Updates In The Management of HER2+ve Metastatic Breast Cancer

M-IN-00003135, valid till 11/08/2024

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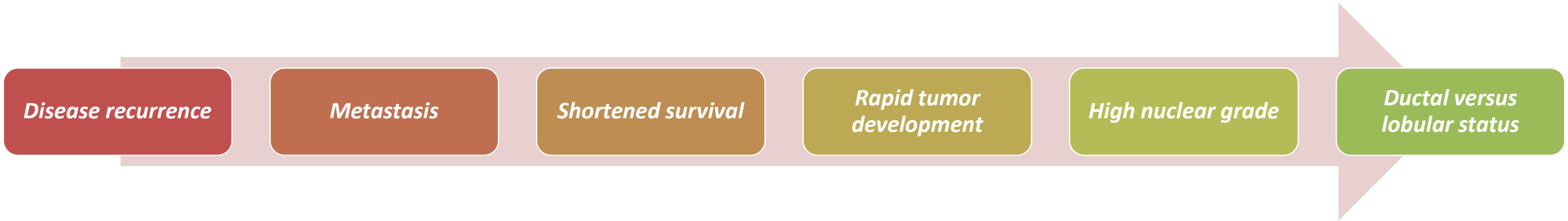
Epidemiology and unmet need

***HER2-positive** tumors and high serum HER2 levels correlate with **aggressive** breast tumor behaviour*[1]



5 year survival % for breast cancers that are HER2+ve is lower than HR+ve breast cancers [2]

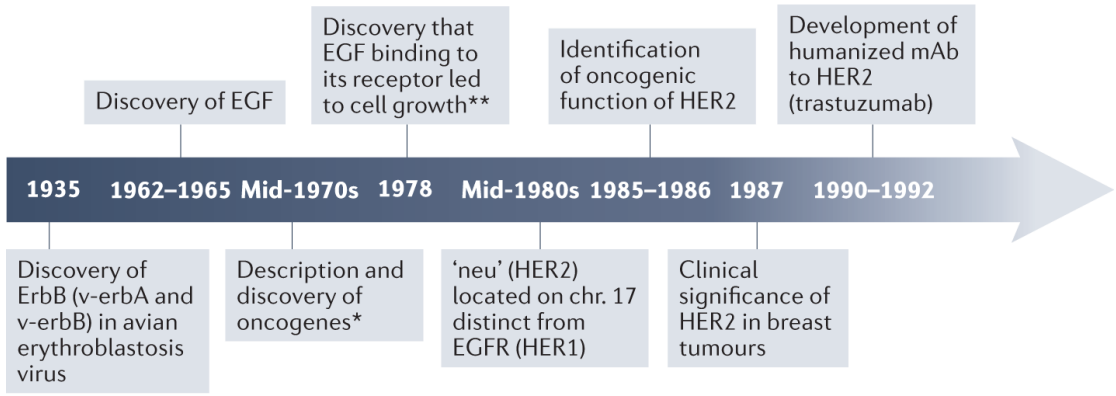
Usage of HER2 targeted treatment has ensured that the 5-year OS rates no longer remain different between the HER2+ve and HR+ve breast cancer subtypes (88.3% vs. 90.4%, HR = 1.24, P = .17)

178361 new cases of breast cancer were reported in India as per the GLOBOCAN 2020 [3]

Indian breast cancer patients have reported a variable range of HER2 positivity ranging from 26-50% [4]

1. Ross JS, *et al. Oncologist* 2003; **8**:307–325 2. Marczyk, Vicente Rodrigues et al. *Clinical breast cancer* vol. 22,5 (2022): 418-423.; 3. GLOBOCAN 2020 4. Doval, D.C. et al. Sci Rep 10, 5886 (2020) 4.. A, Singh R, Wadhwa J, et al. *South Asian J Cancer.* 2018;7(2):102-105.

Preclinical

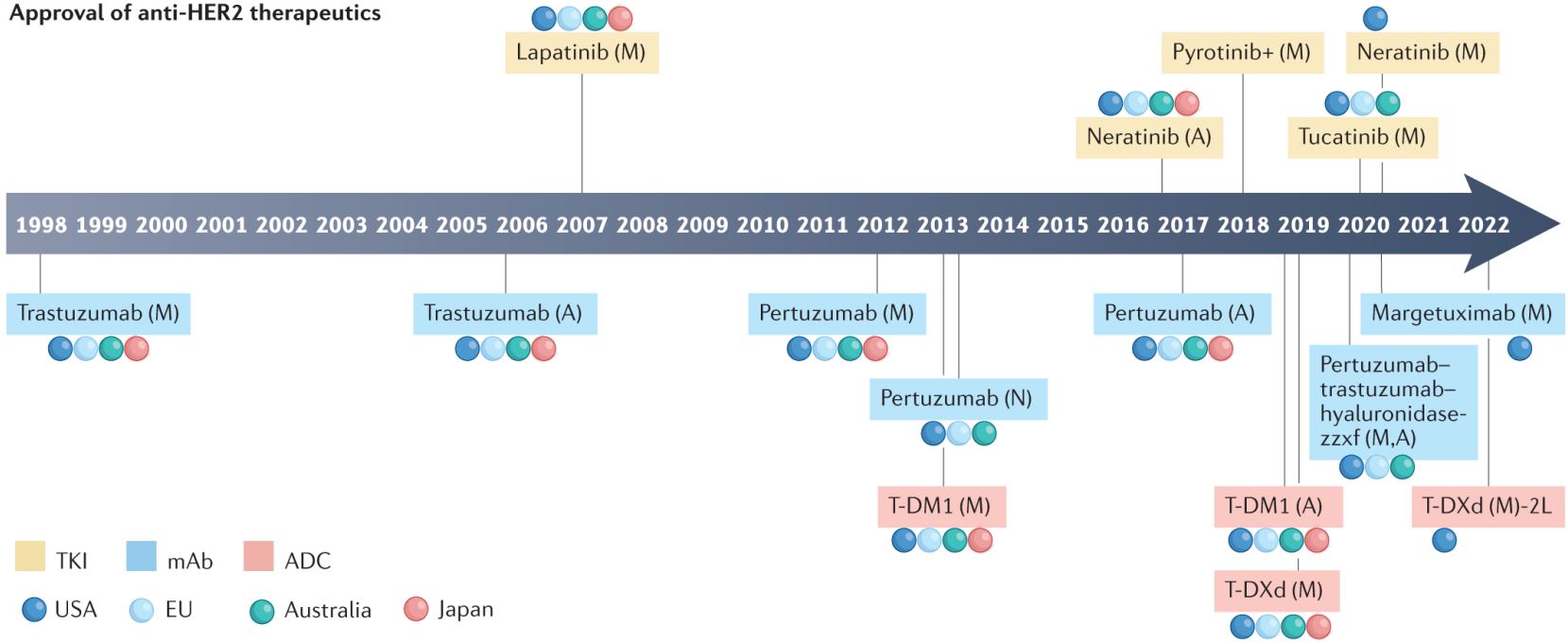


Roche

The 2022 Prix Galien Golden Jubilee Award Winners

Best Biotechnology Product	**Gold Medal**	Roche / Genentech	Herceptin (trastuzumab)

Approval of anti-HER2 therapeutics



https://media.springernature.com/full/springer-static/image/art%3A10.1038%2Fs41573-022-00579-0/MediaObjects/41573_2022_579_Fig1_HTML.png

PERJETA, Kadcyla and PHESGO have built on the solid foundation established by Herceptin

H0648g 30% 5-year survival

HERA 74% 10-year survival

HannaH 5 mins to administer

CLEOPATRA +15.7 months mOS

NeoSphere 2x pCR

APHINITY 28% reduction in risk of recurrence or death

EMILIA +6 months mOS

KATHERINE 50% reduction in risk of recurrence or death

FeDeriCa 5 mins to administer

1998 **mBC** 1L

2006 **eBC** adjuvant

2013 **SC**

2012 **mBC** 1L

2013 **eBC** neoadjuvant

2017 **eBC** adjuvant (node-positive)

2013 **mBC** 2L

2019 **eBC** Adjuvant (residual invasive disease)

2020 **SC**

Herceptin® trastuzumab Precision • Power • Promise

PERJETA® pertuzumab

Kadcyla® trastuzumab emtansine

PHESGO™ PERTUZUMAB-TRASTUZUMAB

3,278,329[1]
BC patients treated
1,290,132 mBC patients

395,817[1]
BC patients treated
135,827 mBC patients

122,584[1]
BC patients treated
116,533 mBC patients

368*
BC patients treated in clinical trials

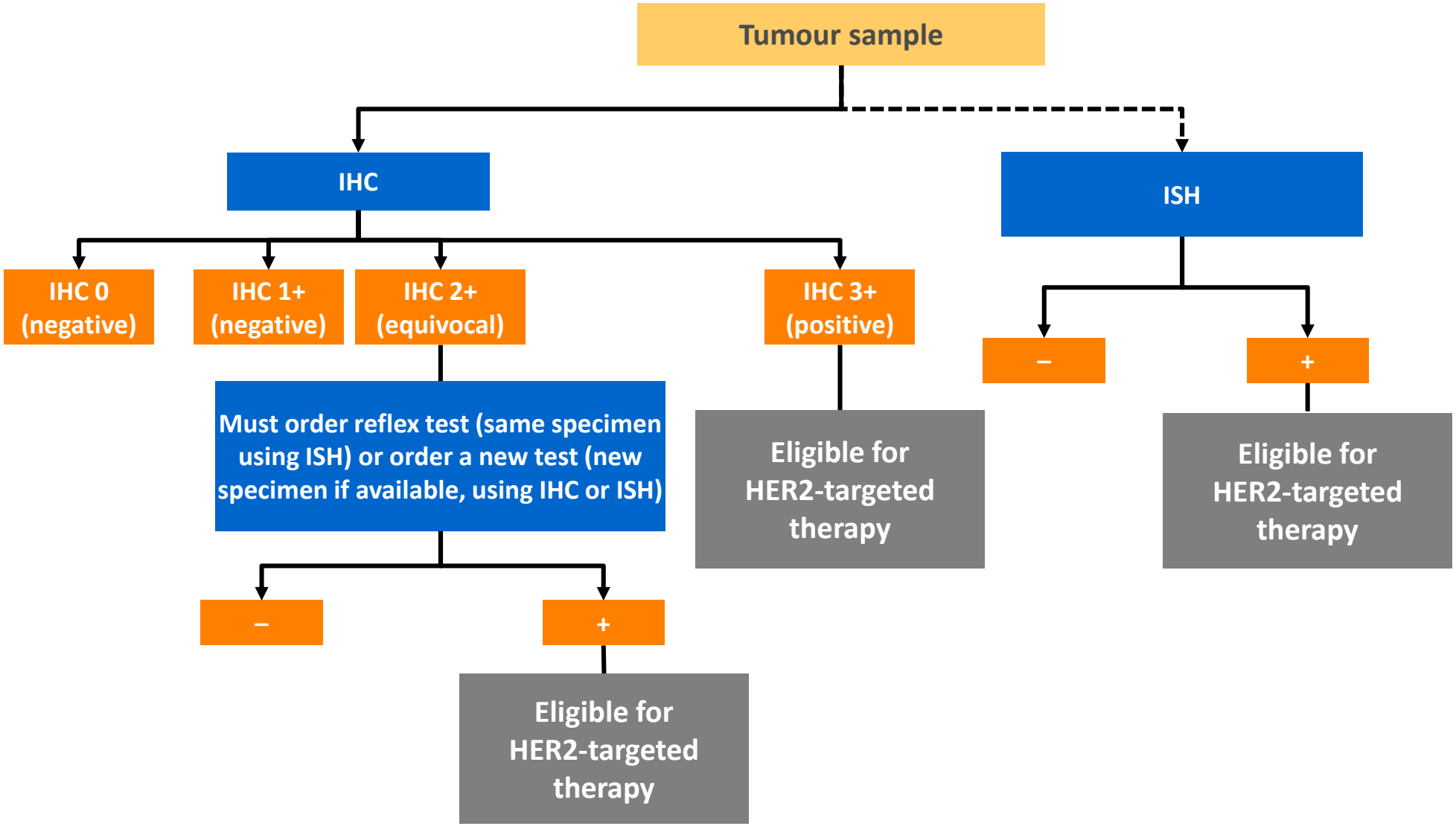
* Patients receiving PHESGO in PHranceSCa, Federica and BO30185.

BC, breast cancer; eBC, early breast cancer; mBC, metastatic breast cancer; mOS, median overall survival; pCR, pathological complete response; SC, subcutaneous.

1. Roche, Data on file (approximate number of patients treated to end of 2019)

2 Recommendations for the identification and treatment of HER2-positive breast cancer

HER2-positivity is determined by IHC and/or ISH[1,2]



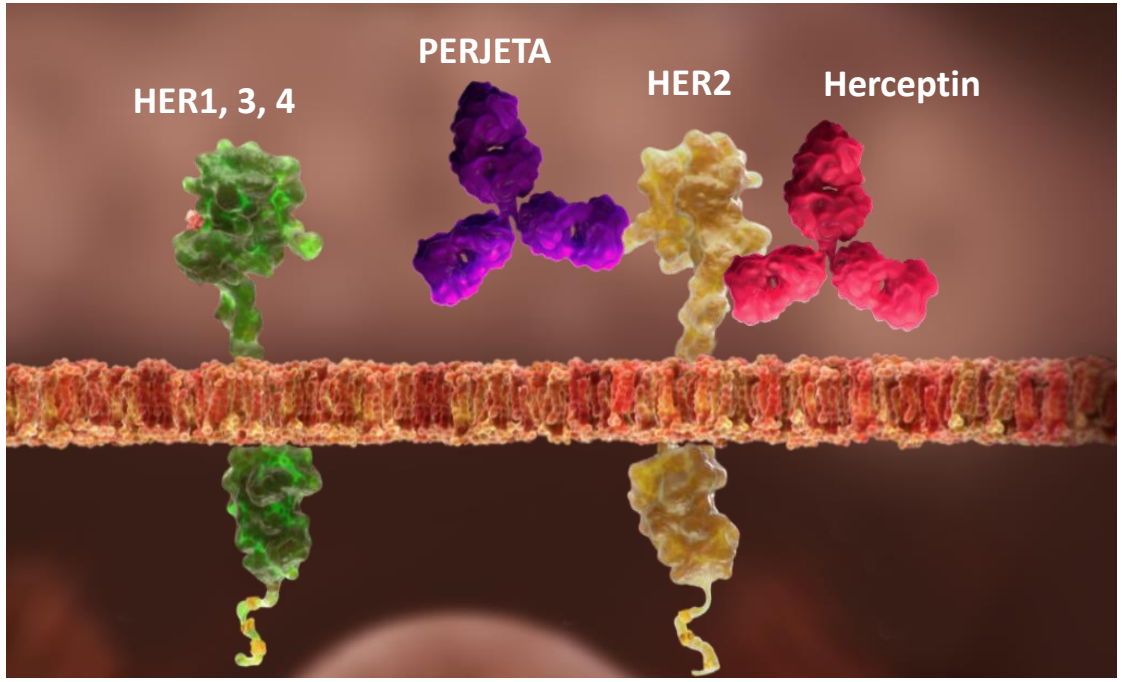
H, Herceptin; IHC, immunohistochemistry; ISH, *in situ* hybridisation; K, Kadcyla; P, PERJETA.

