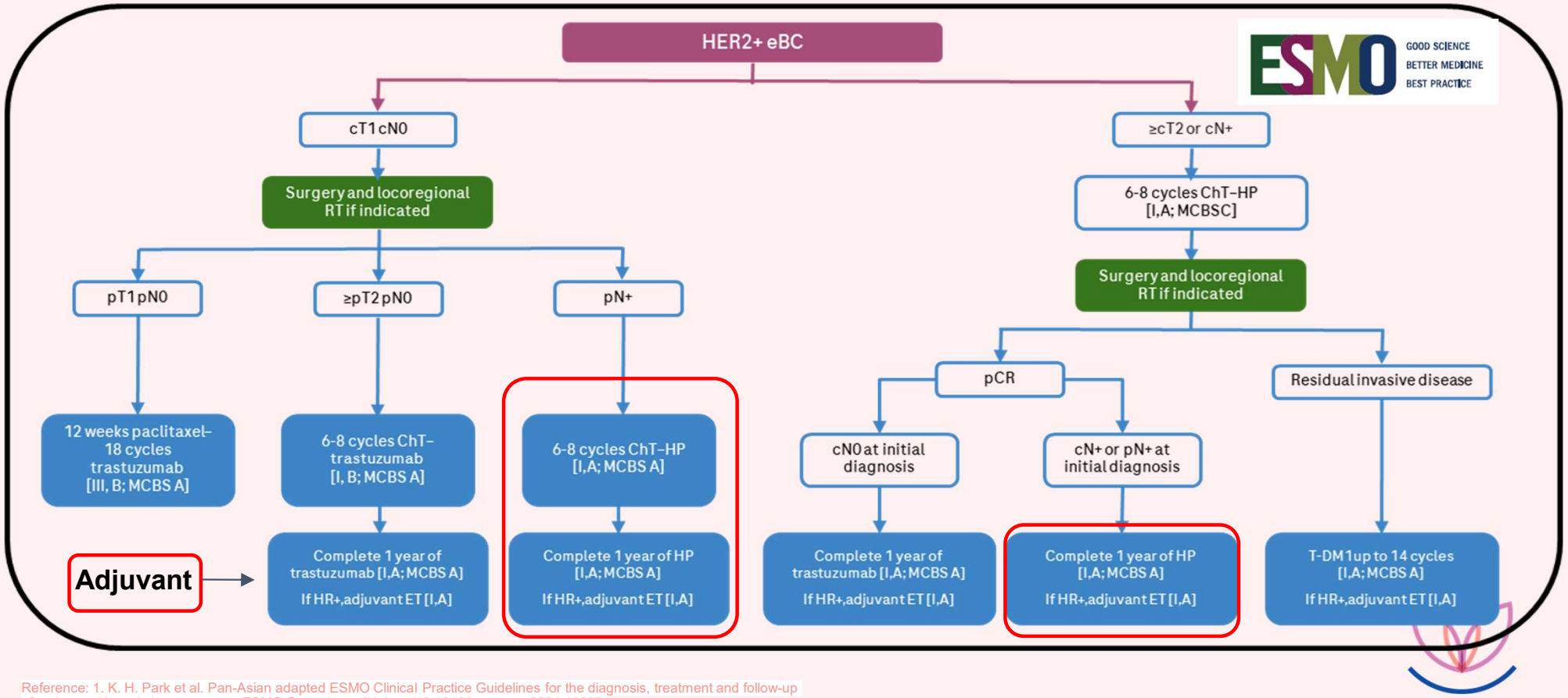
- **15–20%** of patients still experience **relapse** within 5 years.[1]
  - This is despite achieving pCR after neoadjuvant treatment in eBC.[1]

International guidelines recommend **continuing adjuvant Pertuzumab-trastuzumab** treatment in patients with **node-positive eBC even after achieving pCR**.[2-4]

Abbreviations: eBC, early breast cancer; NCCN, National Comprehensive Cancer Network; pCR, pathological complete response.

References: 1. Huober J, van Mackelenbergh M, Schneeweiss A, et al. Identifying breast cancer patients at risk of relapse despite pathological complete response after neoadjuvant therapy. *NPJ Breast Cancer*. 2023;9(1):23. 2. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 1.2024. Accessed 27 January 2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. 3. Loibl S, Andre F, Bachelot T, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2024;35(2):159-182. 4. Park YH, Senkus-Konefka E, Im SA, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with early breast cancer: a KSMO-ESMO initiative endorsed by CSCO, ISMPO, JSMO, MOS, SSO and TOS. Ann Oncol. 2020;31(4):451-469.

Pan Asian ESMO: Complete 1 Year Pertuzumab+Trastuzumab for Nodes positive at initial diagnosis and for pCR patients after neoadjuvant treatment



Reference: 1. K. H. Park et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with early breast cancer. ESMO Open. https://doi.org/10.1016/j.esmoop.2024.102974
. 2. BPOM. Product Information PHESGO. Feb 2025. 3. BPOM. Product Information Perjeta. 2024

Pertuzumab is approved for 3-6 cycles in neoadjuvant setting for early breast cancer treatment.

Guidelines support pertuzumab-trastuzumab even after achieving pCR[1-3]

NCCN guidelines

The NCCN guidelines recommend **adjuvant pertuzumab-trastuzumab** treatment in patients with **node-positive eBC at initial staging, irrespective of HR status after achieving pCR,** with a category 1 recommendation.[1]

ESMO

Patients who are cN+ or pN+ at initial diagnosis are recommended to **complete one year of adjuvant pertuzumab-trastuzumab even after achieving pCR** with neoadjuvant pertuzumab-trastuzumab + chemotherapy. [I,A][2]

Pan-Asian adapted ESMO (ESMO PAGA)

The Pan-Asian ESMO guideline recommends to complete one year of **dual HER2 blockade** in patients who are initially **node-positive** (or ER-negative) that **achieve pCR** after neoadjuvant therapy. [I,A][3]

