Advancing Patient Care in HER2+ Breast Cancer

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Disclosures

- **Advisory board**

  : IPSEN, Sanomics, Pfizer, Takeda

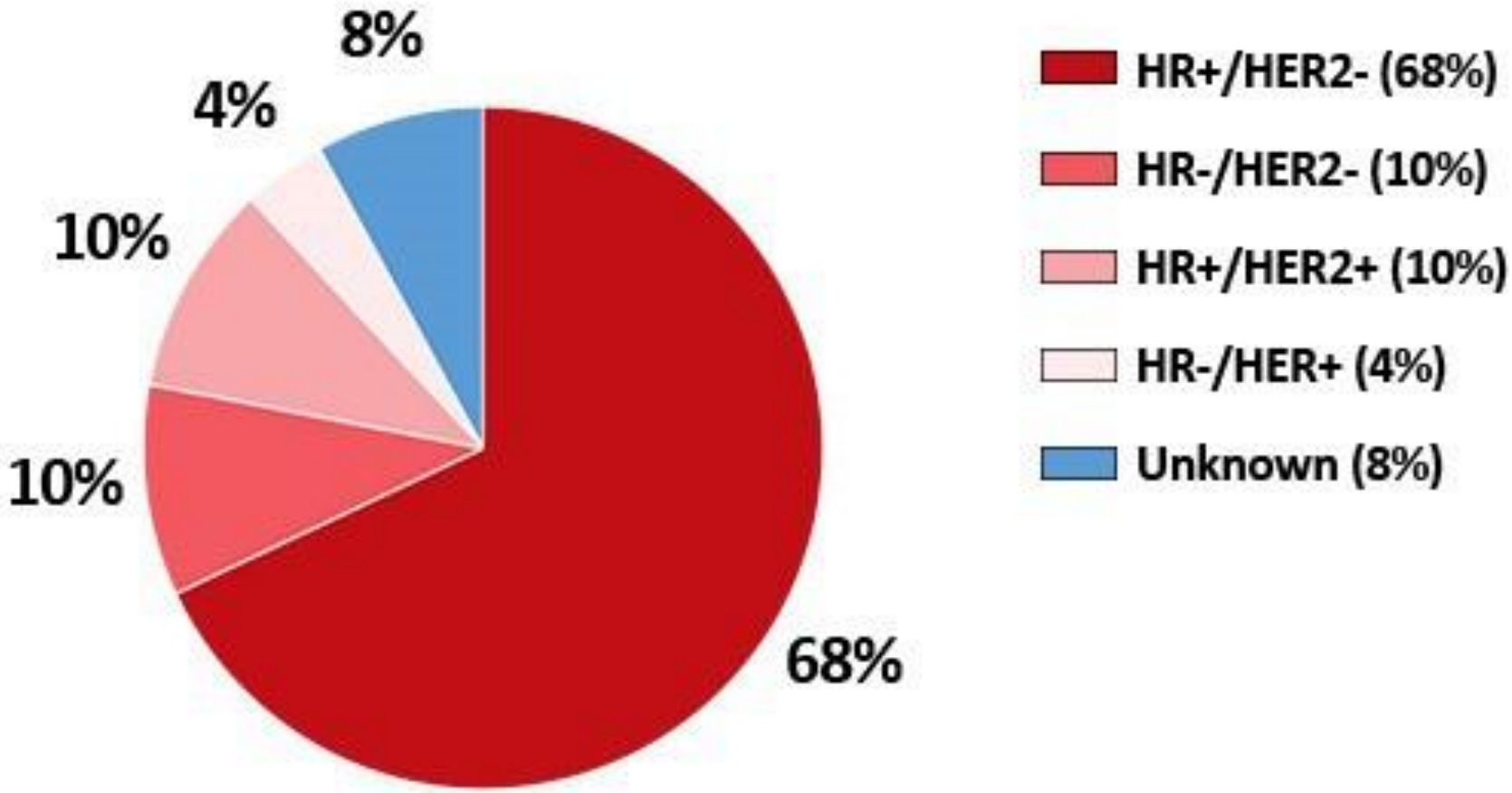
- **Speaker**

  : Alliance pharma, Astellas, AstraZeneca, Bayer, Dr.Reddy, IPSEN, Esai, Jansenn, Merck, MSD, Novartis, Roche, Sandoz, Sanofi, Takeda, ZP therapeutics

Topics

- Role of anti-HER2 drug in adjuvant setting
- Role of anti-HER2 drug in metastatic setting
- Introduction for fixed-dose combination subcutaneous

Percent of Female Breast Cases by Cancer Subtype[1]



SEER 21 2013-2017

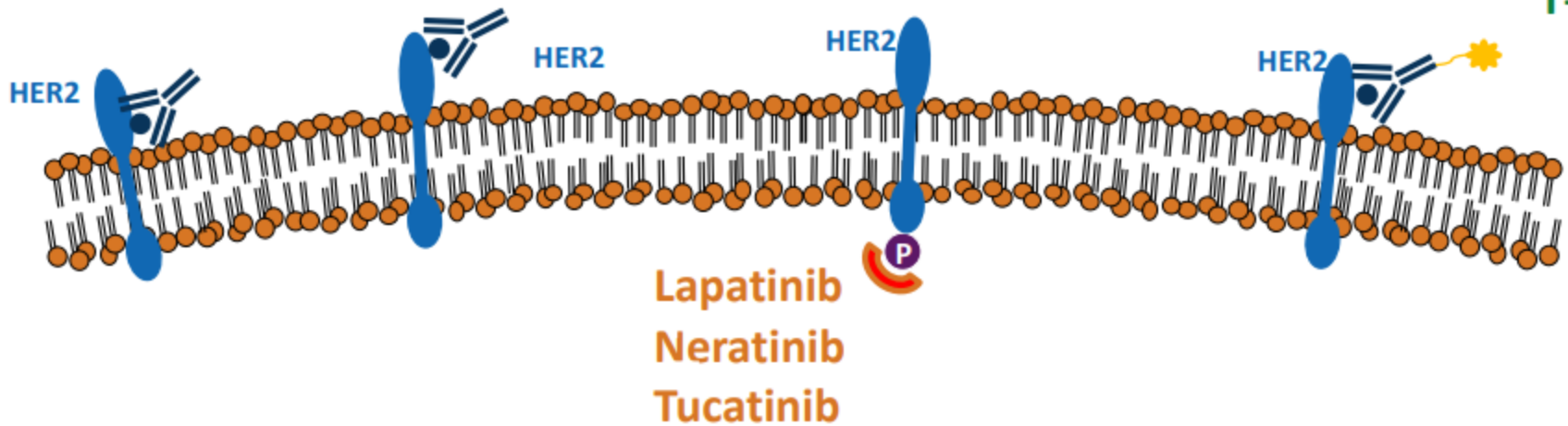
Targeted Therapies for HER2+ Breast Cancer