Adapted from Hanna WM & Kwok K. *Mod Pathol* 2006; **19**:481–487; 2. Wolff AC, *et al*. *J Clin Oncol* 2018; **36**:2105–2122.

3 PERJETA in HER2-positive mBC

PERJETA–Herceptin dual HER2-targeted therapy provides more comprehensive HER2 blockade to improve outcomes

- Despite the success of Herceptin, approximately 50% of patients with HER2-positive mBC experience disease progression within a year[1,2]
- PERJETA–Herceptin allows more comprehensive HER2 blockade to improve outcomes[2]



- **PERJETA blocks HER2 dimerisation and activates antibody-dependent cellular cytotoxicity[3-7]**
- **Herceptin and PERJETA have complementary MoAs, binding to different domains on HER2[6,8]**
- **PERJETA can be administered with Herceptin IV or SC [9-11]**
- **PHESGO, PERJETA–Herceptin FDC SC, received FDA approval in June 2020[12,13]**

IV, intravenous; FDC, fixed-dose combination; mBC, metastatic breast cancer; MoA, mechanism of action; SC, subcutaneous.

1. Marty M, *et al. J Clin Oncol* 2005; **23**:4265–4274; 2. Swain SM, *et al. N Engl J Med* 2015; **372**:724–734; 3. Agus DB, *et al. Cancer Cell* 2002; **2**:127–137; 4. Hughes JB, *et al. Mol Cancer Ther* 2009; **8**:1885–1892; 5. Baselga J. *Cancer Cell* 2002; **2**:93–95; 6. Franklin MC, *et al. Cancer Cell* 2004; **5**:317–328; 7. Scheuer W, *et al. Cancer Res* 2009; **69**:9330–9336; 8. Junttila TT, *et al. Cancer Cell* 2009; **15**:429–440; 9. Baselga J, *et al. N Engl J Med* 2012; **366**:109–119; 10. Kümmel S, *et al.* SABCS 2019. Poster P1-18-05; 11. Woodward N, *et al. Clin Breast Cancer* 2019; **19**:216–224; 12. https://www.roche.com/media/releases/med-cor-2020-06-29c.htm; 13. FDA. PHESGO PI. Accessed July 2020.

PERJETA is first-line SoC in HER2-positive mBC

Indications: in combination with Herceptin and docetaxel in adult patients with HER2-positive:

- Metastatic or locally recurrent unresectable breast cancer (SmPC)[1]
- mBC (PI)[2]

who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease[1,2]

Dosing

- Sequential PERJETA–Herceptin administration:[1,2]
  - PERJETA–Herceptin should be administered sequentially and can be given in any order
  - Initial PERJETA dose (loading dose): 840 mg administered as 60-min IV infusion
  - Thereafter (maintenance dose): 420 mg q3w administered as 30–60 min IV infusion
  - When administered with PERJETA, a Q3W Herceptin IV or SC and taxane administration schedule is recommended
  - PERJETA and Herceptin should be administered prior to taxane

- PHESGO (PERJETA–Herceptin FDC):[3]
  - Initial dose is 1200 mg PERJETA, 600 mg Herceptin, and 30 000 units hyaluronidase administered SC over approximately 8 mins, followed q3w by a FDC dose of 600 mg PERJETA, 600 mg Herceptin and 20 000 units hyaluronidase administered SC over approximately 5 mins

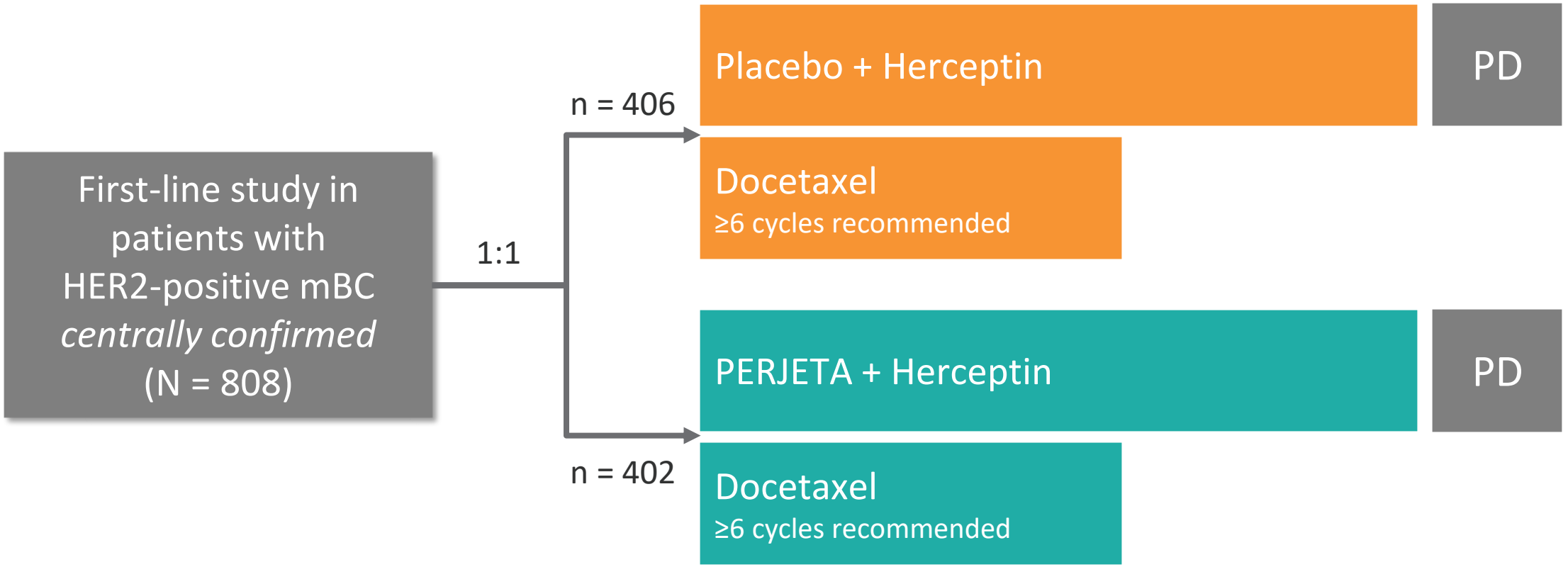
FDC, fixed-dose combination; IV, intravenous; mBC, metastatic breast caner; PI, Prescribing Information; q3w, every 3 weeks; SoC, standard of care; SC, subcutaneous; SmPC, Summary of Product Characteristics.

1. EMA. PERJETA SmPC. Accessed May 2020; 2. FDA. PERJETA PI. Accessed May 2020; 3. FDA. PHESGO PI. Accessed July 2020.

CLEOPATRA*: A Phase III trial that established PERJETA–Herceptin plus chemotherapy as the standard of care for first-line HER2-positive mBC

* CLinical Evaluation Of Pertuzumab And TRAstuzumab

CLEOPATRA: Phase III trial of PERJETA–Herceptin + docetaxel in patients with HER2-positive mBC



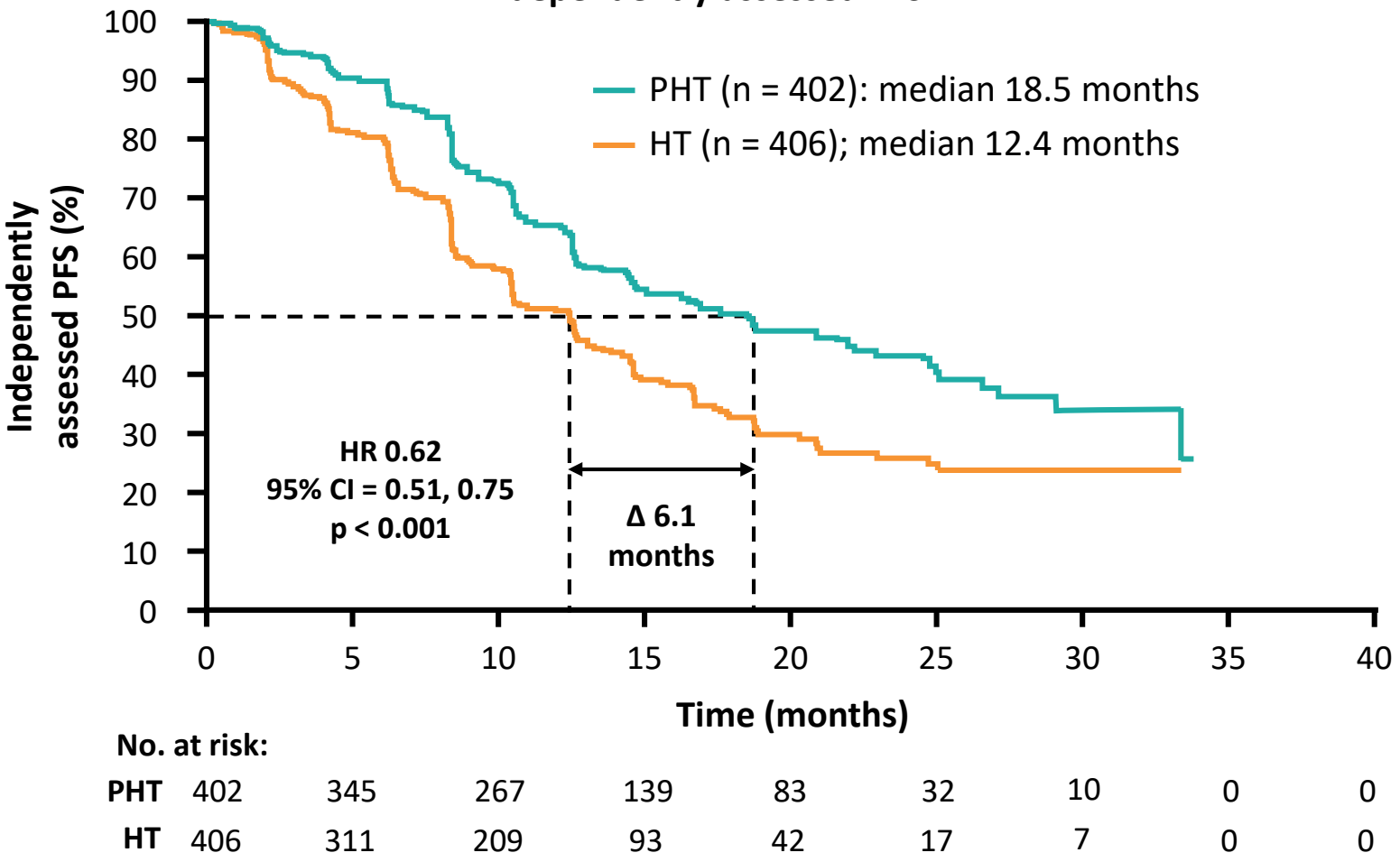
- **Primary endpoint:** PFS by independent review
- **Secondary endpoints** included:
  - OS, PFS by investigator assessment, ORR, Safety

mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival, PD, progressive disease; PFS, progression-free survival.

Baselga J, *et al. N Engl J Med* 2012; **366**:109–119.

CLEOPATRA: PERJETA–Herceptin significantly prolonged independently assessed PFS versus placebo–Herceptin

Primary analysis[1*]
Independently assessed PFS



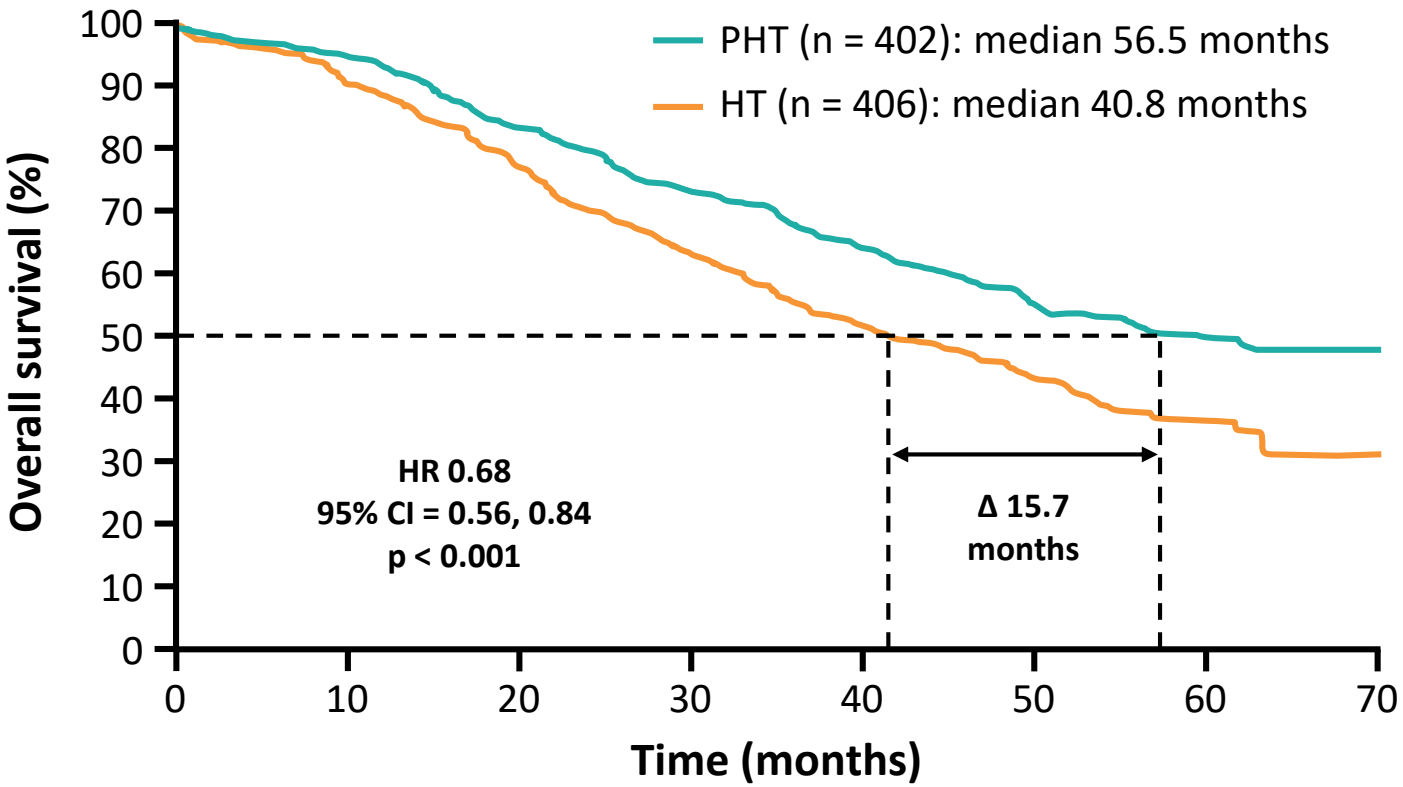
End of study analysis
(10-year follow-up)[2†]
Investigator-assessed PFS

	PHT (n = 402)	HT (n = 406)
Median investigator-assessed PFS, months	18.7	12.4
Stratified HR (95% CI)	0.69 (0.59, 0.81)	
8-year landmark PFS rates	16%	10%

* Data cut-off: May 2011; † Data cut-off: November 2018.
CI, confidence interval; H, Herceptin; HR, hazard ratio; P, PERJETA; PFS, progression-free survival; T, docetaxel.
1. Baselga J, *et al. N Engl J Med* 2012; **366**:109–119; 2. Swain SM, *et al. Lancet Oncol* 2020; **21**:519–530.