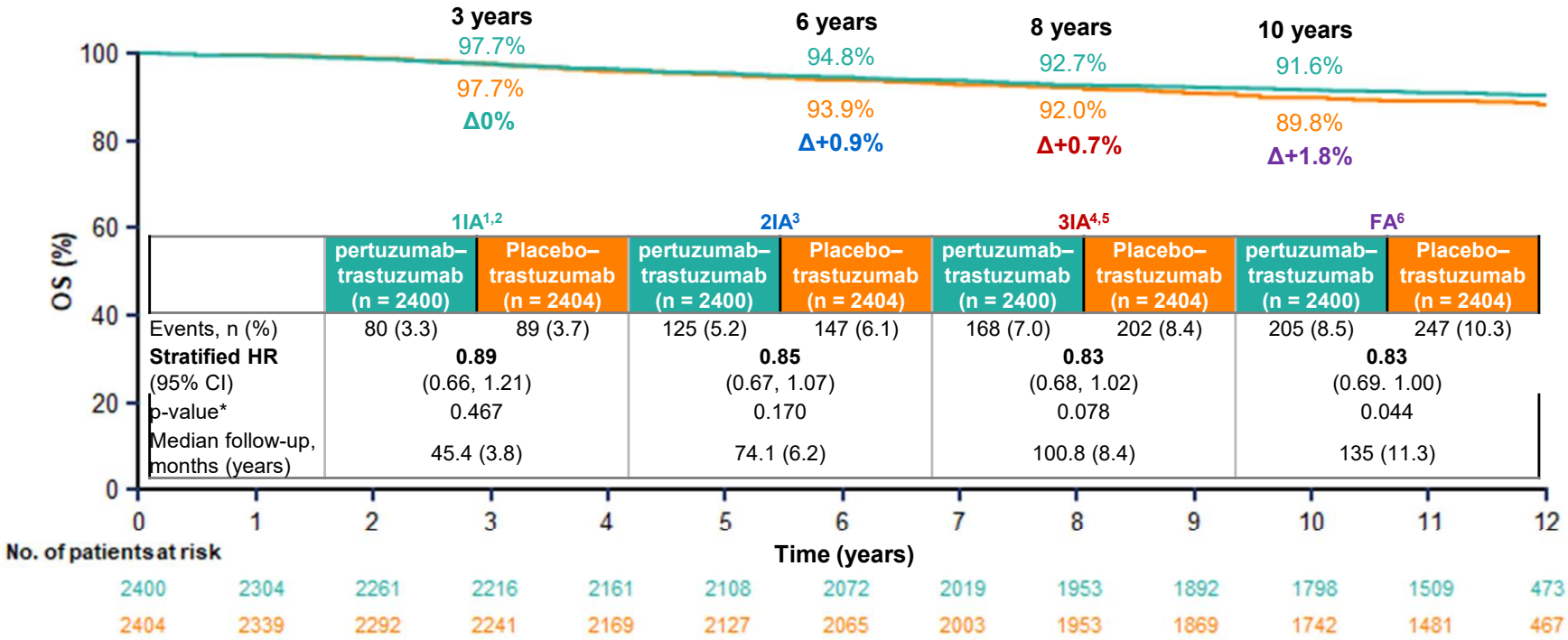
Abbreviations: c, clinical; CPG, clinical practice guideline; ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NCCN, National Comprehensive Cancer Network; p, pathological; pCR, pathological complete response.

References: 1. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 1.2024. Accessed 27 January 2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. 2. Loibl S, Andre F, Bachelot T, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol. 2024;35(2):159-182*. 3. Park YH, Senkus-Konefka E, Im SA, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with early breast cancer: a KSMO-ESMO initiative endorsed by CSCO, ISMPO, JSMO, MOS, SSO and TOS. *Ann Oncol*. 2020;31(4):451-469.

APHINITY OS Final Analysis

PHESGO showed significant and clinically meaningful OS improvement

PA
2IA
3IA
FA



	1IA[1,2]		2IA[3]		3IA[4,5]		FA[6]	
	pertuzumab–trastuzumab (n = 2400)	Placebo–trastuzumab (n = 2404)	pertuzumab–trastuzumab (n = 2400)	Placebo–trastuzumab (n = 2404)	pertuzumab–trastuzumab (n = 2400)	Placebo–trastuzumab (n = 2404)	pertuzumab–trastuzumab (n = 2400)	Placebo–trastuzumab (n = 2404)
Events, n (%)	80 (3.3)	89 (3.7)	125 (5.2)	147 (6.1)	168 (7.0)	202 (8.4)	205 (8.5)	247 (10.3)
Stratified HR (95% CI)	**0.89** (0.66, 1.21)		**0.85** (0.67, 1.07)		**0.83** (0.68, 1.02)		**0.83** (0.69. 1.00)	
p-value*	0.467		0.170		0.078		0.044	
Median follow-up, months (years)	45.4 (3.8)		74.1 (6.2)		100.8 (8.4)		135 (11.3)	

At the calendar-driven† FA (median FU of 11.3 years) there was a statistically significant and clinically meaningful OS improvement when adjuvant pertuzumab was added to trastuzumab + chemotherapy (17% reduction in the risk of death)[6]

* p-values of <0.00001, 0.0012, 0.0060 and ≤0.0496 were required for statistical significance at the 1IA, 2IA, 3IA and FA of OS, respectively.[1,3–6]
† Following the 3IA of OS, the timing of the final OS analysis was changed from event-driven to calendar-driven due to a lower than anticipated overall death rate.[6]
Strata: nodal status, protocol version, intended adjuvant chemotherapy regimen, central hormone receptor status, geographical region; HRs were estimated by Cox regression.
CI, confidence interval; FA, final analysis; FU, follow-up; HR, hazard ratio; IA, interim analysis; ITT, intention-to-treat; OS, overall survival; Q, quarter.

1. von Minckwitz G, *et al. N Engl J Med* 2017;
2. von Minckwitz G, *et al. ASCO* 2017 (LBA500; oral presentation);
3. Piccart M, *et al. J Clin Oncol* 2021;
4. Loibl S, *et al.* ESMO Virtual Plenary July 2022;
5. Loibl S, *et al. J Clin Oncol* 2024;
6. Loibl S, *et al.* ESMO BC 2025 (LBA1; oral presentation).