HER2-Targeted mAbs

Trastuzumab
Pertuzumab
Margetuximab

HER2-Targeted ADCs

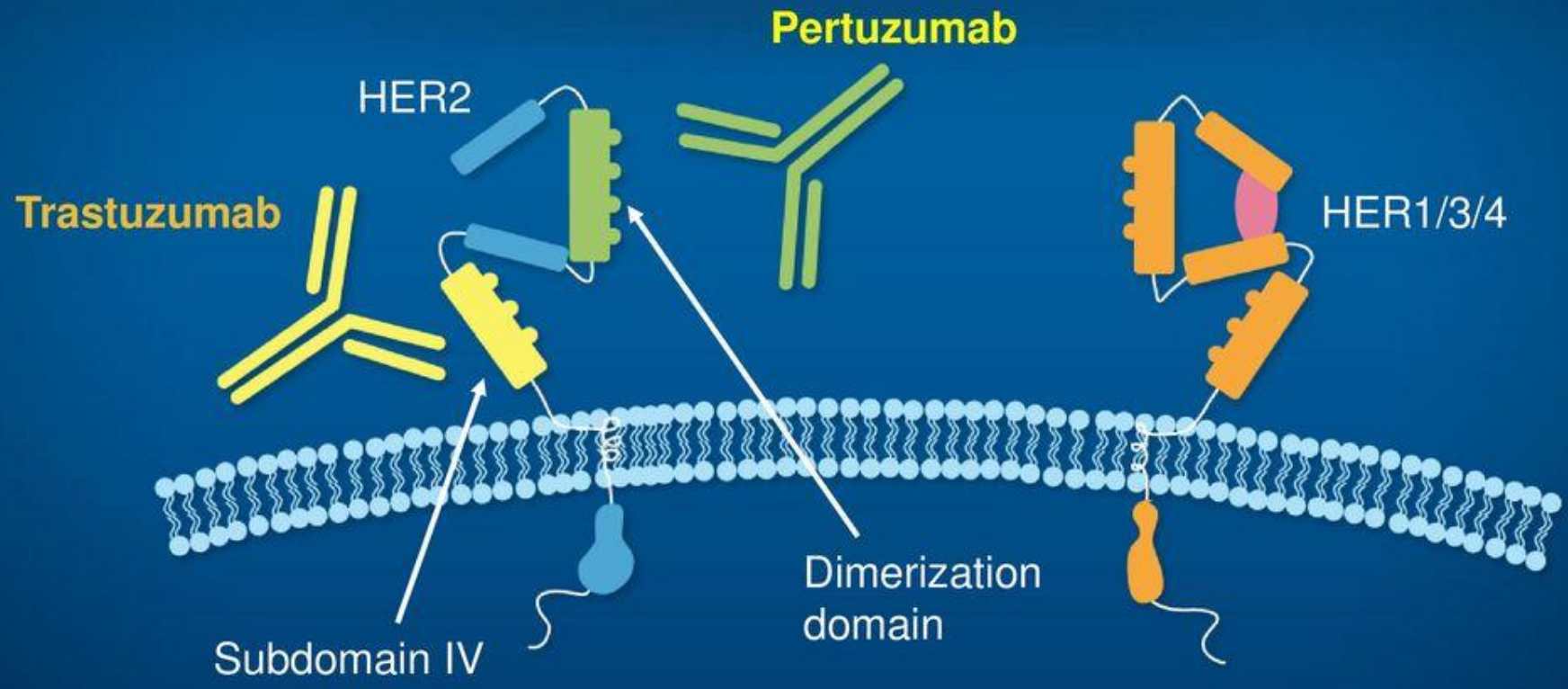
T-DM1
T-DXd



Lapatinib
Neratinib
Tucatinib

HER2-Targeted TKIs

Pertuzumab and Trastuzumab: Mechanisms of Action



Trastuzumab:

- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

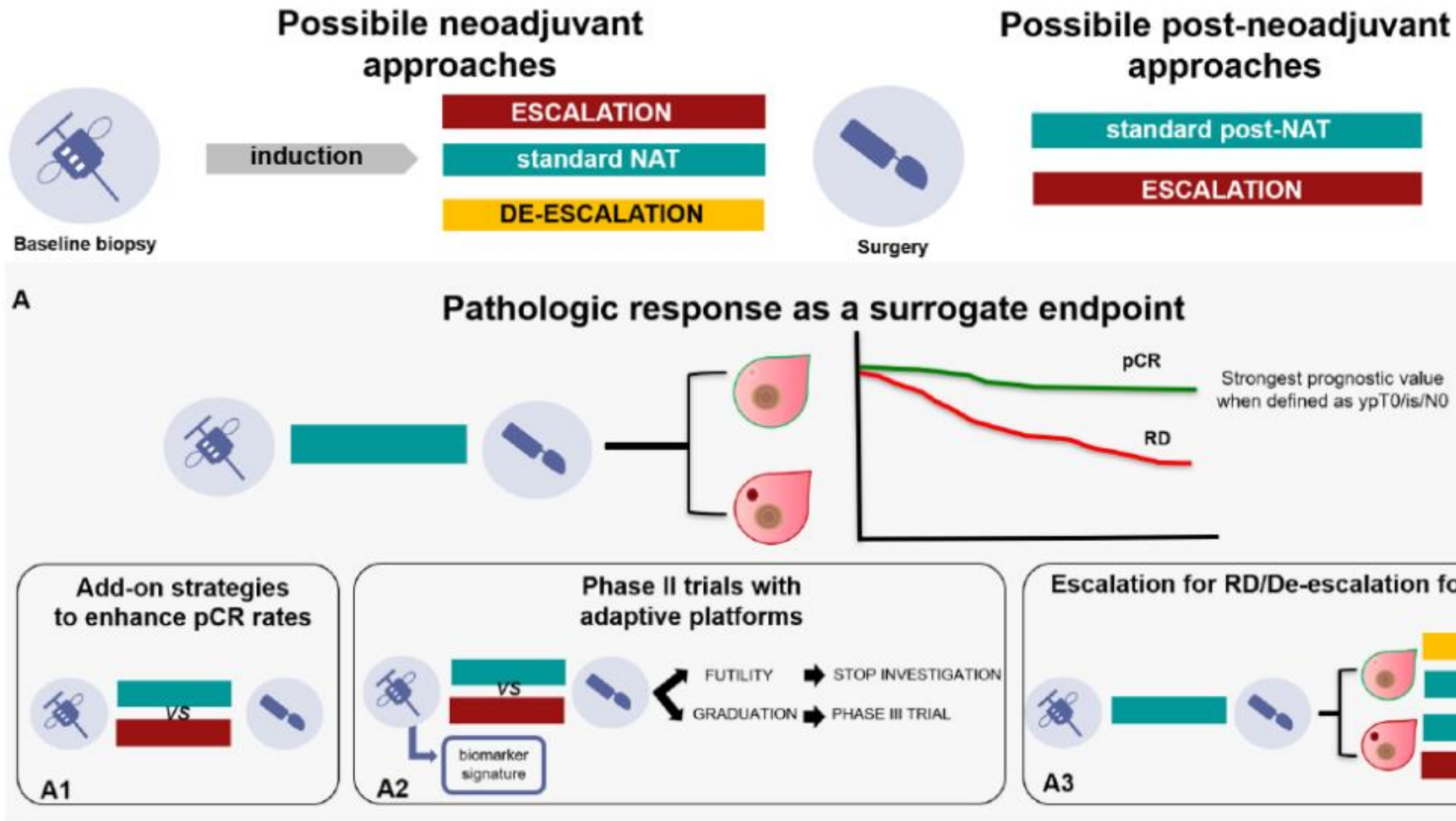
Pertuzumab:

- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC

ADCC = antibody-dependent cell-mediated cytotoxicity; ECD = extracellular domain

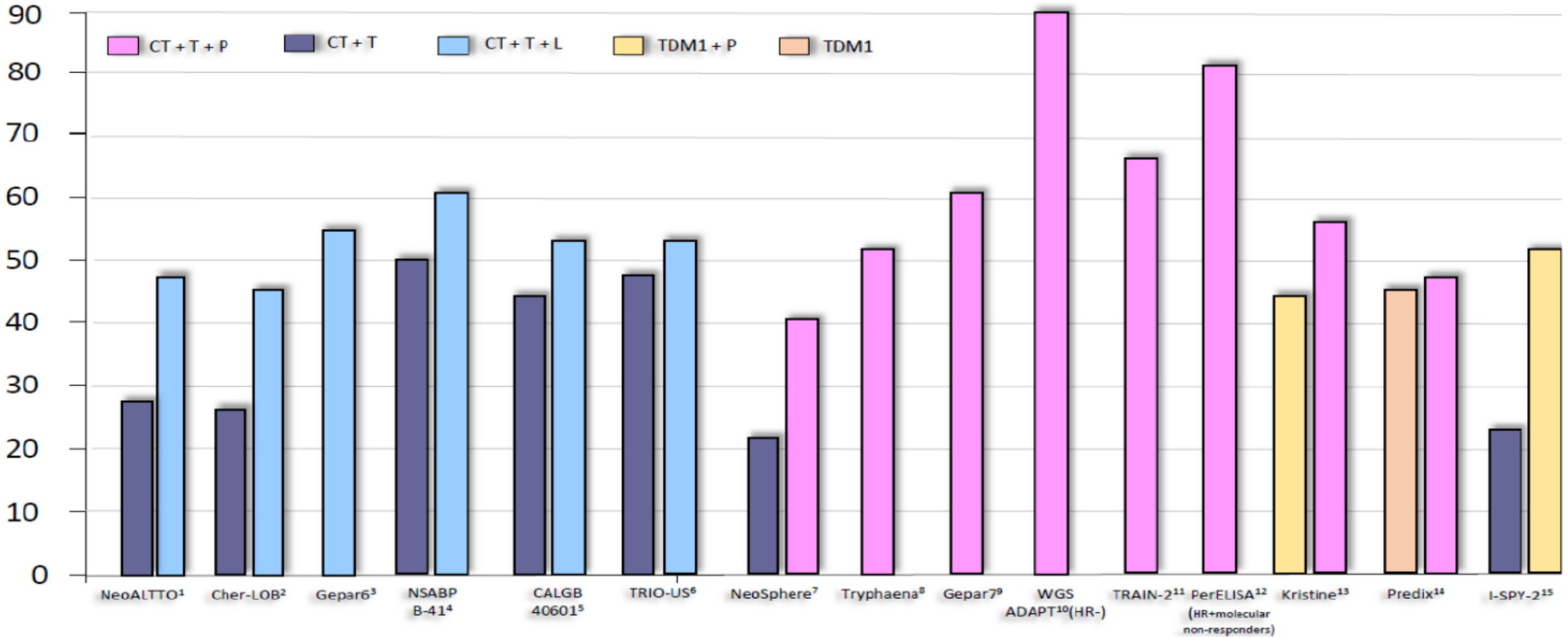
Adapted from Harbeck N et al. *Breast Care (Basel)* 2013;8(1):49-55.