CLEOPATRA: PERJETA–Herceptin significantly prolonged OS compared with placebo–Herceptin

Final analysis[1*]



No. at risk:

PHT	402	371	318	268	226	104	28	1
HT	406	350	289	230	179	91	23	0

End of study analysis (10-year follow-up)[2†]

	PHT (n = 402)	HT (n = 406)
Median OS, months	57.1	40.8
Stratified HR (95% CI)	0.69 (0.58, 0.82)	
8-year landmark OS rates	37%	23%

* Data cut-off: February 2014; † Data cut-off: November 2018.
CI, confidence interval; H, Herceptin; HR, hazard ratio; OS, overall survival; P, PERJETA; T, docetaxel.
1. Swain SM, *et al. N Engl J Med* 2015; **372**:724–734; 2. Swain SM, *et al. Lancet Oncol* 2020; **21**:519–530.

CLEOPATRA: Most common all grade AEs during docetaxel treatment included alopecia, diarrhoea and neutropenia*†

During docetaxel treatment‡

AE, n (%)	PERJETA–Herceptin + docetaxel (n = 408)	Placebo–Herceptin + docetaxel (n = 396)
Alopecia	248 (60.8)	240 (60.6)
Diarrhoea	279 (68.4)	193 (48.7)
Neutropenia	218 (53.4)	198 (50.0)
Nausea	183 (44.9)	168 (42.4)
Fatigue	155 (38.0)	148 (37.4)
Rash	153 (37.5)	95 (24.0)
Asthenia	113 (27.7)	122 (30.8)
Decreased appetite	121 (29.7)	106 (26.8)
Peripheral oedema	98 (24.0)	111 (28.0)
Vomiting	106 (26.0)	97 (24.5)
Myalgia	99 (24.3)	99 (25.0)
Mucosal inflammation	111 (27.2)	79 (19.9)
Headache	105 (25.7)	76 (19.2)
Constipation	65 (15.9)	101 (25.5)

References and footnotes in slide notes.

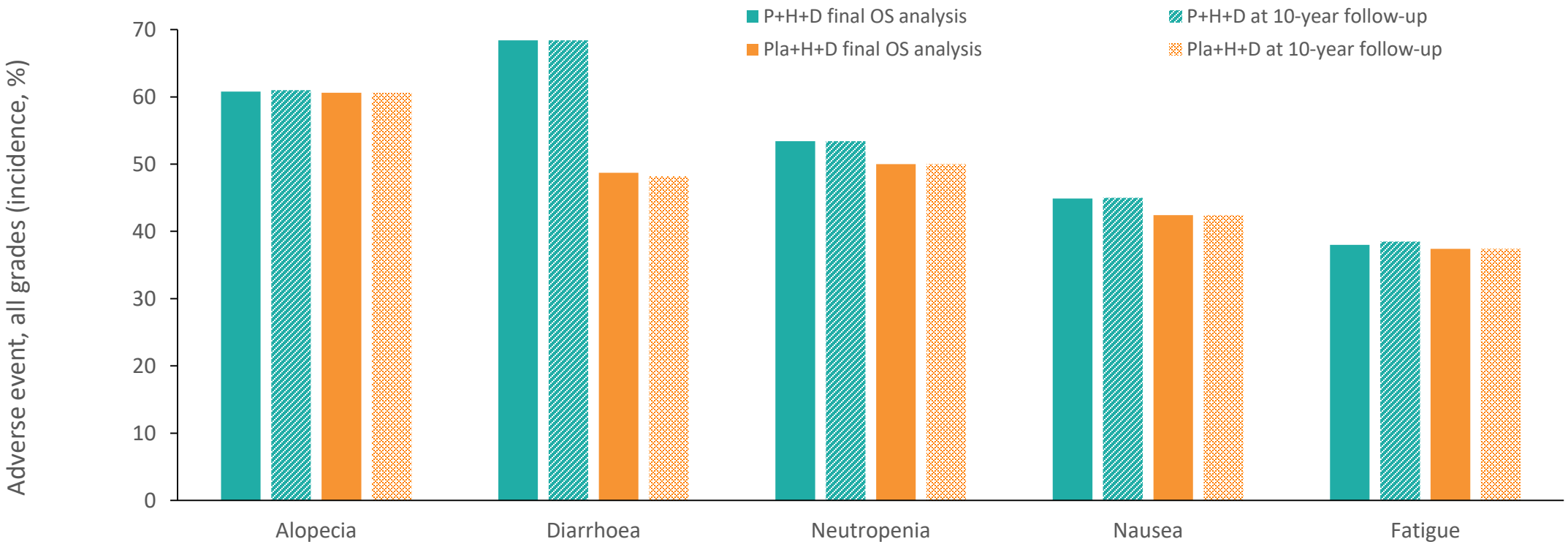
CLEOPATRA: The incidence of most common AEs reduced after docetaxel treatment*†

	During docetaxel treatment‡		After docetaxel treatment‡	
AE, n (%)	PERJETA–Herceptin + docetaxel (n = 408)	Placebo–Herceptin + docetaxel (n = 396)	PERJETA–Herceptin + docetaxel (n = 306)	Placebo–Herceptin + docetaxel (n = 261)
Alopecia	248 (60.8)	240 (60.6)	5 (1.6)	6 (2.3)
Diarrhoea	279 (68.4)	193 (48.7)	86 (28.1)	37 (14.2)
Neutropenia	218 (53.4)	198 (50.0)	10 (3.3)	13 (5.0)
Nausea	183 (44.9)	168 (42.4)	39 (12.7)	30 (11.5)
Fatigue	155 (38.0)	148 (37.4)	41 (13.4)	25 (9.6)
Rash	153 (37.5)	95 (24.0)	56 (18.3)	21 (8.0)
Asthenia	113 (27.7)	122 (30.8)	41 (13.4)	23 (8.8)
Decreased appetite	121 (29.7)	106 (26.8)	22 (7.2)	14 (5.4)
Peripheral oedema	98 (24.0)	111 (28.0)	28 (9.2)	32 (12.3)
Vomiting	106 (26.0)	97 (24.5)	30 (9.8)	17 (6.5)
Myalgia	99 (24.3)	99 (25.0)	25 (8.2)	19 (7.3)
Mucosal inflammation	111 (27.2)	79 (19.9)	11 (3.6)	4 (1.5)
Headache	105 (25.7)	76 (19.2)	52 (17.0)	32 (12.3)
Constipation	65 (15.9)	101 (25.5)	17 (5.6)	18 (6.9)

References and footnotes in slide notes.

CLEOPATRA: Safety profile of PERJETA–Herceptin was maintained at 10-year follow-up[1,2]

- At 10-year follow-up, there was a higher incidence of diarrhoea and rash with PERJETA compared with placebo, both at any grade and at grade ≥3[1]
- Neutropenia was the most common grade 3–4 AE (PERJETA 49% [200/408], placebo 46% [183/396])[1]



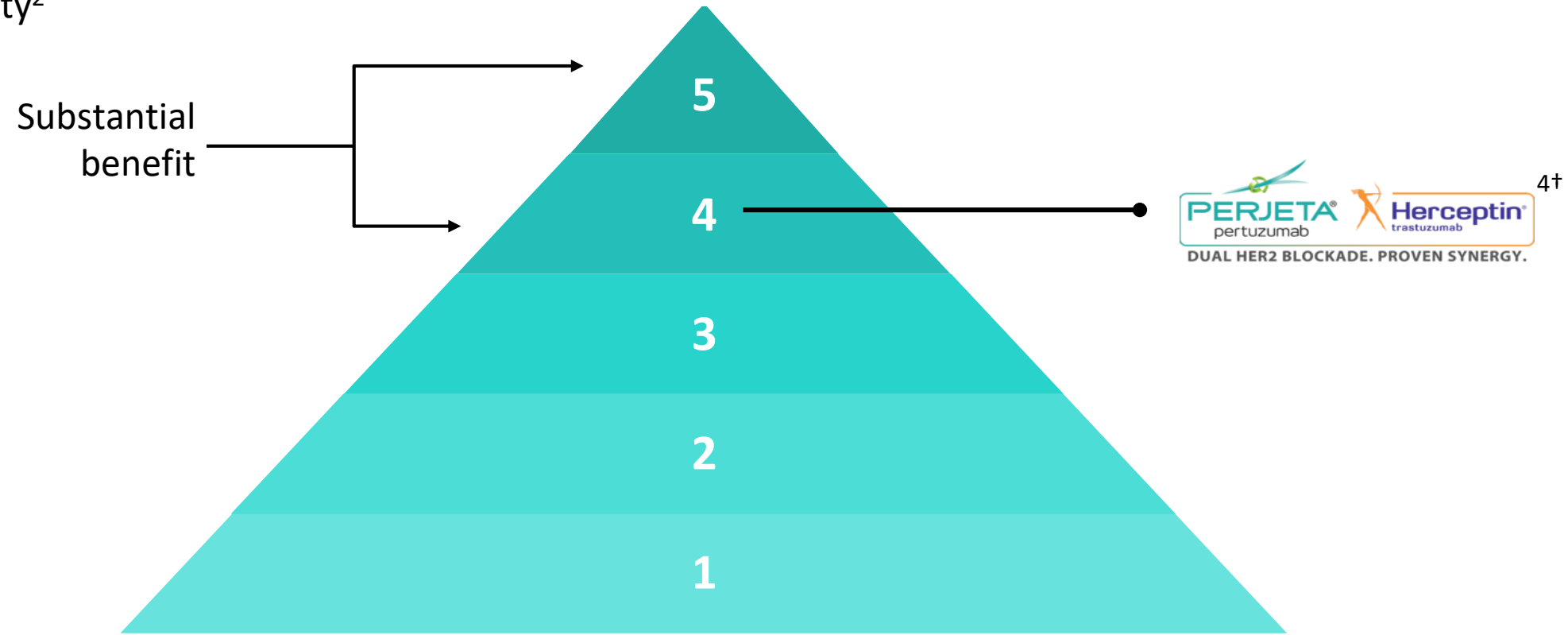
AE,, adverse event, D, docetaxel; H, Herceptin; P, PERJETA; Pla, placebo.

1. Swain SM, *et al. Lancet Oncol* 2020; **21**:519–530; 2. Swain SM, *et al. N Engl J Med* 2015; **372**:724–734 (suppl. appendix).

ESMO Magnitude of Clinical Benefit Scale ranking for PERJETA in mBC

ESMO MCBS scale: Independent ranking of clinically meaningful benefit

- The ESMO MCBS provides a relative ranking of the magnitude of clinically meaningful benefit that can be expected from anti-cancer treatments[1–3]*
- Drugs are given an initial score based on efficacy (maximum score of 4), which is then adjusted for QoL and toxicity[2]



* ESMO MCBS scale is different for early breast cancer (A, B, C, with A and B representing substantial magnitude of clinical benefit).
† PERJETA was rated '4' for efficacy with no further adjustments.
MCBS, Magnitude of Clinical Benefit Scale; QoL, quality of life.
1. https://www.esmo.org/guidelines/esmo-mcbs; 2. Cherney NI, *et al. Ann Oncol* 2015; **26**:1547–1573; 3. Cherney NI, *et al. Ann Oncol* 2017; **28**:2340–2366;
4. https://www.esmo.org/guidelines/esmo-mcbs/esmo-magnitude-of-clinical-benefit-scale/scorecard-4-1.

PHESGO is the first formulation in oncology to combine two mAbs, pertuzumab and trastuzumab, in one vial for SC injection

PHESGO

Contains the same antibodies as approved for IV PERJETA and Herceptin, but has a different route of administration[1,2]

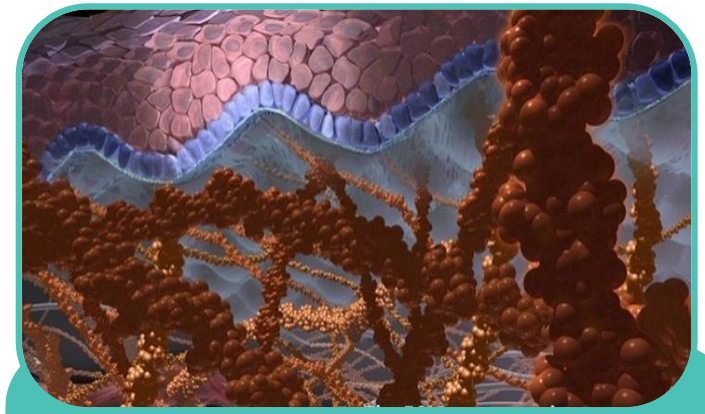
Is formulated with rHuPH20 (recombinant human hyaluronidase) to allow SC administration of higher drug volumes (15 mL loading dose; 10 mL maintenance dose)[1,2]

Is a ready-to-use fixed-dose formulation, administered by an SC injection in the thigh over approximately 5–8 minutes[2]

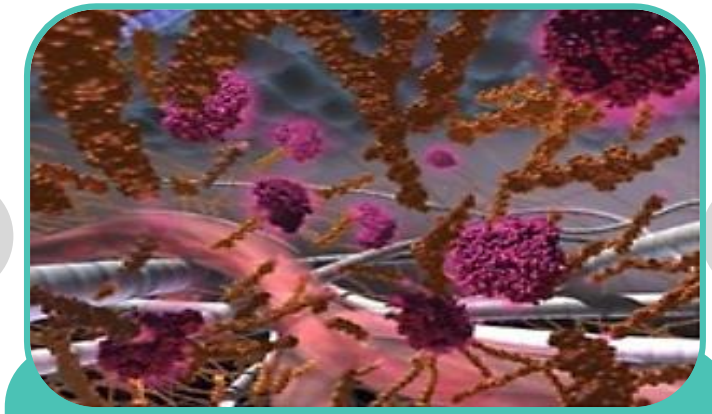
IV, intravenous; mAb, monoclonal antibody; rHuPH20, recombinant human hyaluronidase; SC, subcutaneous.