Continuity of care with pertuzumab-trastuzumab

Pertuzumab-trastuzumab across neoadjuvant and adjuvant settings improves EFS[1]

- A pooled analysis* from 5 neoadjuvant studies (n=1763) evaluated outcomes with respect to single versus dual HER2 targeting in neoadjuvant and adjuvant settings.
- Amongst those who achieved pCR, patients treated with pertuzumab-trastuzumab in both settings had the highest 4-year EFS rate compared with those who switched from pertuzumab-trastuzumab to receive adjuvant trastuzumab therapy alone (95% vs 90%).[1]

4-year EFS in patients with pCR[1]

	Trastuzumab -> Trastuzumab (n=236)	Pertuzumab-trastuzumab -> Trastuzumab (n=185)	Pertuzumab-trastuzumab -> Pertuzumab-trastuzumab (n=352)
Patients remaining at risk, n	179	155	219
4-year event-free survival rate, % (95% CI)	**86** (81–89)	**90** (85–94)	**95** (92–97)

Adapted from Swain SM, Macharia H, Cortes J, et al. *Cancers (Basel)* 2022.[1]

*Refer to the appendix for further details of this pooled analysis.
Abbreviations: CI, confidence interval; EFS, event-free survival; H, trastuzumab; pCR, pathological complete response; PH, pertuzumab-trastuzumab.
Reference: 1. Swain SM, Macharia H, Cortes J, 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 (Basel)* 2022;14(20):5051.

Pertuzumab-trastuzumab demonstrates an established cardiac safety profile[1-3]

- The safety profile of pertuzumab-trastuzumab plus chemotherapy was consistent with the previous trials
  - No new or unexpected safety signals emerged
  - Follow-up duration was for 8.4 years[1-3]

Cardiac toxicity at the 8.4 year follow-up of the APHINITY* trial[3]

Patients, n(%)	Pertuzumab-trastuzumab (n=2364)	Trastuzumab (n=2405)
Primary cardiac, n(%)	**19 (0.8)**	**10 (0.4)**
Heart failure NYHA III/IV + LVEF drop^	16 (0.7)	6 (0.2)
Cardiac death†	3 (0.1)	4 (0.2)

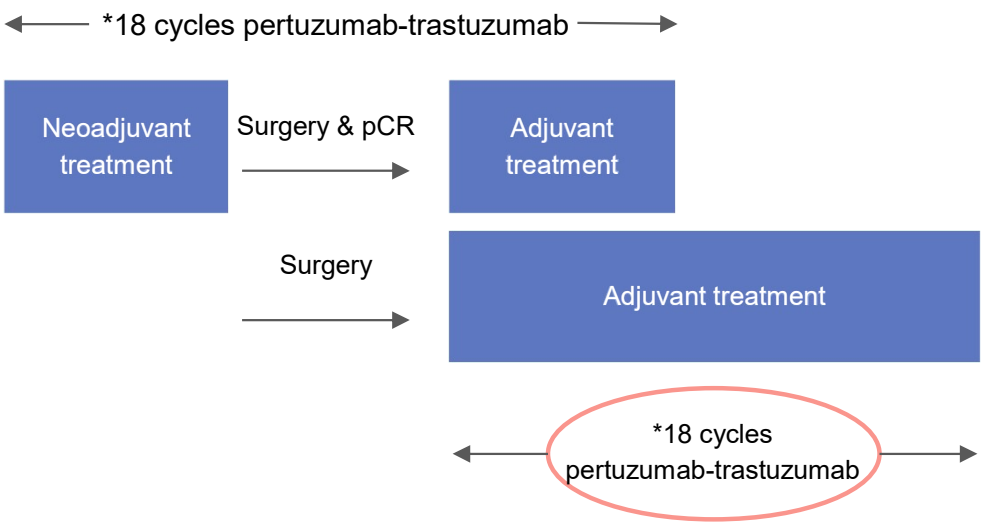
Adapted from Loibl S, et al. ESMO Virtual Plenary. July 2022.[3]

Incidence of primary cardiac events remained low (<1% in both treatment arms).[3]

*Refer to the appendix for the APHINITY trial design.
^LVEF drop = ejection fraction drop >10% from baseline AND to below 50%.
†Identified by the Cardiac Advisory Board for the trial according to a prospective definition.
Abbreviations: LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
References: 1. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med*. 2017;377(2):122-131. 2. Piccart M, Procter M, de Azambuja E et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer in the APHINITY trial: 6 years' follow-up. *J Clin Oncol*. 2021;39(13):1448-1457. 3. Loibl S, Jassem J, Sonnenblick A, et al. Updated results of APHINITY at 8.4 years median follow up. Presented at ESMO Virtual Plenary. July 14–15, 2022.

Continue with pertuzumab-trastuzumab all the way*[1,2]

Complete HER2+ eBC treatment



- Patients who achieve pCR after neoadjuvant pertuzumab-trastuzumab treatment are still at risk of recurrence.[1]
- Continue pertuzumab-trastuzumab **after surgery** in patients with **high risk of recurrence** for the better outcomes.[2]

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

References: 1. Swain SM, Macharia H, Cortes J, 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 (Basel) 2022;14(20):5051. 2. BPOM. Product information PERJETA (Pertuzumab). July 2023

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Improving treatment outcome beyond efficacy
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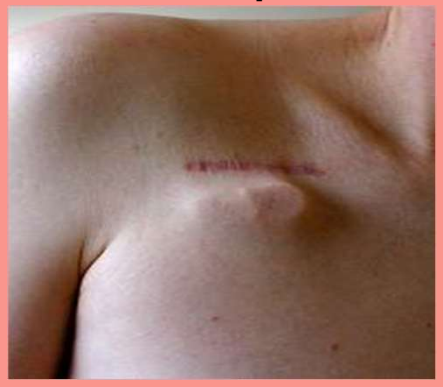
Challenges of long-term IV administration

Central port

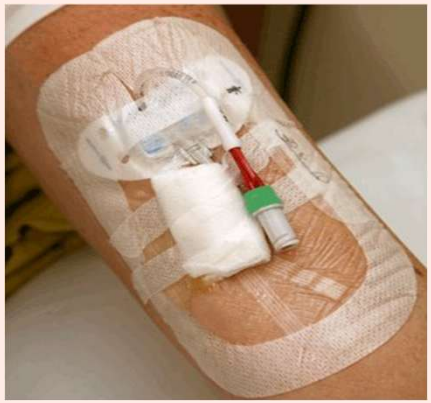


- Central ports invasive
- Takes time for implanting/removing
- Some women feel they've had enough chest surgery
- Infection, leakages and blockages
- Cumbersome, limiting active lifestyle

IV Cannulation

- Repeated cannulation unpleasant for patients
- Potential for necrosis following extravasation
- Damage to peripheral veins over time