Neoadjuvant platform to personalize treatment



Miglietta F, Dieci MV, Griguolo G, Guarneri V. Cancer Treat Rev 2021

Escalating neoadjuvant treatment: dual HER2 blockade



2021 ESMO congress

1. Baselga J. Lancet 2012; 2. Guarneri V. J Clin Oncol 2012; 3. von Minckwitz. Lancet Oncol 2014; 4. Robidoux A. Lancet Oncol 2013; 5. Carey L .ASCO 2013; 6. Hurvitz S SABCS 2013 7. Gianni L . Lancet Oncol 2012; 8. Schneeweiss A . Ann Oncol 2013 ; 9 Untch M. 10. Nitz UA Ann Oncol 2017; 11. Ramshorst MS The Lancet 2018; 13. 12. Guarneri V. Ann Oncol 2019; 13. Hurvitz SA The Lancet 2017; 14. Bergh J ASCO 2019; 15. press release

Adjuvant Trastuzumab

RCTs supporting the incorporation of trastuzumab to adjuvant chemotherapy

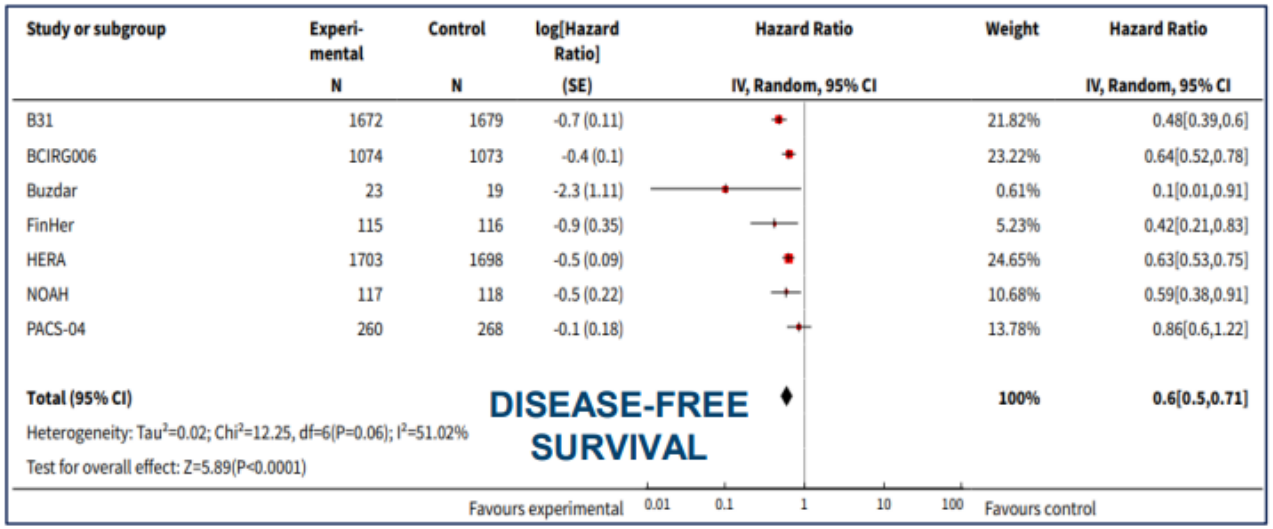
RCT	Population, n	Control arm	Experimental arm
NSABP B31 Romond et al, NEJM 2005	2102	CT (anthra-tax)	CT + Trastuzumab (qw) x 1 y
NCCTG N9831 Perez et al, JCO 2014	1944	CT (anthra-tax)	CT + Trastuzumab (qw) x 1 y
HERA Piccart-Gebhar et al, NEJM 2005	5081	CT (anthra+/-tax)	CT + Trastuzumab (q3w) x 1 y CT + Trastuzumab (q3w) x 2 y
BCIRG006 Slamon et al, NEJM 2011	3222	CT (anthra-tax)	CT (anthra-tax) + Trastuzumab (qw) → Trastuzumab (q3w) x 1 y CT (anthra-free) + Trastuzumab (qw) → Trastuzumab (q3w) x 1 y
FinHER Joensuu et al, NEJM 2006	232 (HER2+)	CT (anthra+/-tax)	CT + Trastuzumab (qw) x 9 w
PACS-04 Spielmann et al, JCO 2009	528	CT (anthra+/-tax)	CT (anthra+/-tax) + Trastuzumab (q3w) x 1 y