1. Tan AR, *et al. Lancet Oncol* 2021; **22:**85–97;
2. PHESGO PI 2020.

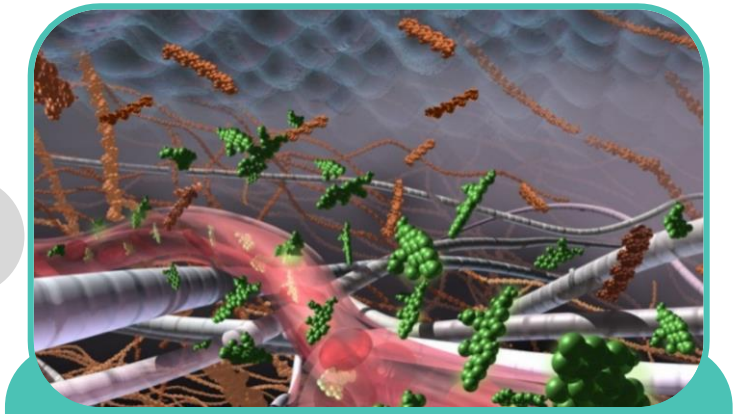
Impact of rHuPH20 on the SC injection of large fluid volumes



The SC layer contains a matrix of hyaluronan fibres and collagen fibres, which limits SC administration of volumes to <1 mL[1]



The addition of rHuPH20 to PHESGO temporarily and locally degrades hyaluronan at the injection site, with no changes in the structure-providing macromolecules, collagen and elastin[1,2]



The degradation of hyaluronan results in a temporary increase in the local SC dispersion area, enabling large volumes of fluids to be administered[1]

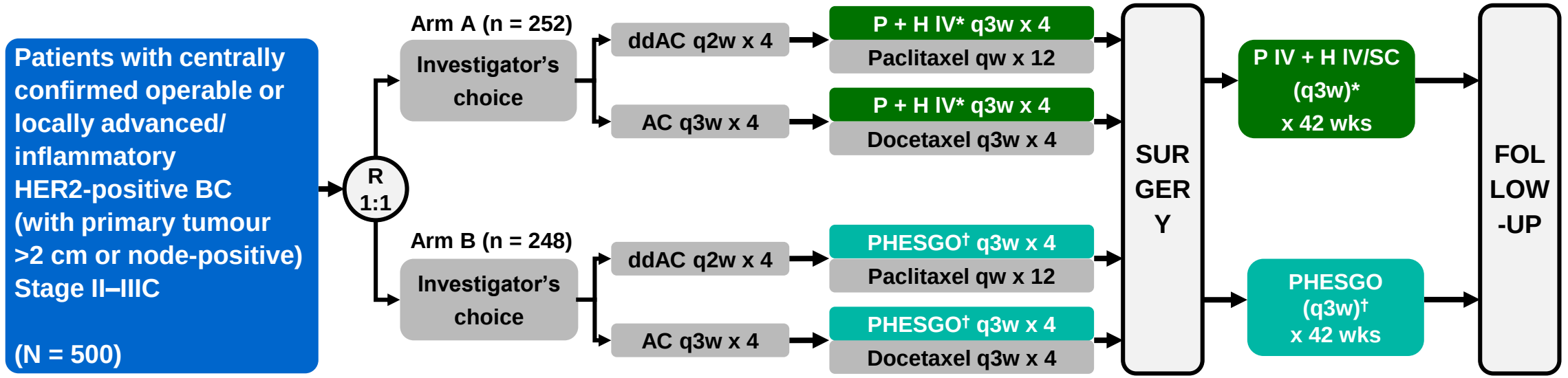
After SC administration, the architecture of the skin is re-formed within 1–2 days due to rapid clearance of rHuPH20 and fast hyaluronan turnover[3]

Formulation with rHuPH20 allows SC administration of large volumes, >1 mL

1. Jackisch C, *et al*. *Geburtshilfe Frauenheilkd* 2014; **74**:343–349;
2. Tan AR, *et al. Lancet Oncol* 2021; **22:**85–97;
3. Frost GI. *Expert Opin Drug Deliv* 2007; **4**:427–440.
Images courtesy of Halozyme Therapeutics.

rHuPH20, recombinant human hyaluronidase; SC, subcutaneous.

FeDeriCa: Phase III study assessing the PK, efficacy, and safety of PHESGO vs. P + H IV



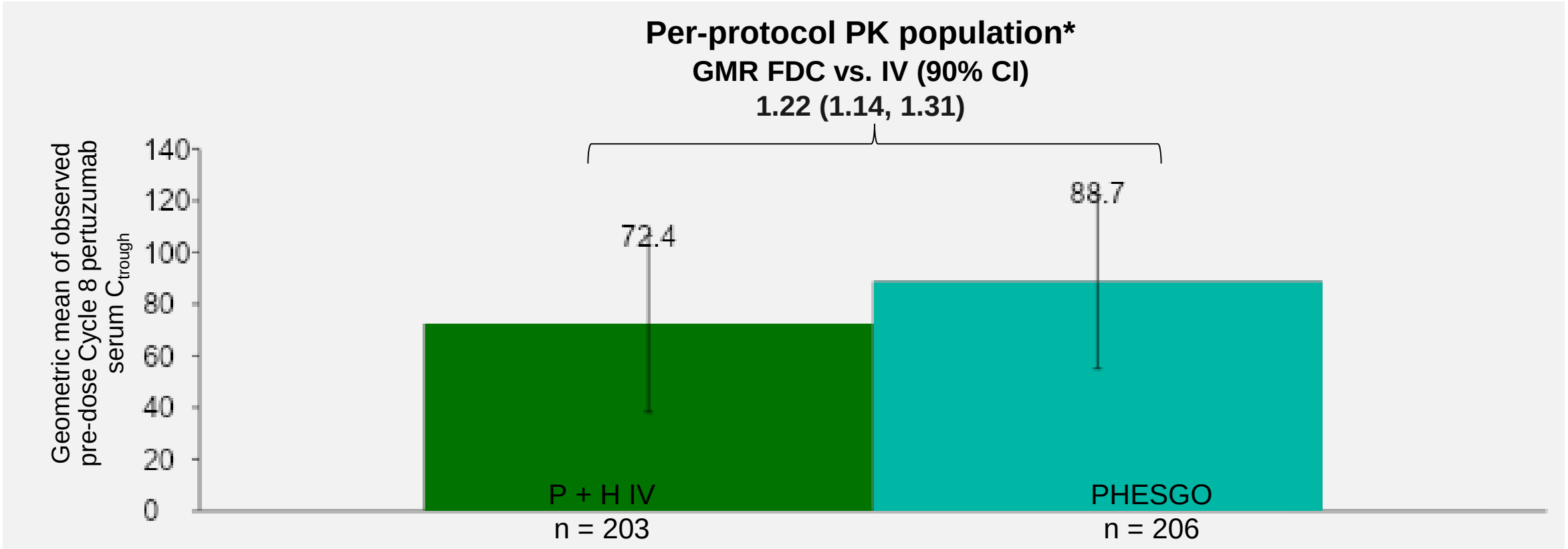
Stratification factors: Hormone receptor status; clinical stage at presentation (Stage II–IIIA or IIIB–IIIC); type of chemotherapy

Primary endpoint: Non-inferiority of Cycle 7 (pre-dose Cycle 8) pertuzumab serum C_{trough}
Key secondary endpoints: Non-inferiority of the pre-dose Cycle 8 trastuzumab serum $C_{trough,}$ tpCR, safety, IDFS, EFS, DRFI, OS

* P IV loading dose: 840 mg; maintenance: 420 mg q3w. H IV loading dose if needed: 8 mg/kg; maintenance: 6 mg/kg IV q3w.
† PHESGO loading dose: P 1200 mg/H 600 mg in 15 mL; maintenance: P 600 mg/H 600 mg in 10 mL q3w.
AC, doxorubicin + cyclophosphamide; C_{trough}, serum trough concentration; ddAC, dose-dense doxorubicin + cyclophosphamide; eBC, early breast cancer;
DRFI, distant relapse-free interval; EFS, event-free survival; H, Herceptin; IDFS, invasive disease-free survival; IV, intravenous; OS, overall survival; P, PERJETA; PK, pharmacokinetics; qw, every week; q2w, every 2 weeks; q3w, every 3 weeks; SC, subcutaneous; tpCR, total pathological complete response (ypT0/is ypN0).

Tan AR, *et al. Lancet Oncol* 2021; **22:**85–97.

FeDeriCa met its primary endpoint: Cycle 7 (pre-dose Cycle 8) pertuzumab serum C_{trough} within PHESGO was non-inferior to P IV

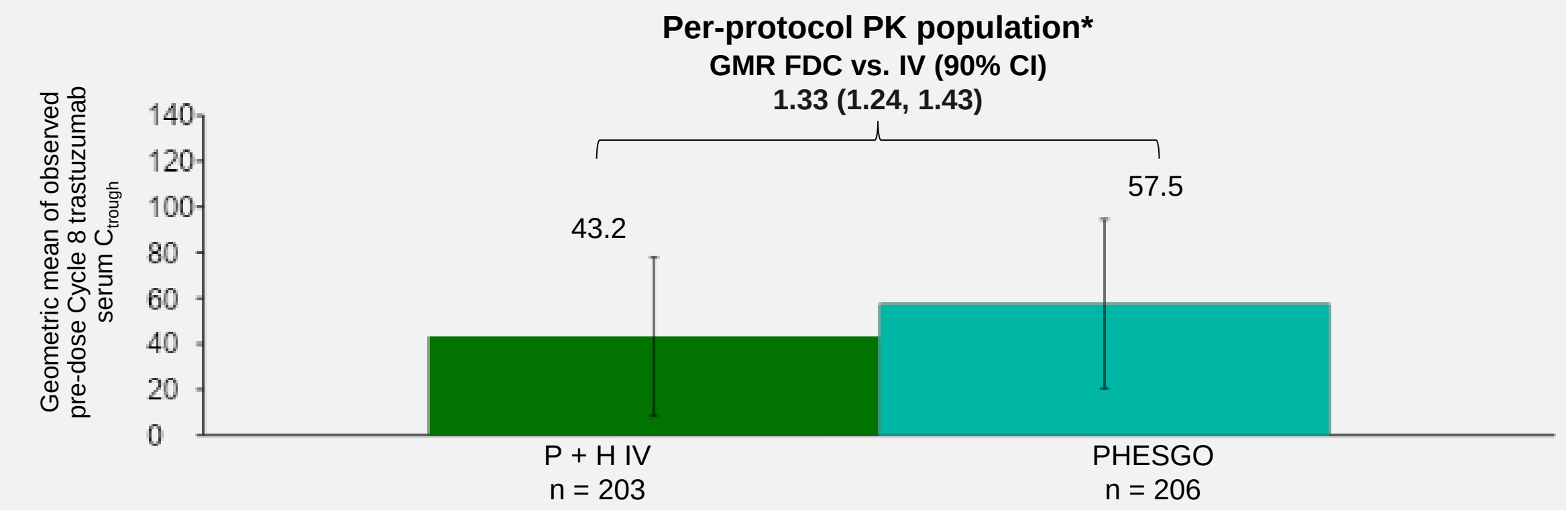


Lower limit of the 90% CI for pertuzumab serum C_{trough} GMR exceeded the non-inferiority margin of 0.8

* This population includes only patients who adhered to the pre-specified criteria for the schedule of PK assessments.
CI, confidence interval; C_{trough}, serum trough concentration; FDC, fixed-dose combination; GMR; geometric mean ratio; H, Herceptin; IV, intravenous; P, PERJETA; PK, pharmacokinetic.

Tan AR, *et al. Lancet Oncol* 2021; **22:**85–97.

Cycle 7 (pre-dose Cycle 8) trastuzumab serum C_{trough} within PHESGO was non-inferior to H IV



Lower limit of the 90% CI for trastuzumab serum C_{trough} GMR exceeded the non-inferiority margin of 0.8

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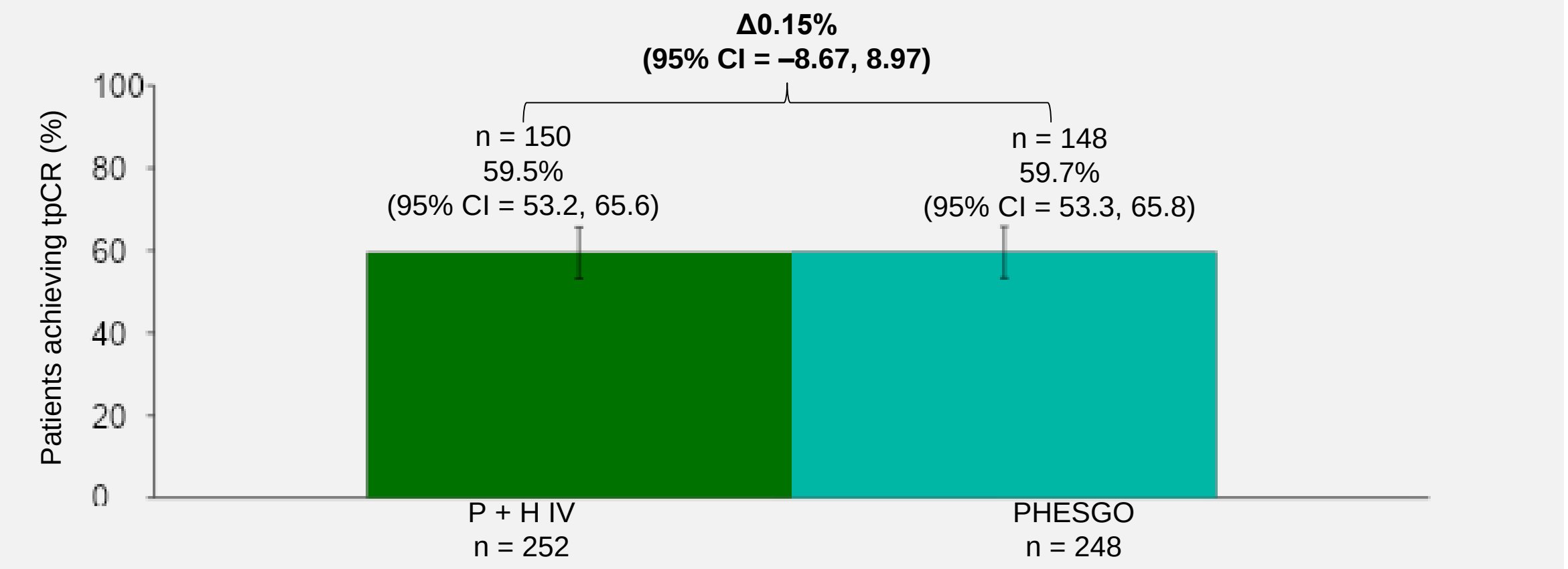
Tan AR, *et al. Lancet Oncol* 2021; **22:**85–97.