PICC line

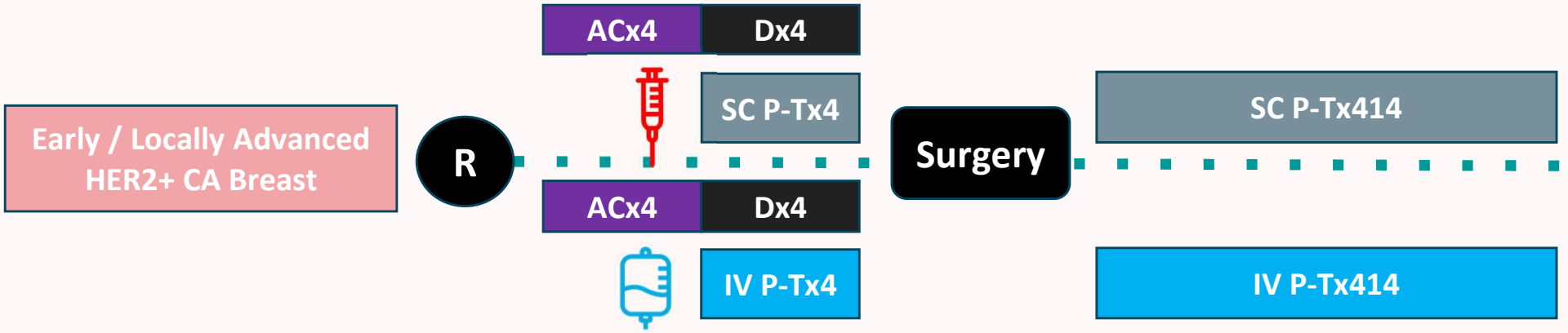


- Expert insertion needed
- Frequent flushing and dressing to prevent infection and blockage
- Very limiting for active lifestyle

PICC, peripherally inserted central catheter

Courtesy of Lesley Fallowfield

There is Evidence supporting the Clinical Efficacy of PHESGO



Phase 3 FeDeriCa	IV P-T (252)	SC P-T (248)	
Pre-C7 Pertuzumab serum C_{trough}	Geometric Mean Ratio 1.22 (90% CI 1.14-1.31)		Non-Inferior
Pathological Complete Response	59.7%	59.5%	HR 0·15 (–8·67 to 8·97) Not affected by BMI
4y Invasive DFS	89.5%	88.5%	HR 1.13 (0.64-1.97)
4y Overall Survival	95.5	94.1	HR 1.26 (0.58-2.72)

Toxicities were similar in FeDeriCa

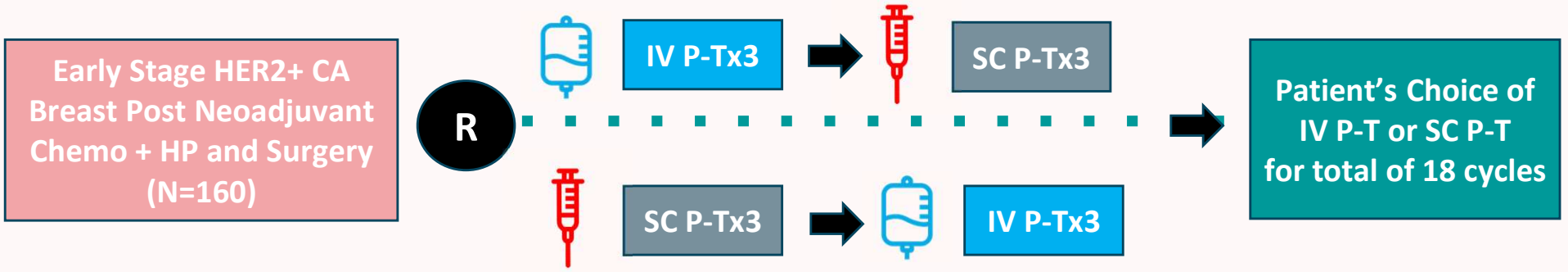
- Infusion Reactions: 10% IV vs 1% SC
- Injection Site Reactions: 0% IV vs 13% SC

FDChina study (n=200) showed similar Pharmacokinetics and pCR results in a Chinese Population

Tan AR, et al. Lancet Oncol 2021
.Shao Z, et al. ESMO Asia 2022 (Abstract 1MO, mini oral presentation)

There is Evidence supporting Patient Preference for PHESGO

PHranceSCa



85.0% of Patients preferred SC P-T over IV

- 13.8% preferred IV P-T over SC
- 86.9% of patients chose to continue with SC P-T

- 88.1% were Very Satisfied / Satisfied with SC P-T
- 67% were Very Satisfied / Satisfied with IV P-T

Main reasons for SC Preference

- Reduced Clinic Time
- Comfort during Administration

Majority of Healthcare Professionals agreed that SC P-T was associated with shorter preparation time, and less drug wastage

Switching from P + H IV to PH FDC SC can lead to ~80% reduction in non-drug costs

For a typical patient receiving treatment for HER2+ eBC in Western Europe,* switching from P + H IV to PH FDC SC can lead to:

Up to **85%** savings on **chair time costs**

Up to **65%** savings on **patients' productivity losses**

Up to **76%** savings on active **HCP time costs**

Up to **69%** savings on **non-drug consumables costs**

* Data from a model-based cost-minimisation analysis to quantify non-drug cost differences per patient over a full course of eBC therapy (18 cycles of P + H IV vs. PH FDC SC). Western Europe estimates.
eBC, early breast cancer; H, trastuzumab; HCP, healthcare professional; IV, intravenous; P, pertuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection.
Manevy F, *et al.* ASCO 2021 (Poster 544).