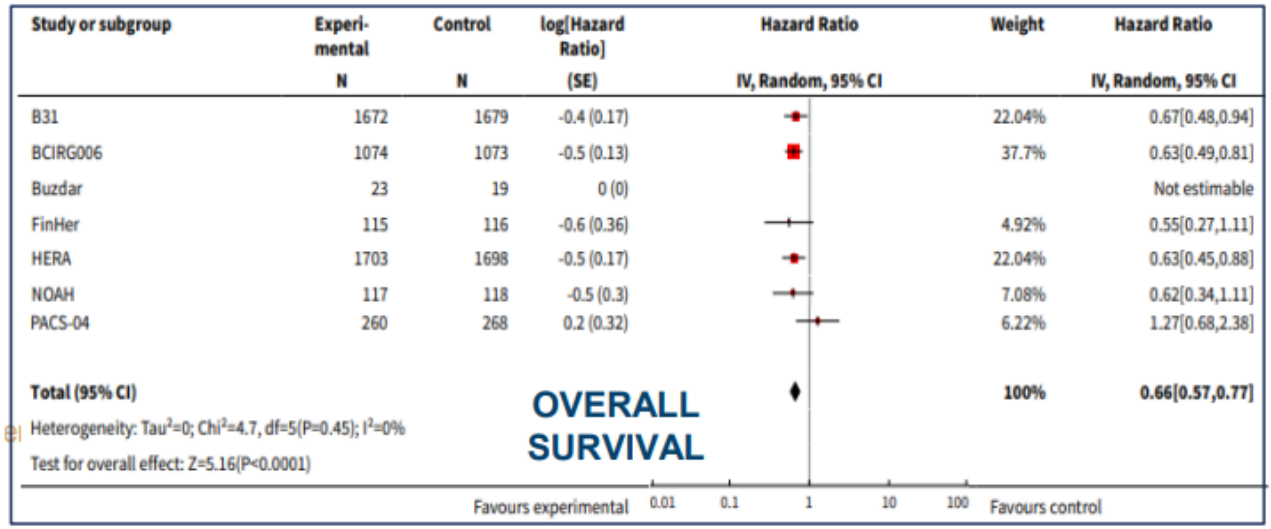
Node +/-

Node positive

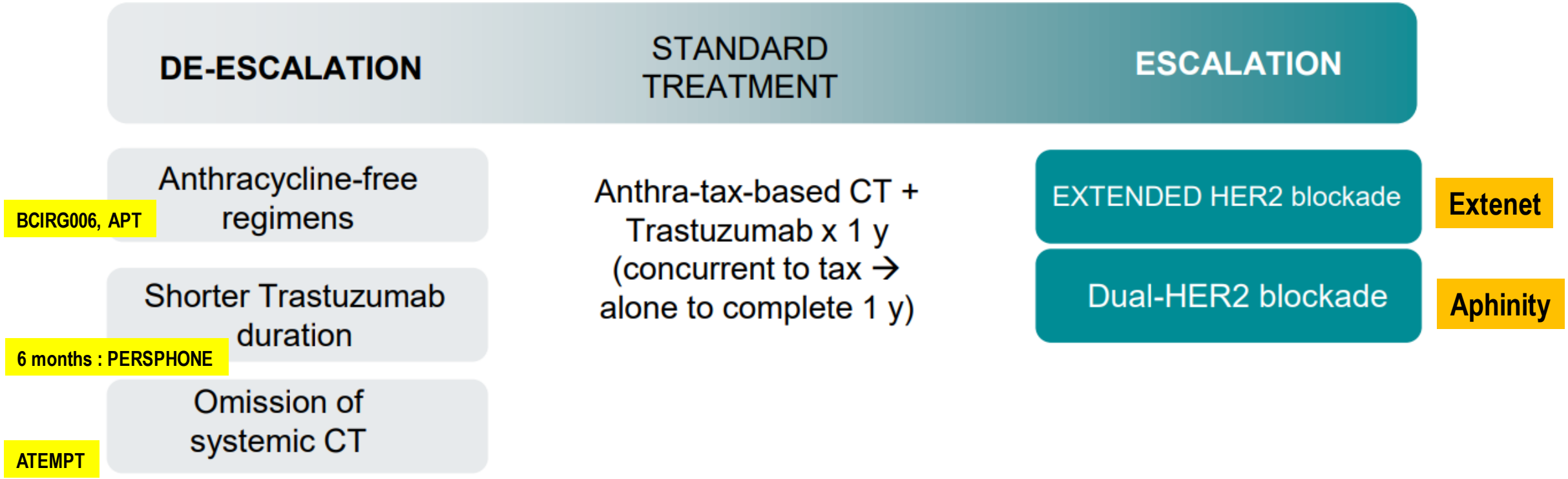
Node positive, >1 cm
ER + >2 cm

Moya et al, Cochrane Library, 2012





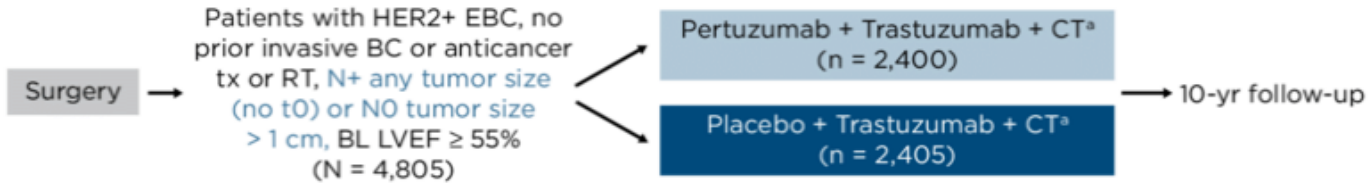
Personalizing adjuvant treatment



Escalating adjuvant therapy

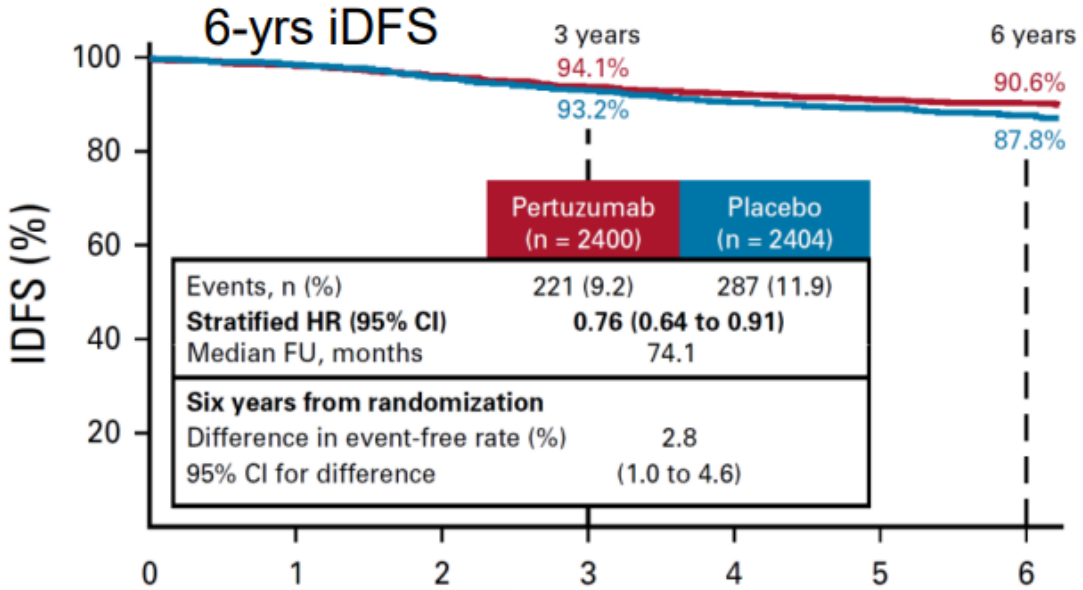
Dual HER2-blockade: Trastuzumab + Pertuzumab