PHESGO had almost identical tpCR rates to P + H IV[1]

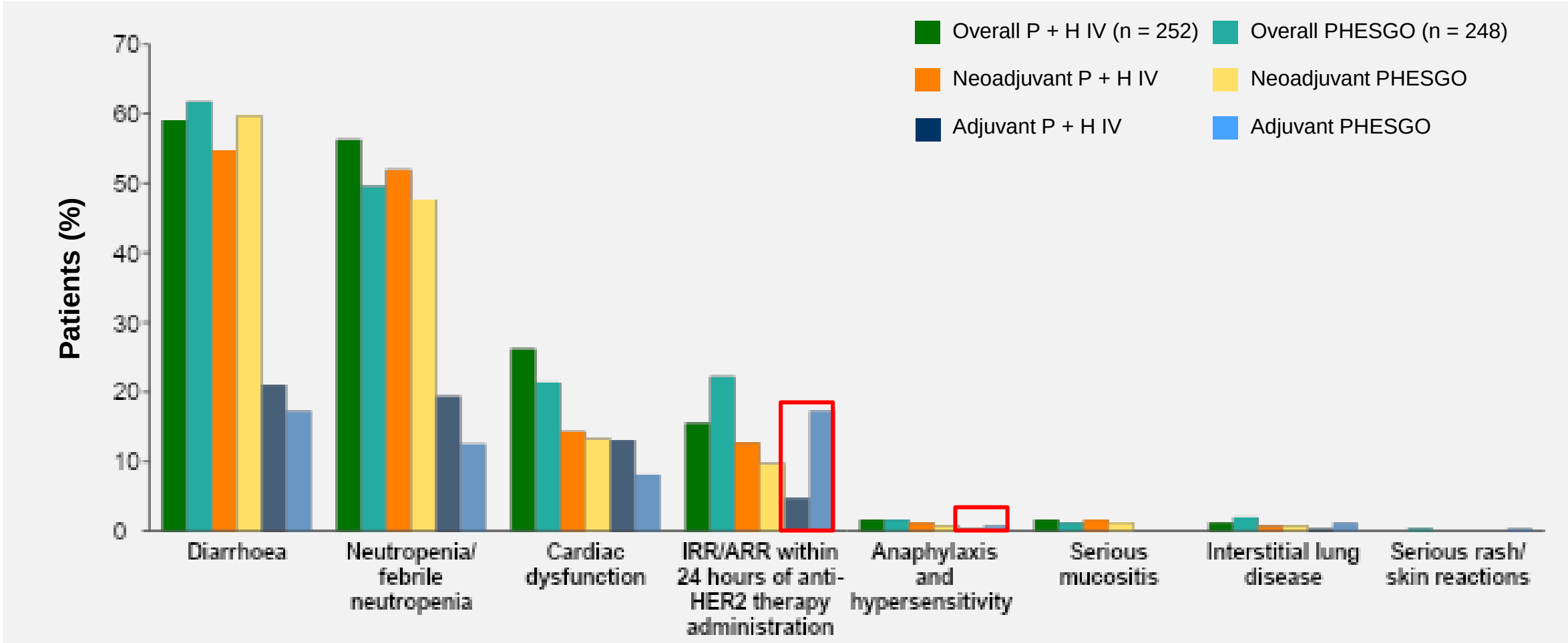


tpCR rates observed are in keeping with data from previous studies of PERJETA–Herceptin + chemotherapy in the neoadjuvant setting[2–5]

CI, confidence interval; H, Herceptin; IV, intravenous; P, PERJETA; tpCR, total pathological complete response (ypT0/is ypN0).

1 Tan AR, *et al. Lancet Oncol* 2021; **22:**85–97; 2. Schneeweiss A, *et al*. *Ann Oncol* 2013; **24**:2278–2284; 3. Loibl S, *et al*. *Ann Oncol* 2017; **28**:497–504; 4. Hurvitz SA, *et al*. *Lancet Oncol* 2018; **19**:115–126; 5. Swain SM, *et al*. *Ann Oncol* 2018; **29**:646–653.

At the updated safety analysis,* the incidence rates of any grade-specific AEs to monitor were generally comparable between treatment arms



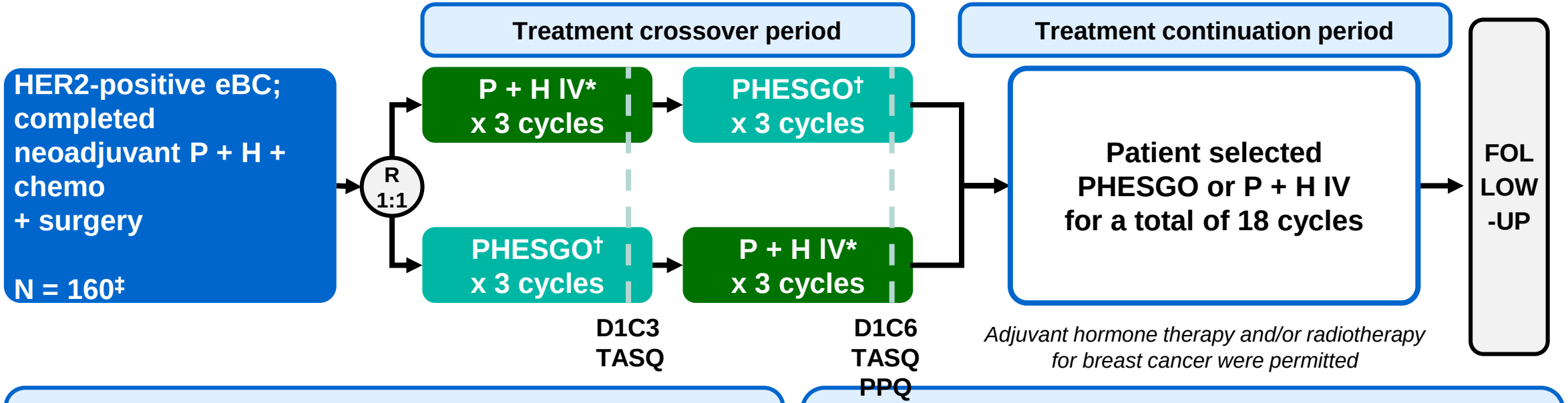
Incidence rates of specific AEs to monitor were generally balanced between treatment arms during the adjuvant phase of FeDeriCA, with the exception of AEs associated with the different routes of administration

* Updated descriptive safety analysis from the neoadjuvant and adjuvant phases of FeDeriCa (CCOD 10 July 2020).

AE, adverse event; ARR, administration-related reaction; CCOD, clinical cut-off date; H, Herceptin; IRR, infusion-related reaction; IV, intravenous; P, PERJETA.

Seock-Ah Im, *et al.* ESMO BC 2021 (Abstract 476; poster presentation).

PHranceSCa: Phase II, open-label, randomised crossover study evaluating patient preference for PHESGO vs. P + H IV



Stratification factors:

- Neoadjuvant chemotherapy regimen
- Neoadjuvant treatment response (pCR vs. non-pCR)
- Hormone receptor status

Primary objective: Patient preference for PHESGO

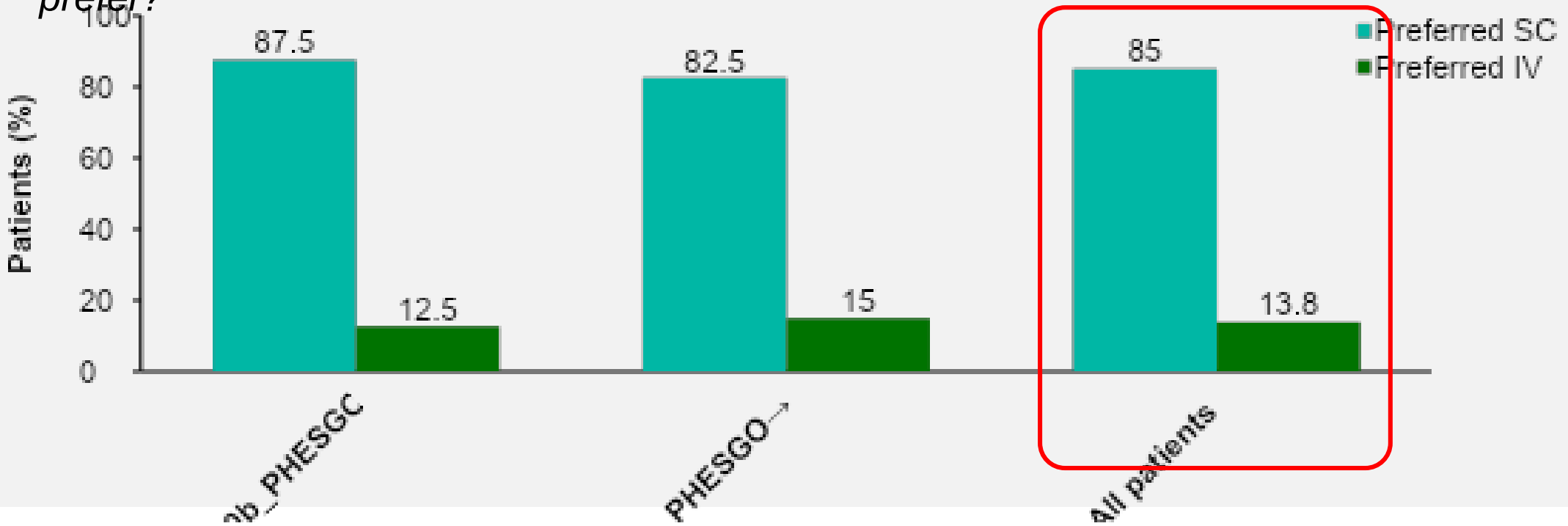
Key secondary objectives: Patient satisfaction; patients' choice of formulation for the continuation period; HRQoL, HCP perception on time/resource, safety and tolerability (including safety of switching from SC to IV formulations and vice versa), efficacy

All patients were female; median age was 49 years.
* P IV loading dose if needed: 840 mg; maintenance: 420 mg q3w. H IV loading dose if needed: 8 mg/kg; maintenance: 6 mg/kg IV q3w.
† PHESGO loading dose if needed: P 1200 mg/H 600 mg in 15 mL; maintenance: P 600 mg/H 600 mg in 10 mL q3w.
Loading doses were only required for patients who had ≥6 weeks since their last neoadjuvant dose of P + H IV at study entry, or had ≥6 weeks since their last.
study treatment during the study. Maintenance doses were used for subsequent administrations or dose delays <6 weeks.
‡ Target enrolment 140 patients; actual recruitment = 160 patients.
eBC, early breast cancer; chemo, chemotherapy; H, Herceptin; HCP, healthcare professional; HR, hormone receptor;
HRQoL, health-related quality of life; IV, intravenous; NACT, neoadjuvant chemotherapy; P, PERJETA; pCR, pathological complete response;
PPQ, Patient Preference Questionnaire; q3w, every 3 weeks; SC, subcutaneous; TASQ, Therapy Administration Satisfaction Questionnaire.

O'Shaughnessy J, *et al. Eur J Cancer* 2021; **152:**223–232.

At the primary analysis, 85% of patients (95% CI = 78.5, 90.2) preferred PHESGO, regardless of sequencing[1]

- Based on Q1 of the PPQ: "*All things considered, which method of administration did you prefer?*"



The proportion of patients who preferred the SC method of administration was consistent with PrefHer (89%)[2] and PrefMab (77%)[3]

Clinical cut-off: 24 February, 2020.
95% CI for PHESGO preference: 78.2–93.8; 72.4–90.1; 78.5–90.2, respectively.
* PPQ completion rate = 100%; two patients (1.3%) expressed no preference.
H, Herceptin; IV, intravenous; P, PERJETA; PPQ, Patient Preference Questionnaire; SC, subcutaneous.

1. O'Shaughnessy J, *et al. Eur J Cancer* 2021; **152:**223–232;
2. Pivot X, *et al. Ann Oncol* 2014; **25:**1979–1987;
3. Rummel M, *et al. Ann Oncol* 2017; **28:**836–842.

93% of patients who preferred PHESGO had a very strong or fairly strong preference at the primary analysis[1]

No. patients, n (%)	P + H IV→ PHESGO (n = 80)	PHESGO→ P + H IV (n = 80)	All patients (N = 160)
Strength of preference for SC			
Total number of respondents	70	66	136
Very strong	48 (68.6)	44 (66.7)	92 (67.6)
Fairly strong	17 (24.3)	17 (25.8)	34 (25.0)
Not very strong	5 (7.1)	5 (7.6)	10 (7.4)
Main reason for SC preference*			
Total number of responses	143	139	282
Requires less time in the clinic	60 (42.0)	59 (42.4)	119 (42.2)
Feels more comfortable during administration	41 (28.7)	32 (23.0)	73 (25.9)
Feels less emotionally distressing	21 (14.7)	25 (18.0)	46 (16.3)
Lower level of injection-site pain	14 (9.8)	18 (12.9)	32 (11.3)
Other reason	7 (4.9)	5 (3.6)	12 (4.3)

The main reasons for preferring SC administration ('Requires less time in the clinic' and 'Feels more comfortable during administration') are consistent with PrefHer[2]

* Patients are counted in several categories.
H, Herceptin; IV, intravenous; P, PERJETA; SC, subcutaneous.

1. O'Shaughnessy J, *et al. Eur J Cancer* 2021; **152:**223–232;
2. Pivot X *et al. Ann Oncol* 2014; **25:**1979–1987.

Majority of HCPs felt that switching from P + H IV infusions to PHESGO injections would save time and resources during preparation and treatment

HCP perceptions of PHESGO vs. P + H IV No. patient cases, n (%)	Cases where HCPs 'strongly agreed' or 'agreed', N = 160
Perceptions from HCPs in drug preparation room*†	
Less drug wastage with ready-to-use PHESGO	123 (76.9)
Reduced staff time associated with preparation procedures	128 (80.0)
Perceptions from HCPs in the treatment room‡§	
Less time from start of preparation to finish of administration	152 (95.6)
Less resource needed for administration¶	137 (86.2)
More convenient for patient	138 (86.8)
Better for care optimisation within their treatment site	126 (79.2)
PHESGO preferred by patients	123 (77.4)

HCP perceptions (drug preparation room)

- Median SC preparation time was 5 min vs.15–20 min for IV infusion
- PHESGO was quickest from start of preparation to completion of administration (87.5%)
- PHESGO required less resource usage for preparation and th

HCP perceptions (treatment room)

- Median drug administration time was 7–8 min for PHESGO vs. 60–150 min for P + H IV
- Median patient time in the treatment room during the crossover period was 33–50 min for PHESGO vs. 130–300 min for P + H IV

HCPQs, 99.7%).