Clinical trial data: Safety of PHESGO was consistent with that of P + H IV

Note: this table is not intended for cross-trial comparisons

	FeDeriCa (final analysis; neoadjuvant + adjuvant phases)*,[1]		PHranceSCa (pooled crossover period [primary analysis] and continuation period [final analysis])[2–4]				FDChina (primary analysis; neoadjuvant phase)[5]		US expanded access study (AL42478)[6]	
Patients, n (%)	P + H IV (n = 252)	PHESGO (n = 248)	**P + H IV pooled crossover (n = 160)**	**PHESGO pooled crossover (n = 160)**	**P + H IV continuation (n = 21)**	**PHESGO continuation (n = 138)**	**P + H IV (n = 100)**	**PHESGO (n = 100)**	**PHESGO eBC (n = 74)**	**PHESGO mBC (n = 69)**
Any AE	251 (99.6)	248 (100)	113 (70.6)	120 (75.0)	14 (66.7)	92 (66.7)	97 (97.0)	98 (98.0)	62 (83.8)	62 (89.9)
Grade ≥3 AE	149 (59.1)	132 (53.2)	6 (3.8)	4 (2.5)	2 (9.5)	7 (5.1)	69 (69.0)	72 (72.0)	2 (2.7)	6 (8.7)
Serious AE	52 (20.6)	49 (19.8)	6 (3.8)	2 (1.3)	0	4 (2.9)	19 (19.0)	18 (18.0)	1 (1.4)	3 (4.3)
Grade 5 AE	1 (0.4)[†,7]	1 (0.4)[‡,7]	0	0	0	0	0	1 (1.0)[§]	0	0
Treatment discontinuation due to AE	15 (6.0)[‖]	12 (4.8)[‖]	NR	NR	1 (4.8)	0	2 (2.0)	4 (4.0)	0	3 (4.3)
Cardiac AE **Grade ≥3**	65 (25.8) 12 (4.8)	52 (21.0) 3 (1.2)	3 (1.9) NR	5 (3.1) NR	1 (4.8) 0	1 (0.7) 0	8 (8.0)[¶] 0	7 (7.0)[¶] 0	1 (1.4) NR	3 (4.3) NR

No new AEs were reported with PHESGO at-home administration, across eBC and mBC (US expanded access study)[6]

Please see the Appendix for the study designs.

* Patients received initial chemotherapy, followed by HER2-targeted therapy + chemotherapy, in the neoadjuvant phase; † Urosepsis (reported at the primary analysis); ‡ Acute myocardial infarction (reported at the primary analysis); § Cardiac related; ‖ Percentages shown are for discontinuation of any HER2-targeted therapy; ¶ Cardiac dysfunction.

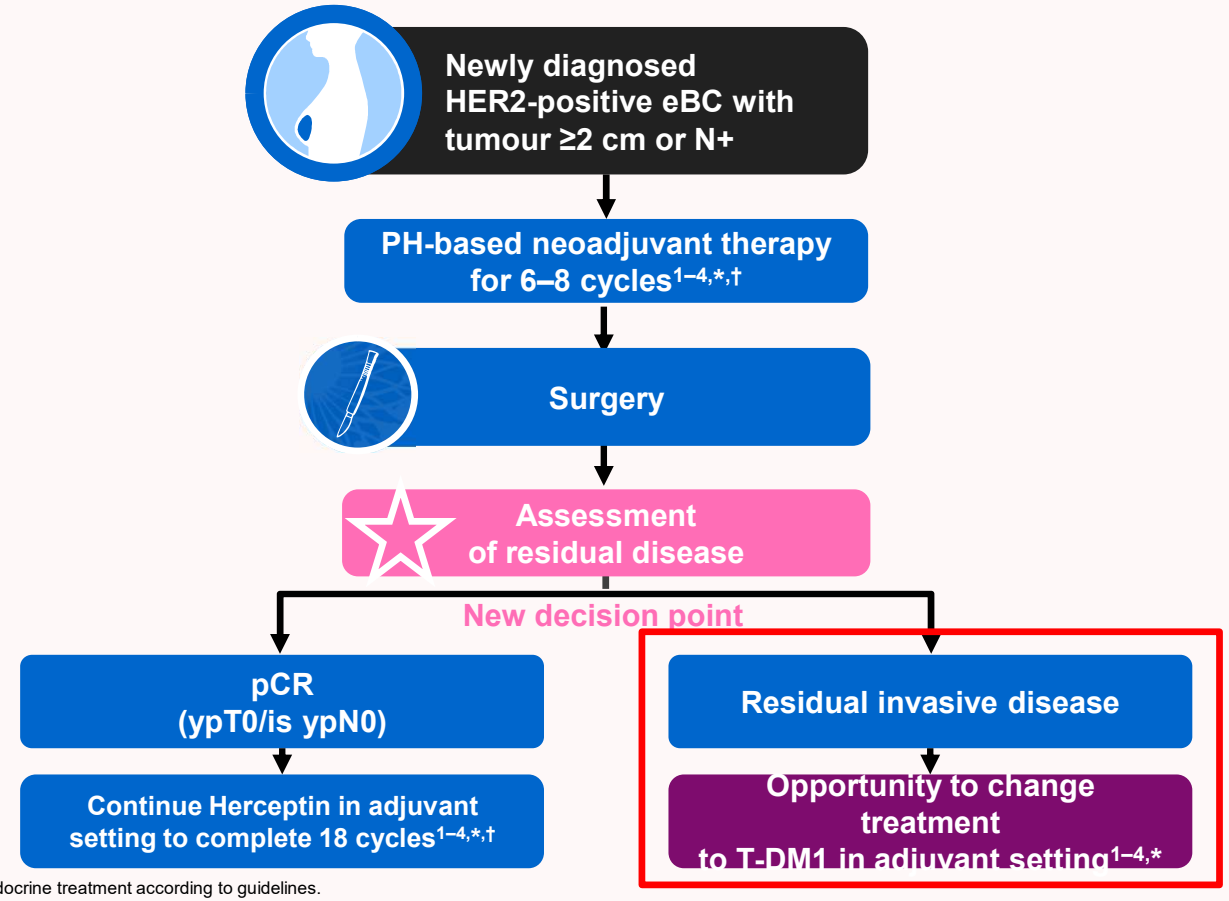
AE, adverse event; eBC, early breast cancer; H, Herceptin, IV, intravenous; mBC, metastatic breast cancer; NR, not reported; P, PERJETA.

1. Jackisch C, *et al.* ESMO BC 2024 (Poster 114P); 2. O'Shaughnessy J, *et al. Eur J Cancer* 2021; **152:**223–23; 3. O'Shaughnessy J, *et al.* ESMO BC 2023 (Poster 97P); 4. O'Shaughnessy J, *et al. Clin Breast Cancer* 2025; epub ahead of print; 5. Shao Z, *et al.* ESMO Asia 2022 (Oral 1MO); 6. Dang C, *et al.* ASCO 2022 (Poster 1515); 7. Tan AR, *et al. Lancet Oncol* 2021; **22:**85–97.

If Mrs. M do not achieve pCR after neoadjuvant, means residual invasive disease; what should we recommend for adjuvant treatment ?