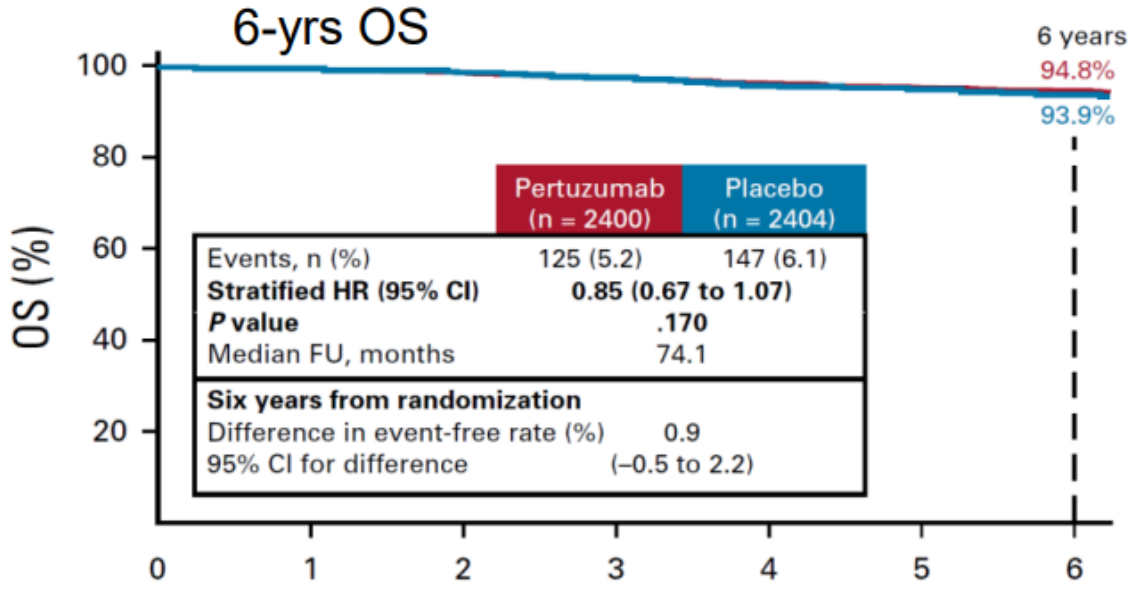
APHINITY trial



N0: 1799 (37%)
N1: 1807 (38%)
N>1: 1198 (25%)

Or node negative with tumors > 0.5 to ≤ 1 cm + at least 1 of following: histologic/nuclear grade 3; ER negative and PgR negative; aged < 35 yr. Node-negative enrollment capped after first 3,655 patients randomized.





Nodal status:
-N+: HR 0.72 (95% CI 0.59-0.87)
-N0: HR 1.02 (95% CI 0.69-1.56)

Hormone Receptor status
-Positive: HR 0.73 (95% CI 0.59-0.92)
-Negative: HR 0.83 (95% CI 0.63-1.10)

Piccart et al, JCO 2021, de Azambuja et al, ASCO 2021

Escalating post-neoadjuvant therapy

Selecting high-risk pts based on pathologic response

Post-neoadjuvant TDM1

KATHERINE trial

- **N= 1486**
- **Centrally confirmed HER2-positive breast cancer**
- **Residual invasive tumor in breast or axillary nodes after PCT including:**
  - **Minimum of 6 cycles of CT**
  - **Minimum of 9 weeks of T**