† Most of the time the HCPQ was completed in the drug preparation room by the pharmacist (51.7%) or nurse (30.7%).

‡ The vast majority of HCPs in the treatment room completed at least one question of the HCPQ during the treatment crossover period (950/960 HCPQs, 99.0%).

§ Most of the time the HCPQ was completed in the drug treatment room by the nurse (97.7%). ¶ E.g. nursing time, facility costs, equipment.

H, Herceptin; HCP, healthcare professional; HCPQ, healthcare professional questionnaire; IV, intravenous; P, PERJETA.

O'Shaughnessy J, *et al. Eur J Cancer* 2021; **152:**223–232.

4 Kadcyla in HER2-positive mBC

Kadcyla: Herceptin is conjugated by a thioether linker to the highly potent anti-microtubule agent DM1

Combined mode of action

Herceptin biological properties[1,2]

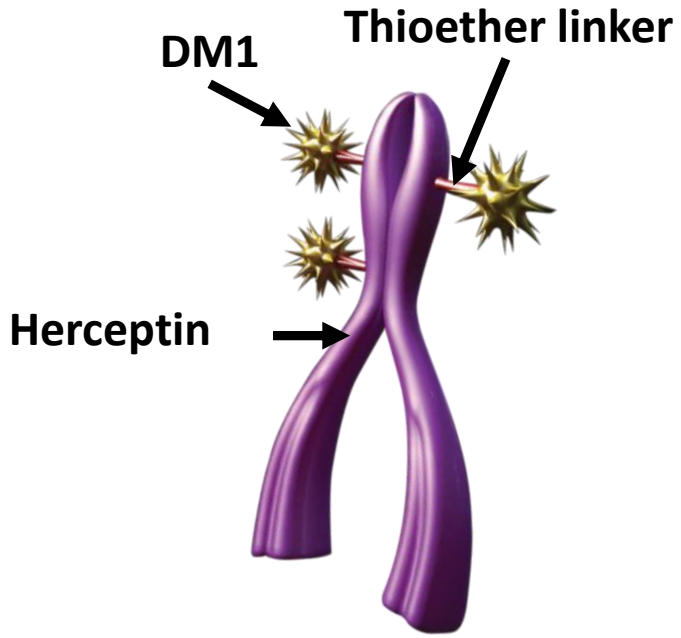
- Targeted delivery of DM1 to cell
- Herceptin properties retained:
  - Downstream signalling inhibition
  - ADCC
  - Prevention of p95HER2 formation

Stable thioether linker[1,3]

- Prevents premature release of DM1, which would result in systemic toxicities
- 3-3.6 DM1 moieties per 1 Herceptin molecule[4]

Targeted intracellular delivery of DM1[1,2,5]

- DM1 is internalised via endocytosis
- DM1 inhibits microtubule assembly, leading to apoptosis
- T-DM1 can reach therapeutically effective concentration in the CNS[6–8]



Abbreviations and references in slide notes.

Kadcyla is second-line treatment option for HER2-positive mBC previously treated with Herceptin-based therapy

Indication: treatment of adult patients with HER2-positive:

- Unresectable locally advanced or mBC (SmPC)[1]
- mBC (PI)[2]

who previously received Herceptin and a taxane, separately or in combination. Patients should have either:

- Received prior therapy for locally advanced or metastatic disease, or
- Developed disease recurrence during or within 6 months of completing adjuvant therapy[1,2]

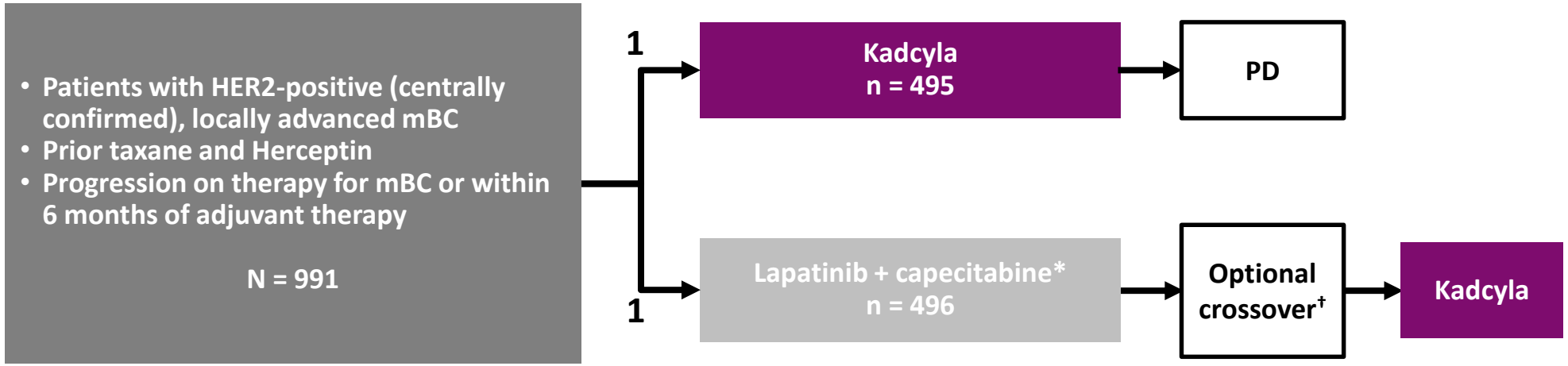
Dosing[1,2]

- Kadcyla dose: 3.6 mg/kg administered as an IV infusion q3w (21-day cycle) until disease progression or unmanageable toxicity
  - First dose administered as a 90-min IV infusion
  - If prior infusions are tolerated, subsequent doses may be administered over 30 mins

IV, intravenous; mBC, metastatic breast cancer; PI, Prescribing Information; SmPC, Summary of Product Characteristics; SoC, standard of care; q3w, every 3 weeks.

1. EMA. Kadcyla SmPC. Accessed May 2020; 2. FDA. Kadcyla PI. Accessed May 2020.

EMILIA: Phase III trial of Kadcyla in patients with HER2-positive ABC previously treated with Herceptin + taxane



- **Co-primary endpoints:** PFS (by independent review), OS, safety
- **Key secondary objectives:** PFS (by investigator), ORR, TTF, CBR
- **Stratification:** World region (USA, Western Europe or other), number of prior chemotherapy regimens for LABC or mBC (0 or 1 vs. >1), and disease involvement (visceral vs. non-visceral)

ABC, advanced breast cancer; CBR, clinical benefit rate; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.
* 1,000 mg/m^2 bid d1-14 q21d.
† Patients allowed to crossover: August 2012 (Amendment A4: 30 May 2012).
Verma S, *et al. N Engl J Med* 2012; **367**:1783–1791.

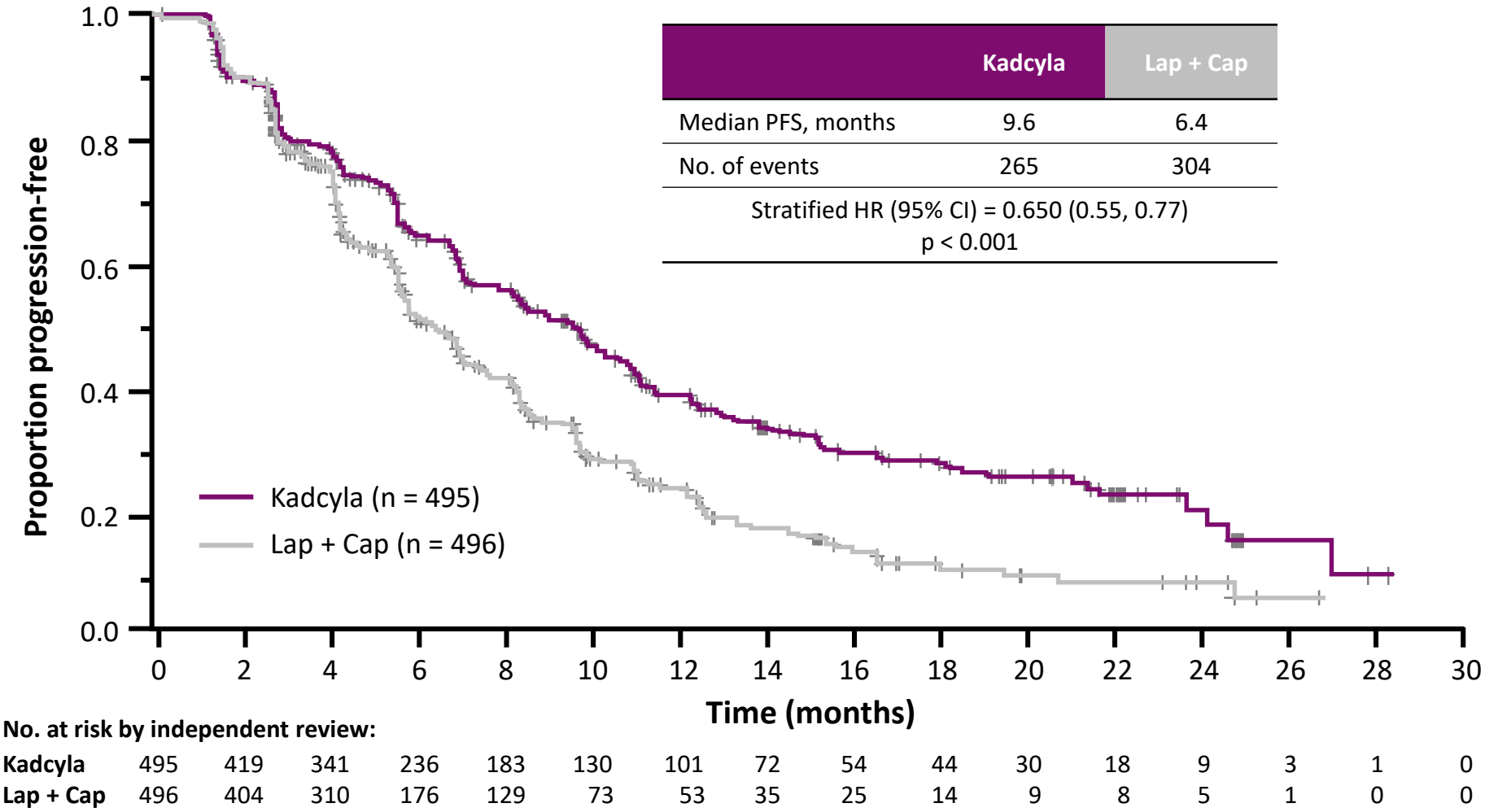
EMILIA: Baseline characteristics were similar across both treatment arms

Characteristic, %	Kadcyla (n = 495)	Lap + Cap (n = 496)
Age, years, median (range)	53 (25–84)	53 (24–83)
Visceral involvement	67	68
ECOG PS		
0	60	63
1	39	35
Not available	<1	2
ER- and/or PR-positive	57	53
Prior systemic therapy		
Anthracycline	61	61
Other chemotherapy	78	77
Endocrine therapy	41	41
Prior chemotherapy regimens for locally advanced or metastatic disease		
0–1	61	61
> 1	39	39
Prior Herceptin treatment		
For mBC, early-stage BC or both	84	84
For early–stage BC only	16	16

Cap, capecitabine; Lap, lapatinib; mBC, metastatic breast cancer

Verma S, *et al. N Engl J Med* 2012; **367**:1783–1791.

EMILIA: Kadcyla significantly prolonged independently assessed PFS compared with lapatinib + capecitabine



	Kadcyla	Lap + Cap
Median PFS, months	9.6	6.4
No. of events	265	304
Stratified HR (95% CI) = 0.650 (0.55, 0.77) p < 0.001		

No. at risk by independent review:

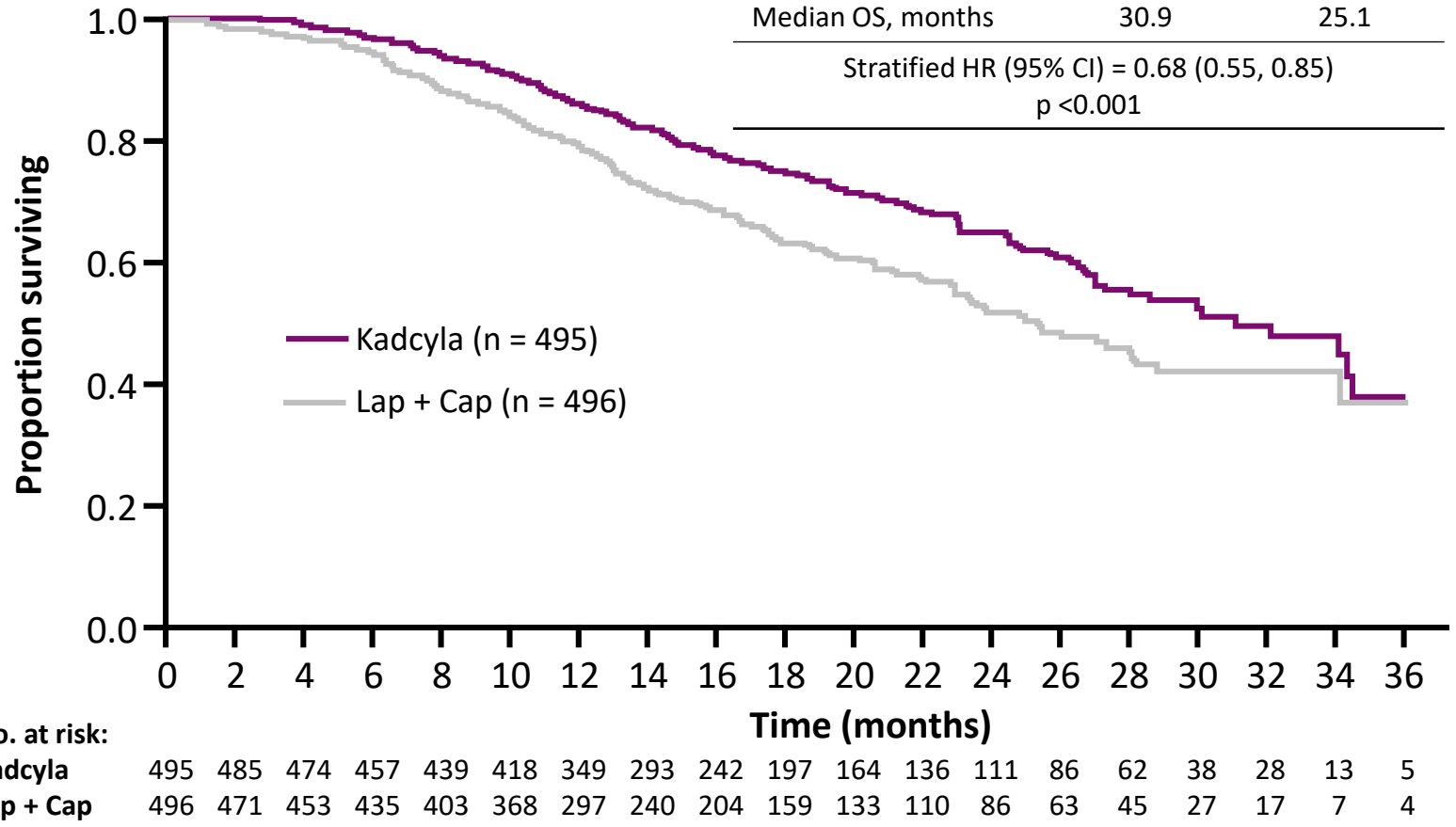
Kadcyla	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0
Lap + Cap	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0

Cap, capecitabine; CI, confidence interval; HR, hazard ratio; Lap, lapatinib; PFS, progression-free survival
Clinical cut-off date: 14 January 2012.
Verma S, *et al. N Engl J Med* 2012; **367**:1783–1791.