1. No Further Treatment
2. Continue pertuzumab - trastuzumab to complete 18 cycles
3. Switch to T-DM1 for 14 cycles

Assessment of residual disease after surgery is a new decision point for adapting adjuvant therapy



* Including loco-regional radiotherapy and adjuvant endocrine treatment according to guidelines.
† AGO and ESMO guidelines: (neo)adjuvant PH is only recommended for the treatment of patients with node-positive disease.
eBC, early breast cancer; N+, node-positive; pCR, pathological complete response; PH, pertuzumab–trastuzumab.

1. NCCN Breast Cancer Guidelines. Version 4. 2025; 2. AGO Breast Cancer Guidelines. 2022; 3. Cardoso F, *et al. Ann Oncol* 2019; 4. Burstein HJ, *et al. Ann Oncol* 2021

The role Kadcyla in Adjuvant Setting

International Guidelines recommend changing treatment to KADCYLA in the adjuvant setting for patients with residual invasive disease[3-8]

NCCN Breast Cancer Guidelines (v2-2024)[3]

If residual invasive disease after preoperative therapy:
Kadcyla® alone for 14 cycles

ESMO Guidelines for eBC (2019)[5]

If residual invasive disease:
Kadcyla® recommended

AGO Guidelines (2022)[4]

If pathological complete response not achieved (non-PCR) :
Kadcyla® recommended for 14 cycles of anti-HER2 therapy (LoE 1b)†

St. Gallen Guidelines (2021)[6]

If residual invasive disease:
Kadcyla® for 14 cycles if residual invasive cancer after neoadjuvant therapy

ASCO Guidelines (2020)[7]

If pathologic invasive residual disease after preoperative therapy
14 cycles of adjuvant Kadcyla® is recommended, unless there is disease recurrence or unmanageable toxicity

Pan Asian Adapted ESMO Guidelines (2020)[8]

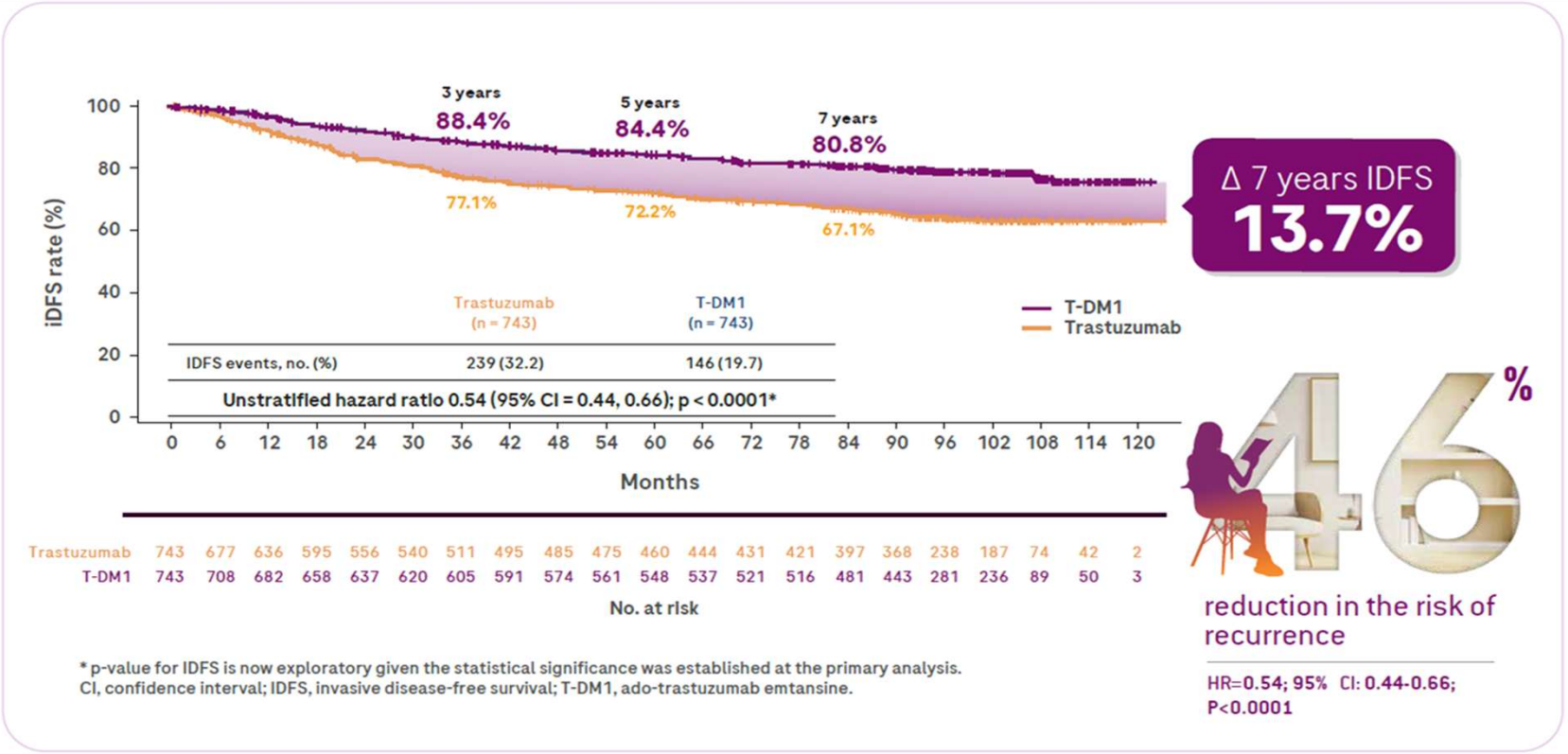
In cases of residual invasive disease after neoadjuvant therapy :
Adjuvant treatment with Kadcyla® for up to 14 cycles (acceptability consensus : 100%)

* Category 1 listings are based on high-level evidence with uniform NCCN consensus that the intervention is appropriate;
† Based on evidence of individual randomised controlled trials;
‡ Grade A recommendation based on strong evidence for efficacy with a substantial clinical benefit; strongly recommended

3. NCCN Clinical Practice Guidelines: Breast Cancer. Version 4.2025. 4. 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 ; 5. 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 ; 6. 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. doi: 10.1016/j.annonc.2023.08.017 ; 7. Denduluri N, et al. Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Guideline Update. J Clin Oncol. 2021 Feb 20;39(6):685-693. doi: 10.1200/JCO.20.02510; 8. Park KH, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with early breast cancer. ESMO Open. 2024 May;9(5):102974. doi: 10.1016/j.esmoop.2024.102974.