1:1R

T-DM1
3.6 mg/kg IV Q3W, 14 cycles

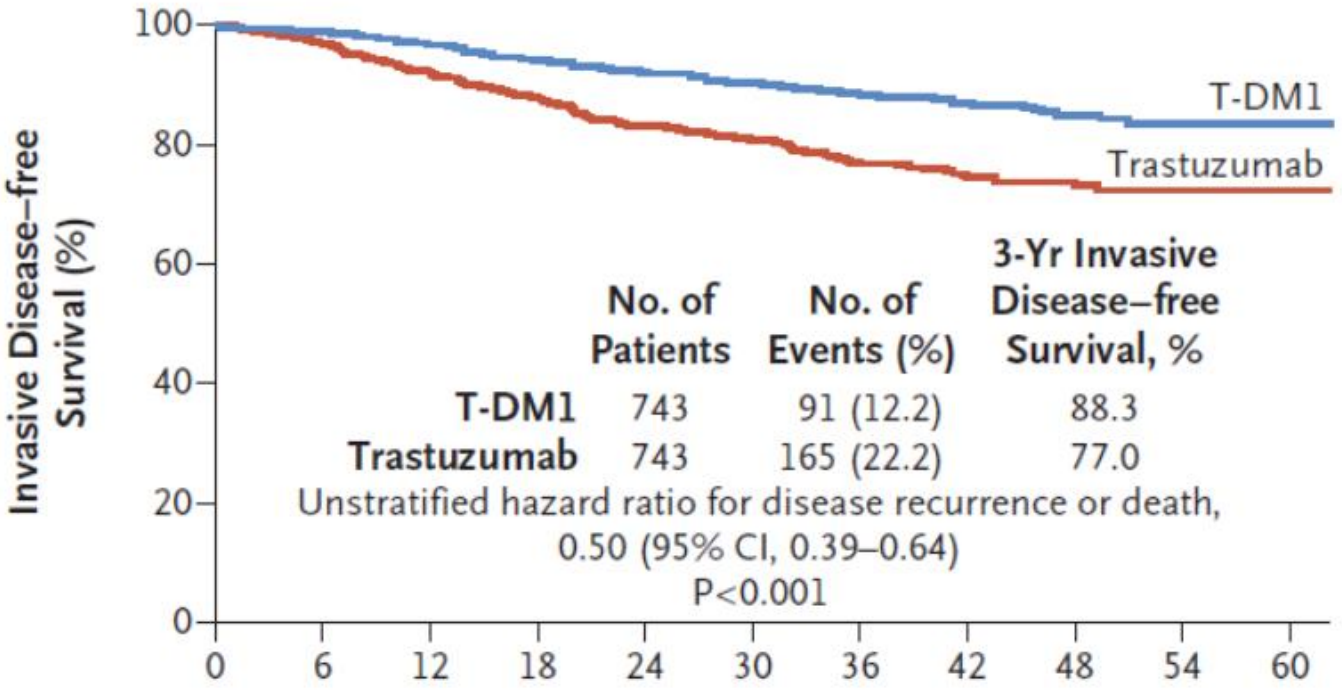
Trastuzumab
6 mg/kg IV Q3W, 14 cycles

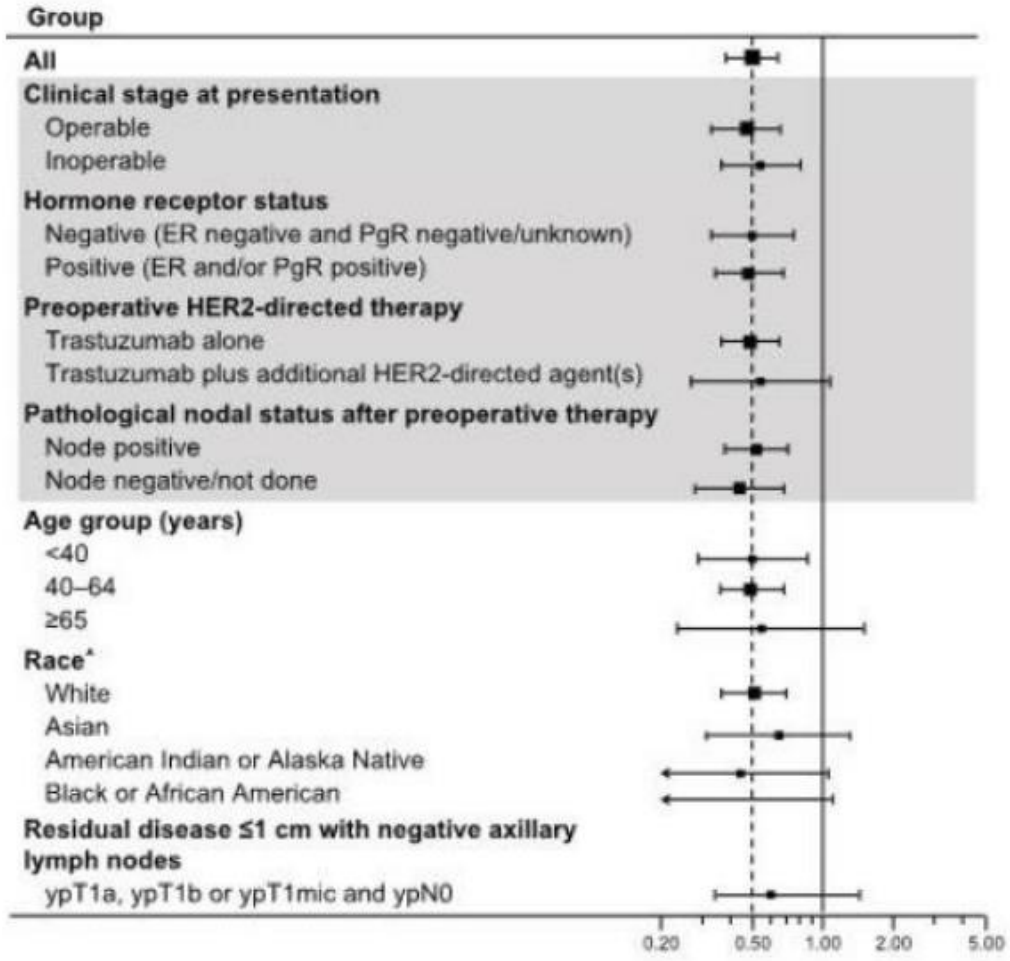
75% operable BC
72% HR+
Neoadjuvant therapy:
- **100% taxane + trastuzumab**
- **78% neoadjuvant anthracyclines**
- 18% neoadjuvant pertuzumab(+trastuzumab)

Escalating post-neoadjuvant therapy

Selecting high-risk pts based on pathologic response

Post-neoadjuvant TDM1





von Minckwitz G, et al. NEJM 2018

cT1a-b and cN0

cT1c and cN0

≥cT2 and/or cN+

enrolled both in the APT and KATHERINE trials
→ discussion on a single-patient basis

UPFRONT SURGERY

≤pT1c and N0

ADJUVANT **paclitaxel + trastuzumab (APT like)**

≥pT2 and/or N+

ADJUVANT CT + Trastuzumab (+ Pertuzumab in N+ or HR-)

Careful assessment of the risk/benefit ratio of extended NERATINIB in N+/HR+

NEOADJUVANT TREAMENT

***CT* + trastuzumab**

CT + trastuzumab+pertuzumab

ypT0/is ypN0

RESIDUAL DISEASE

TRASTUZUMAB (to complete 1 y)

TDM1 (to complete 1 y)

Ongoing clinical trials of de-escalated treatment for pts with pCR

No data on the possibile benefit of including pertuzumab if administered neoadjuvantly

Standard of Care for *HER2*+ Advanced Breast Cancer

First Line

Trastuzumab + pertuzumab + taxane

CLEOPATRA

Second Line

Trastuzumab emtansine (T-DM1)

EMILIA

Trastuzumab deruxtecan (T-DXd)

Destiny 03 trial

Dec 2019-Dec 2020

Third Line

Trastuzumab + chemo
Lapatinib + capecitabine
Trastuzumab + lapatinib

EGF104900, EGF100151

Trastuzumab deruxtecan (T-DXd)