EMILIA: Kadcyla significantly prolonged OS compared with lapatinib + capecitabine

Primary analysis[1*†]

	Kadcyla	Lap + Cap
Median OS, months	30.9	25.1
Stratified HR (95% CI) = 0.68 (0.55, 0.85) p <0.001		



No. at risk:																			
Kadcyla	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5
Lap + Cap	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4

Final analysis[2‡]

	Kadcyla	Lap + Cap
Median OS, months	29.9	25.9
Stratified HR (95% CI) = 0.75 (0.64, 0.88) (Descriptive only)		

Cap, capecitabine; CI, confidence interval; HR, hazard ratio; Lap, lapatinib; OS, overall survival.

* Clinical cut-off date: 31 July 2012. † The data presented are from the second interim analysis of OS (331 deaths). At the first interim analysis (223 deaths), the stratified HR for death from any cause with Kadcyla versus Lap + Cap was 0.62 (95% CI, 0.48, 0.81; p = 0.0005) and did not cross the predefined O'Brien–Fleming stopping boundary (p = 0.0003).

‡ Clinical cut-off date: 31 December 2014.

1. Verma S, *et al. N Engl J Med* 2012; **367**:1783–1791; Dieras V, *et al. Lancet Oncol* 2017; **18**:732–742.

EMILIA: Fewer grade ≥3 AEs with Kadcyla compared with lapatinib + capecitabine

	Kadcyla (n = 490)		Lap + Cap (n = 488)	
	Events of any grade	**Grade ≥3**	**Events of any grade**	**Grade ≥3**
Any event	470 (95.9)	200 (40.8)	477 (97.7)	278 (57.0)
Specific events				
Diarrhoea	114 (23.3)	8 (1.6)	389 (79.7)	101 (20.7)
PPE syndrome	6 (1.2)	0 (0)	283 (58.0)	80 (16.4)
Vomiting	93 (19.0)	4 (0.8)	143 (29.3)	22 (4.5)
Hypokalaemia	42 (8.6)	11 (2.2)	42 (8.6)	20 (4.1)
Neutropenia	29 (5.9)	10 (2.0)	42 (8.6)	21 (4.3)
Fatigue	172 (35.1)	12 (2.4)	136 (27.9)	17 (3.5)
Nausea	192 (39.2)	4 (0.8)	218 (44.7)	12 (2.5)
Anaemia	51 (10.4)	13 (2.7)	39 (8.0)	8 (1.6)
Mucosal inflammation	33 (6.7)	1 (0.2)	93 (19.1)	11 (2.3)
Elevated ALT	83 (16.9)	14 (2.9)	43 (8.8)	7 (1.4)
Elevated AST	110 (22.4)	21 (4.3)	46 (9.4)	4 (0.8)
Thrombocytopenia	137 (28.0)	63 (12.9)	12 (2.5)	1 (0.2)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cap, capecitabine; Lap, lapatinib; PPE, palmar-plantar erythrodysesthesia.

Verma S, *et al*. *N Engl J Med* 2012; **367**:1783–1791.

EMILIA: Adverse events of special interest can be managed by dose modification in the majority of patients

Thrombocytopenia

- For most patients, first occurrence of grade 3-4 thrombocytopenia reported during first two cycles of Kadcyla
- With dose modifications, the majority of patients continued treatment

Hepatotoxicity

- Hyperbilirubinemia (any grade) more frequent with lapatinib+capecitabine than with Kadcyla (8.2% vs.1.2%)
- With appropriate dose modifications, most patients with grade 3-4 serum ALT elevations continued treatment

Left ventricular ejection fraction

- LVEF of ≥45% maintained in the majority of patients
- Three patients in each group had a decrease from baseline to <40%
- 1.7% of patients receiving Kadcyla and 1.6% of patients receiving lapatinib + capecitabine had an ejection fraction of <50% and at least 15% below baseline

LVEF, left ventricular ejection fraction.

Verma S, *et al. N Engl J Med* 2012; **367**:1783–1791.

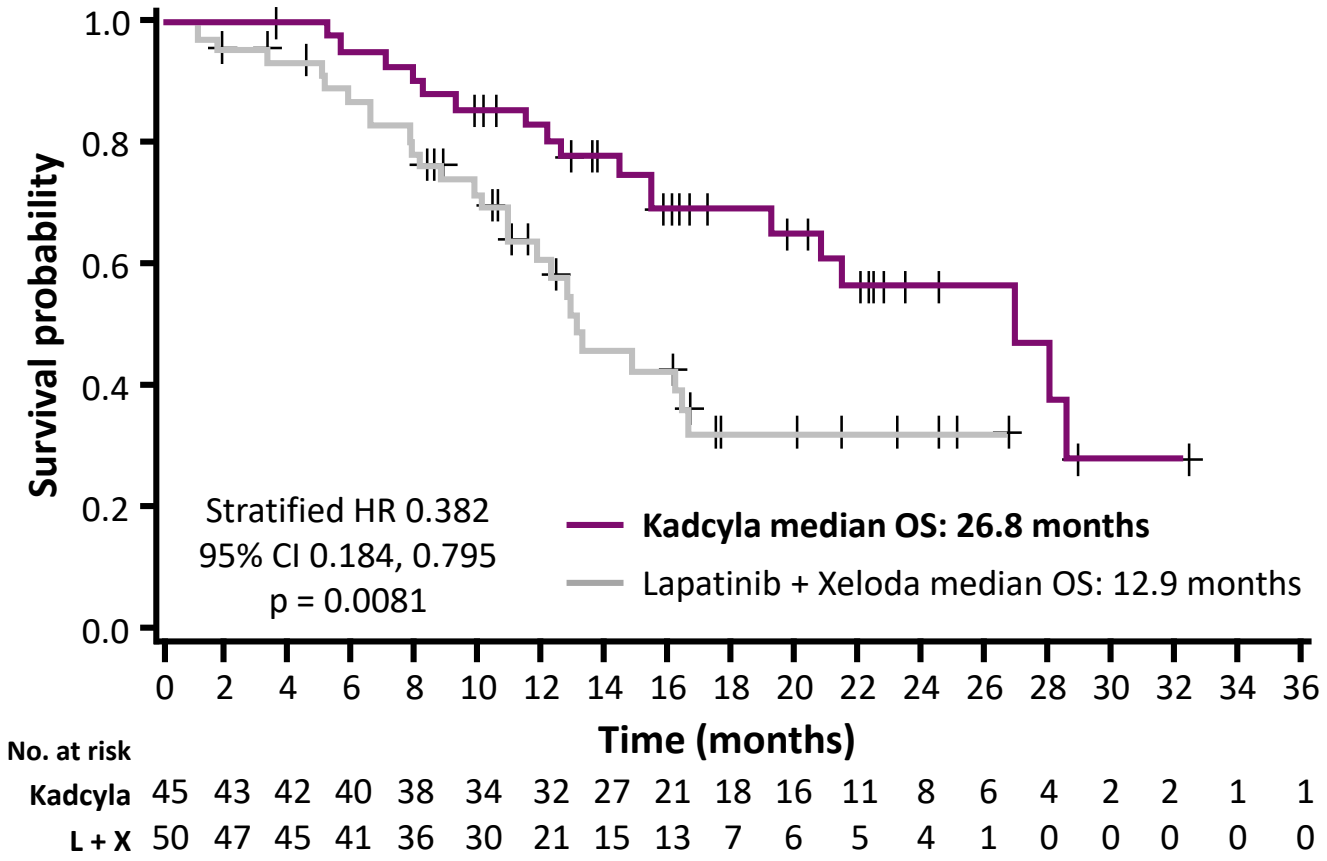
Kadcyla in HER2-positive mBC patients with CNS metastases

EMILIA exploratory analysis: Kadcyla improved OS compared with lapatinib + Xeloda in patients with baseline CNS metastases

Exploratory *post hoc* analysis

- Patients with treated, asymptomatic CNS mets at baseline and patients developing post-baseline CNS mets were retrospectively identified
- Of the 991 randomised patients:
  - 95 had CNS mets at baseline
  - CNS progression occurred in 12 patients without CNS mets at baseline (9/450 in the Kadcyla arm and 3/446 in the L + X arm)
- Median number of prior systemic agents in patients with CNS mets:

n (range)	Kadcyla (n = 42)	L + X (n = 46)
Metastatic setting*	3 (1–8)	3 (1–13)
Any setting	4 (2–13)	5 (2–10)



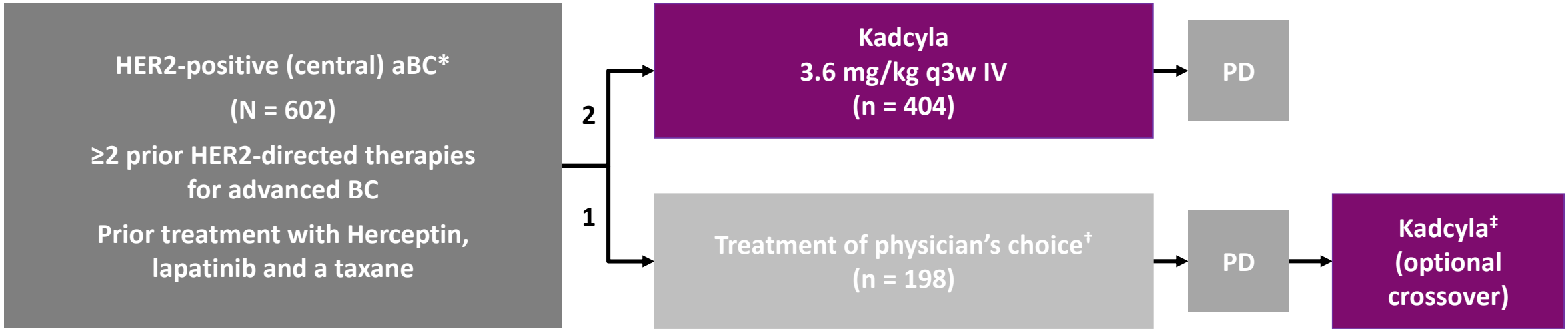
Patients with baseline CNS metastases had a median PFS of 5.9 months with Kadcyla vs. 5.7 months with lapatinib + Xeloda (HR 1.00; 95% CI 0.54, 1.84; p = 1.000)

*Excluding hormonal therapy.
L + X, lapatinib + Xeloda; OS, overall survival.

Krop IE, *et al. Ann Oncol* 2015; **26**:113–119.

Kadcyla in third- and later-line HER2-positive mBC

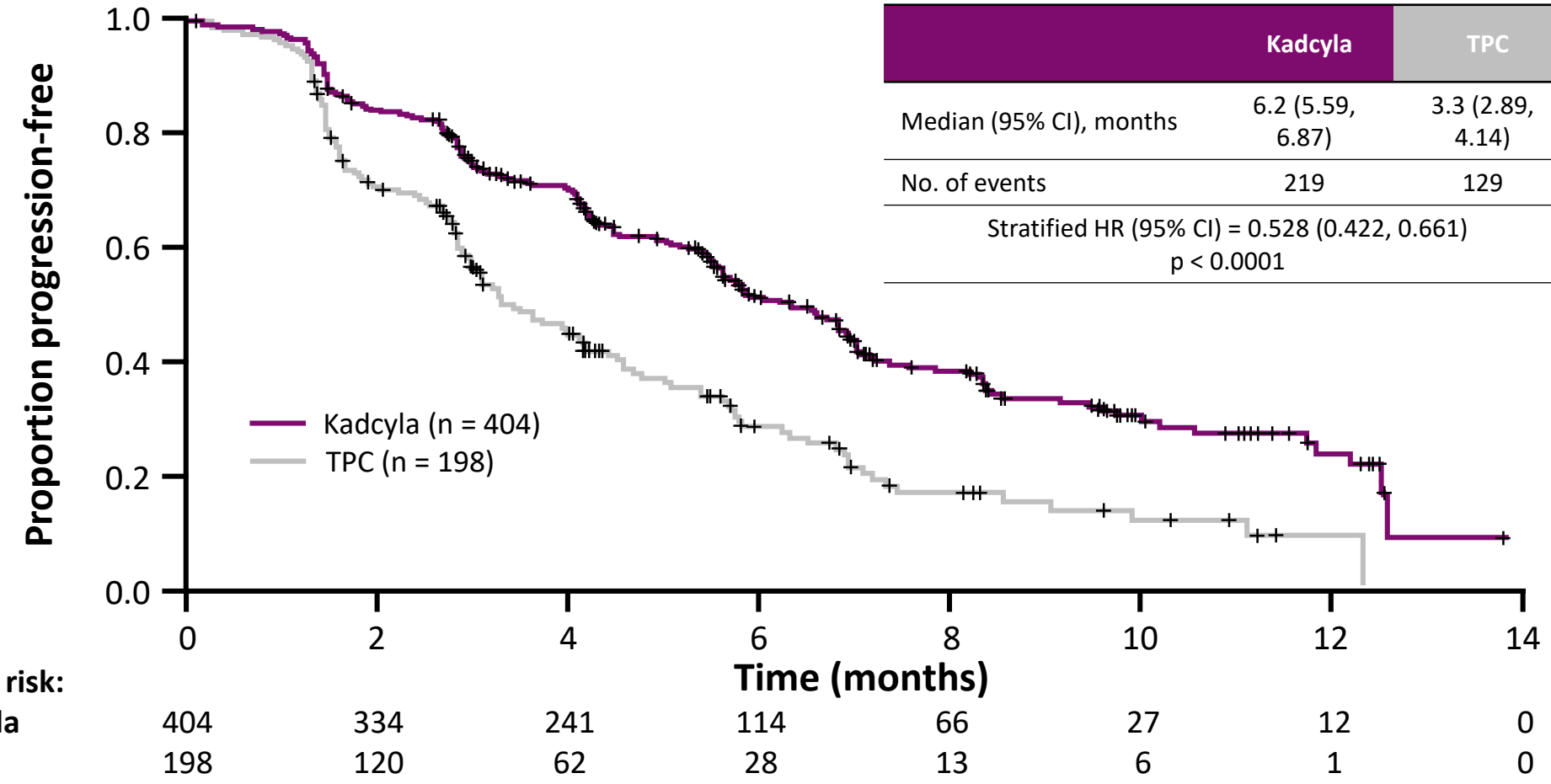
TH3RESA: Phase III trial of Kadcyla in HER2-positive aBC previously treated with Herceptin, lapatinib and a taxane



- **Stratification factors:** world region, number of prior regimens for mBC,§ presence of visceral disease
- **Co-primary endpoints:** PFS by investigator and OS
- **Key secondary endpoints:** ORR, DoR, landmark survival rate, safety

*Advanced BC includes mBC and unresectable locally advanced/recurrent BC.
† TPC could have been single-agent chemotherapy, hormonal therapy or HER2-directed therapy, or a combination of a HER2-directed therapy with a chemotherapy, hormonal therapy, or other HER2-directed therapy.
‡ First patient in: Sep 2011. Study amended Sep 2012 (following EMILIA 2nd interim OS results) to allow patients in the TPC arm to receive T-DM1 after documented PD
§ Excluding single-agent hormonal therapy.
aBC, advance breast cancer; BC, breast cancer; DoR, duration of response; IV, intravenous; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; q3w, every 3 weeks.
Krop IE, *et al*. *Lancet Oncol* 2014; **15**:689–699.