KATHERINE IDFS FINAL ANALYSIS:
KADCYLA reduced the risk of recurrence by 46% compared with Herceptin [1,2]

Final IDFS in the intention to treat (ITT) population at median follow up 8.4 years

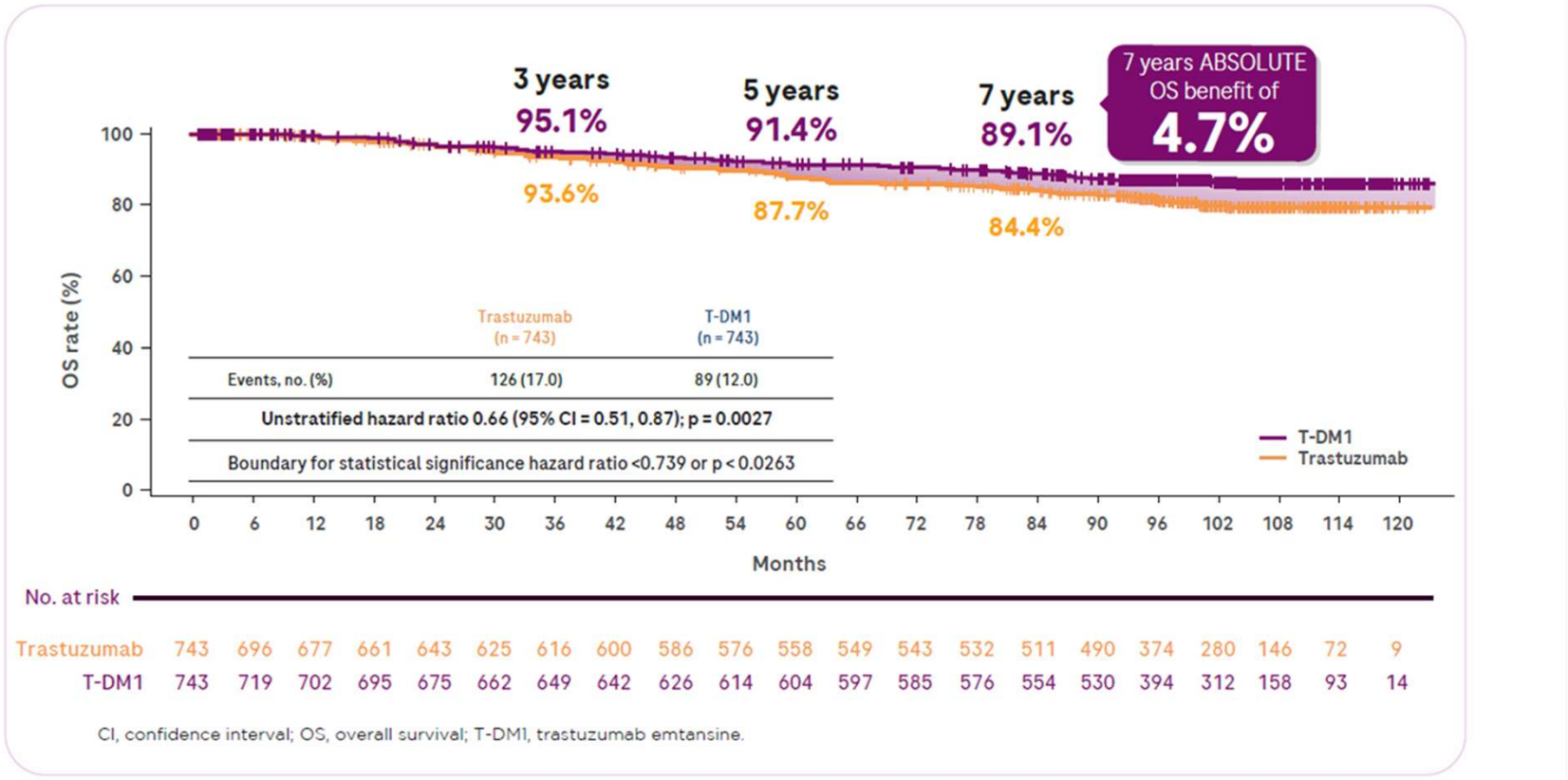


* p-value for IDFS is now exploratory given the statistical significance was established at the primary analysis.
CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

1. von Minckwitz G, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019 Feb 14;380(7):617-628. doi: 10.1056/NEJMoa1814017 ; 2. Loibl S, et al. Phase III study of adjuvant ado-trastuzumab emtansine vs trastuzumab for residual invasive HER2-positive early breast cancer after neoadjuvant chemotherapy and HER2-targeted therapy: KATHERINE final IDFS and updated OS analysis. SABCS 2023. (Abstract GS03-12; oral presentation

KATHERINE OVERALL SURVIVAL (OS) Analysis: KADCYLA significantly reduced risk of death by 34% compared to Herceptin alone[1,2]

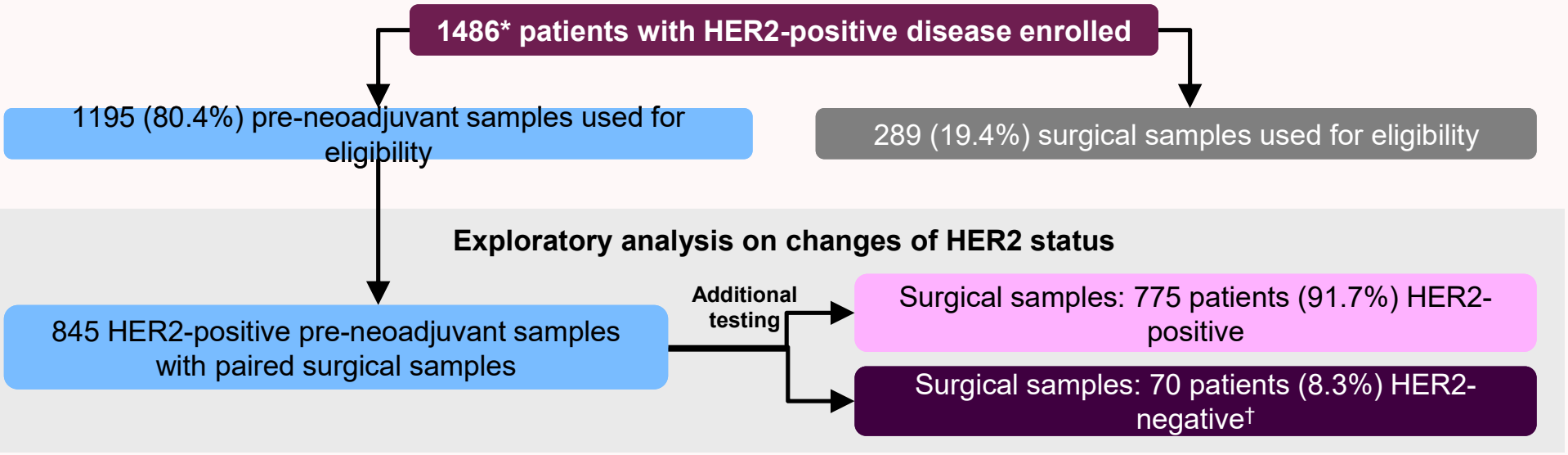
2nd OS Analysis of OTT Population at median follow up 8.4 years



●* The final OS analysis will be performed 12 years after FPI; † PA of IDFS, including 1IA of OS (CCOD 2018);
‡ FA of IDFS, including 2IA of OS (CCOD 2023).
●1IA, first interim analysis; 2IA, second interim analysis; CI, confidence interval; eBC, early breast cancer; FPI, first patient in; HR, hazard ratio; IDFS, invasive disease-free survival; mFU, median follow-up; OS, overall survival.

1. von Minckwitz G, *et al. N Engl J Med* 2019; 380:617–628;
2. Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation).

KATHERINE: HER2-negative status at surgery did not impact on the efficacy of T-DM1



In the 70 patients with HER2-negative disease after re-testing of surgical samples:

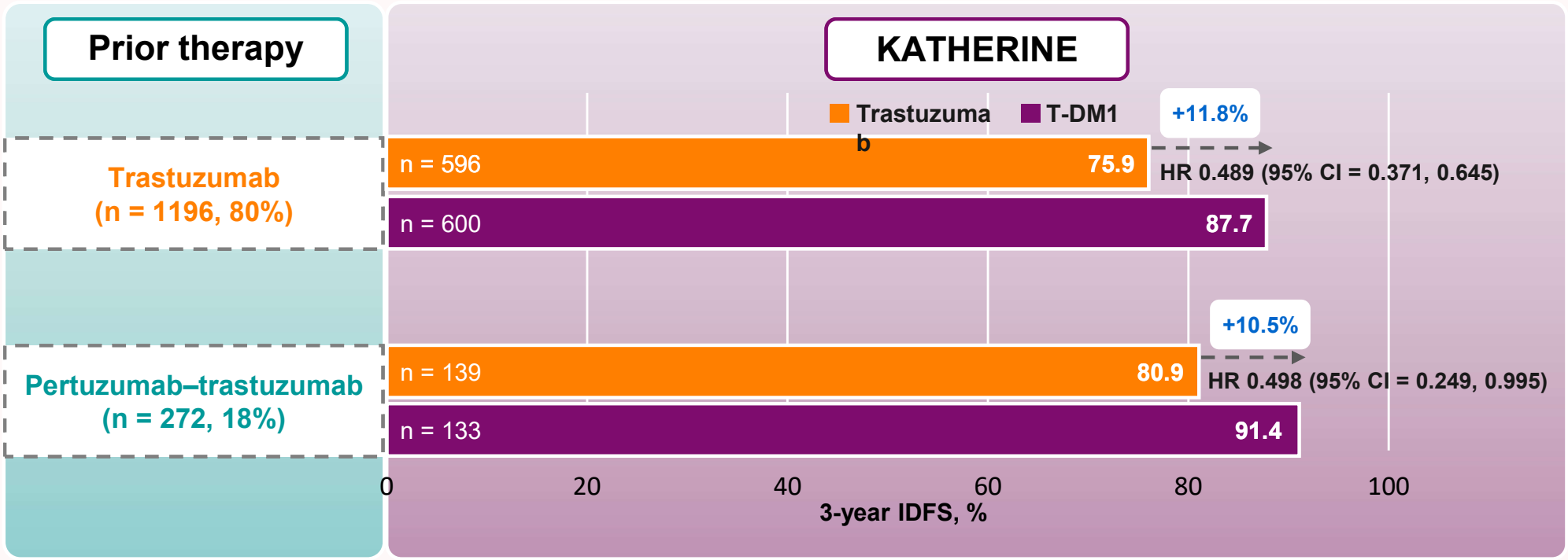
- **No IDFS events in patients randomised to the T-DM1 arm (n = 28)**
- **11 IDFS events in patients randomised to the trastuzumab arm (n = 42)**

Note: These data should be interpreted with caution due to the small sample size

* Two patients (both in the trastuzumab arm) were not included in this analysis: One did not have centrally confirmed HER2-positive disease and one was inadvertently randomised twice.
† Fifty-three HER2-negative and 17 HER2-unknown by IHC 0-1+/ISH unknown.
IDFS, invasive disease-free survival.

Loibl S, *et al*. ESMO Breast Cancer 2020 (Abstract 96O and oral presentation).

Exploratory analysis: Consistent magnitude of IDFS benefit regardless of prior HER2-directed therapy*



Adjuvant T-DM1 builds on the efficacy gain with pertuzumab–trastuzumab in the neoadjuvant setting

* Caution must be exercised as this exploratory analysis involves low patient numbers and the study is not powered to determine the statistical significance of these data.

von Minckwitz G, *et al. N Engl J Med* 2019; **380**:617–628.

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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- Additional information will be requested during a product-exposed pregnancy and the first year of the infant's life. This will enable Roche to better understand the safety of the product and to provide appropriate information to health authorities, healthcare providers, and patients.
- For additional information, please refer to the Product Information.

Roche is committed to the collection and management of safety information relating to our products and we highly encourage reporting adverse events, if any, to Roche Patient Safety at indonesia.safety@roche.com. For inquiries on Roche products or their associated therapeutic area, please contact Roche Medical Information at jakarta.medical_information@roche.com. Alternatively, you may reach out to Roche representative or contact Roche via phone +62 21 3041 3000 or visit https://go.roche.com/medinfoID.

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