TH3RESA: Kadcyla significantly prolonged investigator-assessed PFS compared with TPC in heavily pre-treated patients



	Kadcyla	TPC
Median (95% CI), months	6.2 (5.59, 6.87)	3.3 (2.89, 4.14)
No. of events	219	129
Stratified HR (95% CI) = 0.528 (0.422, 0.661) p < 0.0001		

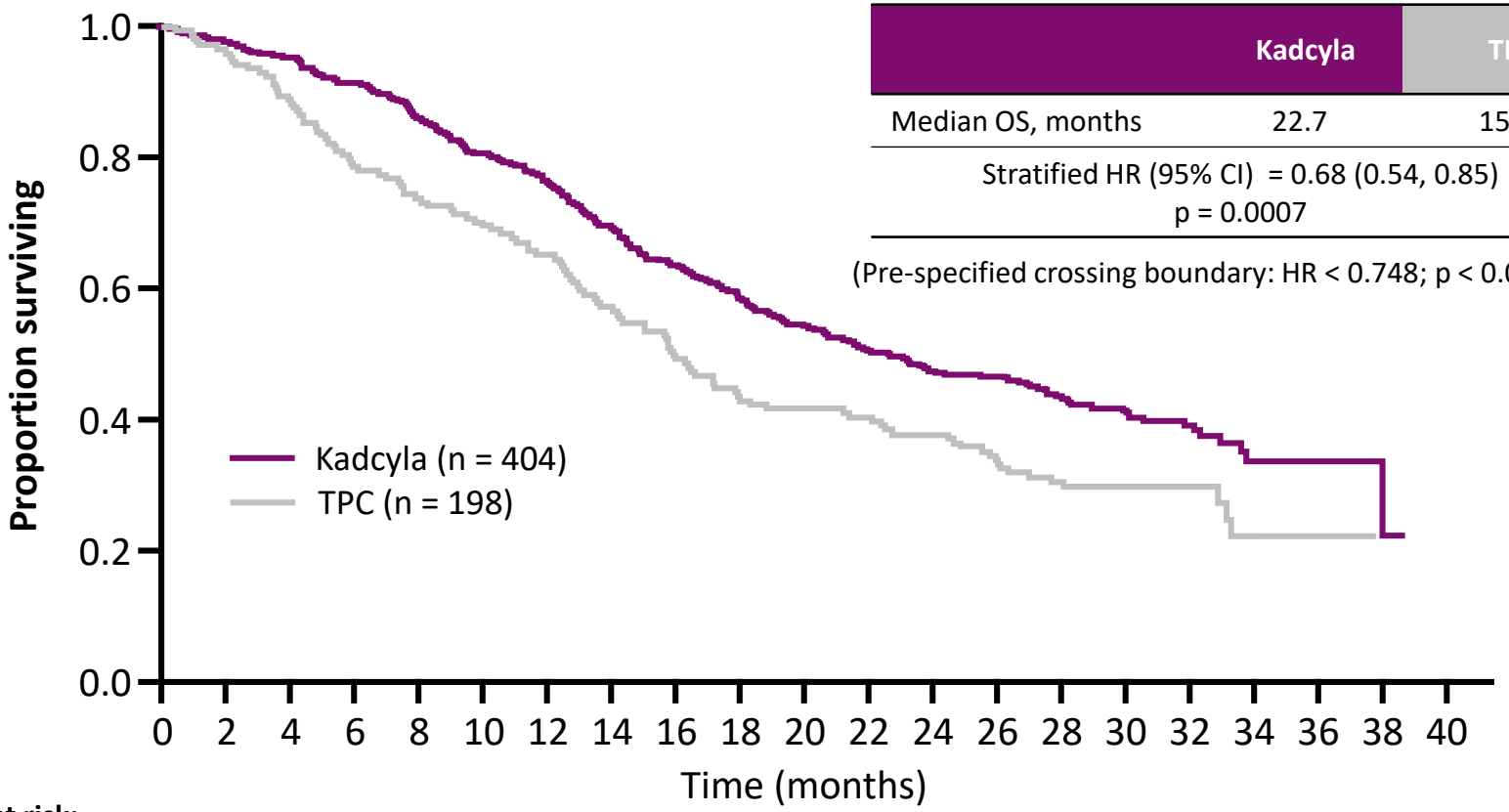
No. at risk:								
Kadcyla	404	334	241	114	66	27	12	0
TPC	198	120	62	28	13	6	1	0

Median follow-up: TPC, 6.5 months; T-DM1, 7.2 months.
Unstratified HR* = 0.521; (95% CI = 0.418–0.648); p < 0.0001

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; TPC, treatment of physician's choice.

Krop IE, *et al. Lancet Oncol* 2014; **15**:689–699.

TH3RESA: Kadcyla significantly prolonged OS compared with TPC in heavily pre-treated patients (final analysis)



	Kadcyla	TPC
Median OS, months	22.7	15.8
Stratified HR (95% CI) = 0.68 (0.54, 0.85) p = 0.0007		

(Pre-specified crossing boundary: HR < 0.748; p < 0.012)

No. at risk:											
Kadcyla	404	368	321	280	226	192	167	132	54	12	0
TPC	198	150	122	107	80	66	59	39	16	1	0

Clinical data cut-off: 13 February 2015.
CI, confidence interval; HR, hazard ratio; OS, overall survival; TPC, treatment of physician's choice.
Krop IE, *et al. Lancet Oncol* 2017; **18**:743–754.

TH3RESA: The incidence of AEs grade ≥3 was lower with Kadcyla compared with TPC

- AEs grade ≥3 occurred in 47% of patients (87/184) receiving TPC and 40% of patients (161/403) receiving Kadcyla

	Kadcyla (n = 403)		TPC (n = 184)	
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**
Fatigue	9 (2%)	0	5 (3%)	0
Diarrhoea	3 (1%)	0	8 (4%)	0
Asthenia	4 (1%)	0	6 (3%)	0
Abdominal pain	5 (1%)	0	5 (3%)	0
Dyspnoea	10 (2%)	0	7 (4%)	0
Anaemia	12 (3%)	2 (<1%)	5 (3%)	1 (1%)
Neutropenia	7 (2%)	3 (1%)	20 (11%)	9 (5%)
AST increased	10 (2%)	0	5 (3%)	0
ALT increased	6 (2%)	0	4 (2%)	0
Leukopenia	2 (<1%)	0	4 (2%)	1 (1%)
Cellulitis	2 (<1%)	0	4 (2%)	0
Thrombocytopenia	19 (5%)	5 (1%)	4 (2%)	1 (1%)
Febrile neutropenia	0	1 (<1%)	5 (3%)	2 (1%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TPC, treatment of physician's choice.

Krop IE, *et al. Lancet Oncol* 2017; **18**:743–754.

Monitoring for ILD and pneumonitis in patients receiving Kadcyla

Compared with other treatments for mBC, cases of ILD and pneumonitis are infrequent with Kadcyla

- ILD is a recognised AE of interest that has been reported following treatment with Kadcyla;[1,2] however, ILD has been observed across several classes of anti-cancer treatments including immunotherapies, systemic chemotherapies, and targeted therapies[3-5]
- Although ILD occurs infrequently in patients receiving Kadcyla, patients should be monitored for signs of ILD and pneumonitis to ensure appropriate management is instigated[1,2]
  - Pneumonitis has been reported at an incidence of 0.8% in patients with mBC who were treated with Kadcyla (with one case of grade 3 pneumonitis)[2]
  - The incidence of ILD/pneumonitis was 1.2% in EMILIA[2] and 0.5% in TH3RESA (with one case of grade 5 pneumonitis)[6]
- Kadcyla has a well-established and manageable safety profile based on experience from clinical trials (Phase III: EMILIA, TH3RESA, MARIANNE and KAMILLA)[6–9] and clinical practice
- PRO data support Kadcyla's acceptable tolerability profile in patients with HER2-positive mBC[10,11] and Kadcyla has also been shown to reduce the number of severe side effects commonly experienced with traditional systemic chemotherapy[12]

AE, adverse event; ILD, interstitial lung disease; mBC, metastatic breast cancer; PRO, patient-reported outcome

1. EMA. Kadcyla SmPC. Accessed May 2020; 2. FDA. Kadcyla PI. Accessed May 2020; 3. Teuwen LA, *et al. Expert Opin Drug Metab Toxicol* 2015; **11**:1695–1707;
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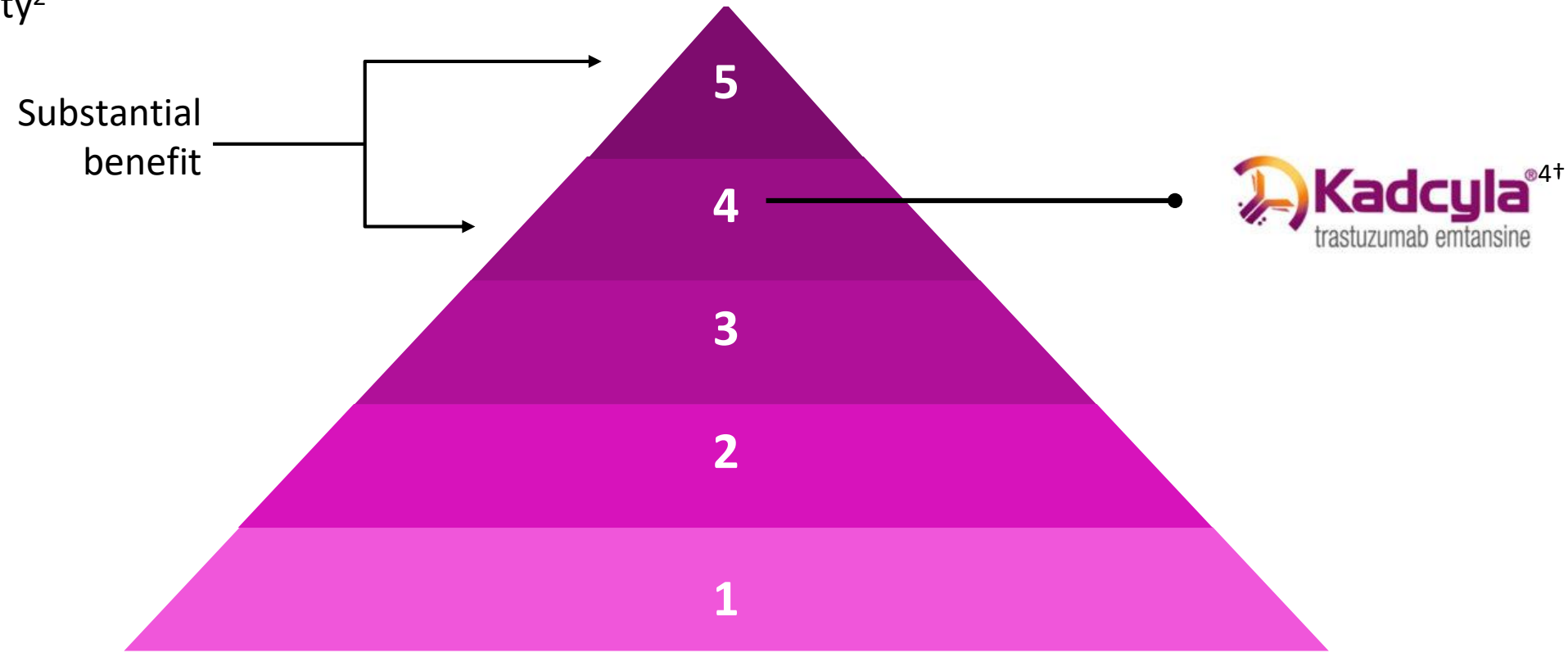
ESMO Magnitude of Clinical Benefit Scale ranking for Kadcyla in mBC

ESMO MCBS scale: Independent ranking of clinically meaningful benefit

- The ESMO MCBS provides a relative ranking of the magnitude of clinically meaningful benefit that can be expected from anti-cancer treatments[1–3]*
- Drugs are given an initial score based on efficacy (maximum score of 4), which is then adjusted for QoL and toxicity[2]



* ESMO MCBS scale is different for early breast cancer (A, B, C, with A and B representing substantial magnitude of clinical benefit).
† Kadcyla was rated '3' for efficacy with a '+1' adjustment for QoL..[4]
MCBS, Magnitude of Clinical Benefit Scale; QoL, quality of life.
1. https://www.esmo.org/guidelines/esmo-mcbs; 2. Cherney NI, *et al. Ann Oncol* 2015; **26**:1547–1573; 3. Cherney NI, *et al. Ann Oncol* 2017; **28**:2340–2366;
4. https://www.esmo.org/guidelines/esmo-mcbs/esmo-magnitude-of-clinical-benefit-scale/scorecard-3-1

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*Pregnancy/Breastfeeding, use in Pediatric/Elderly population, Lack of Efficacy, Overdose, Misuse, Abuse, Off Label Use, Medication Error (including Intercepted Medication Error and Potential Medication Error), Occupational Exposure, data related to a Suspected Transmission of an Infectious Agent via a Medicinal Product (STIAMP), Drug Interaction, Falsified Medicinal Products (whether suspected or confirmed) and suspected AEs from class action lawsuits

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