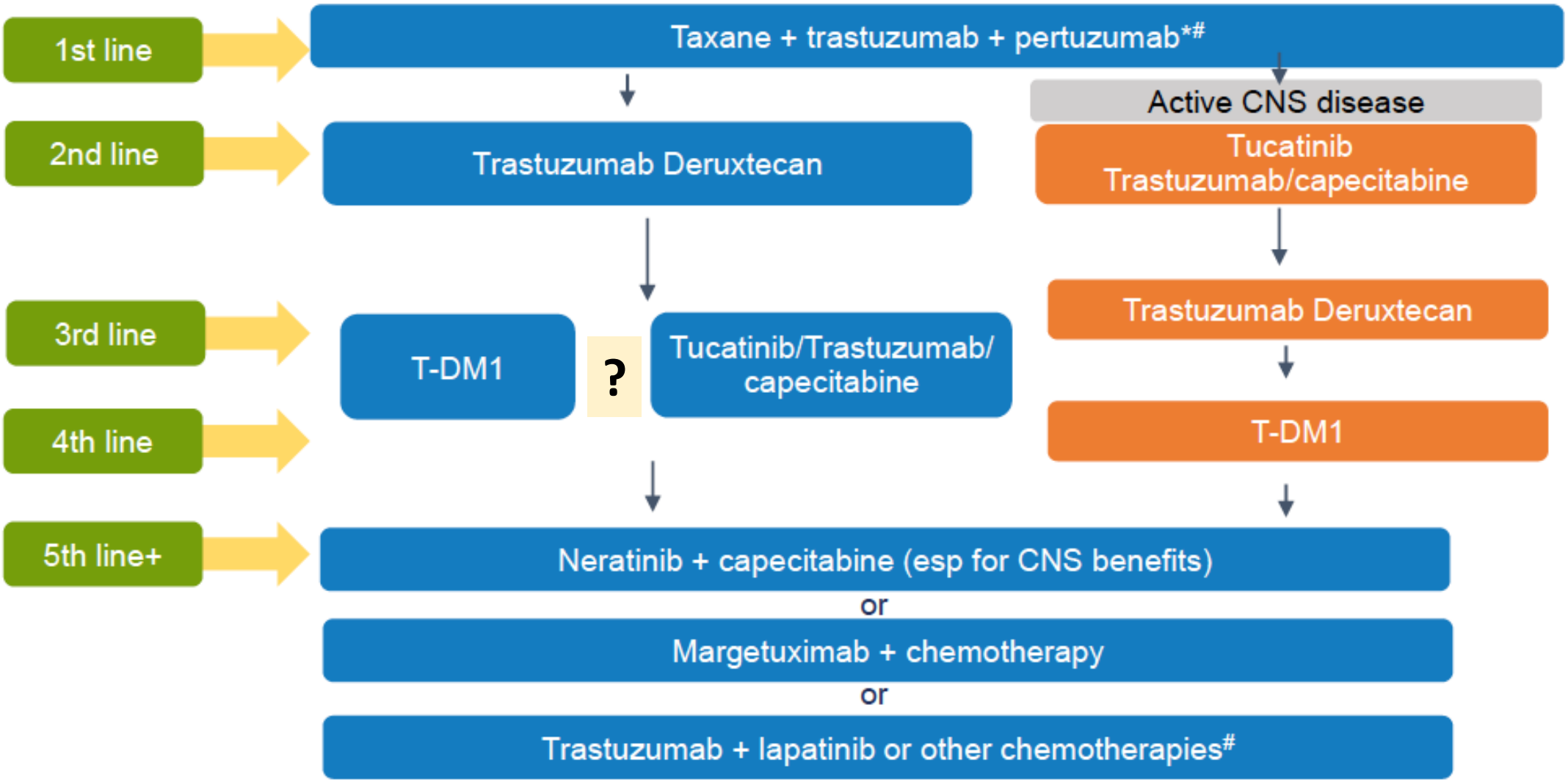
Neratinib + capecitabine

Tucatinib + trastuzumab + capecitabine

Margetuximab + chemo

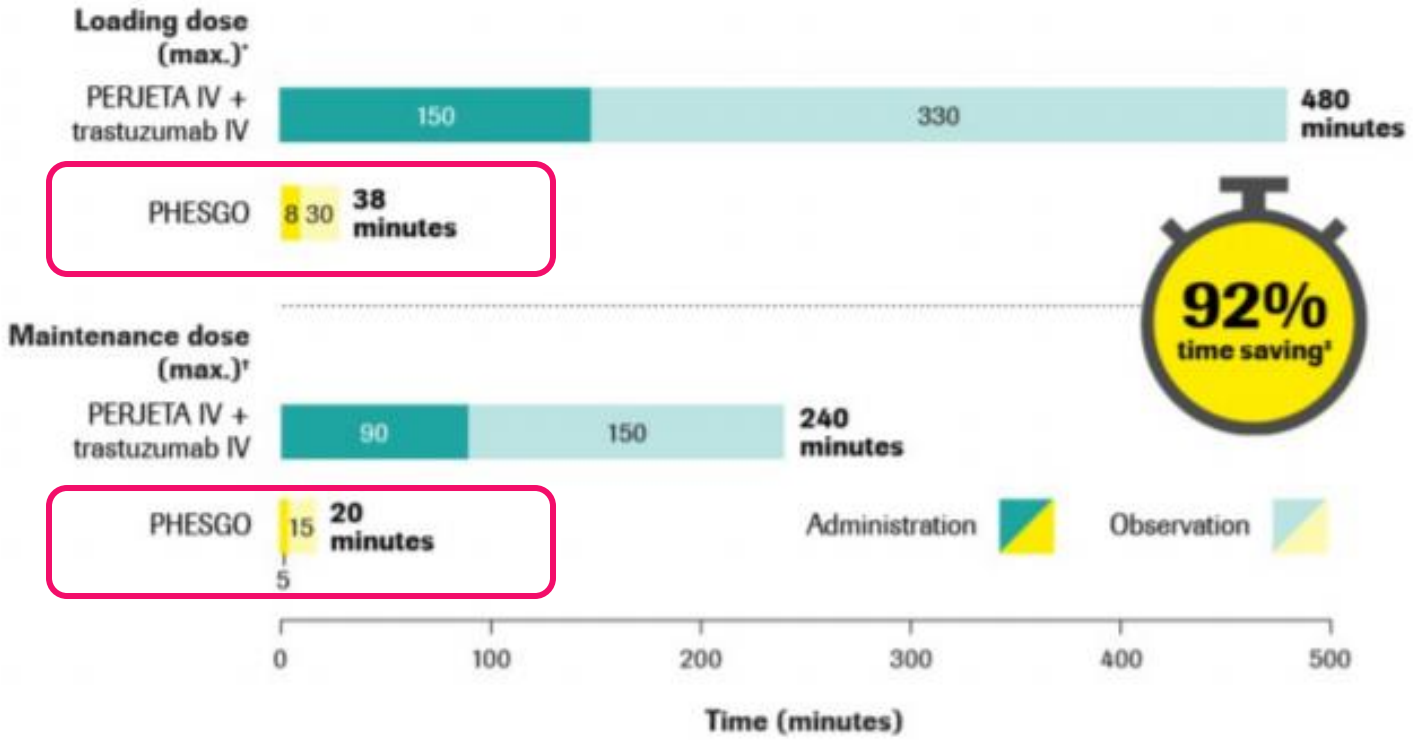
Rimawi M et al SABC 2020; Swain S et al NEJM 2015; Verma S et al 2012; Geyer C et al NEJM 2006; Blackwell K et al JCO 2010

A 2022 Approach to Therapy for Metastatic HER2+ BC:



*AI+TP in select cases and for maintenance in ER+ disease; # endocrine Tx + HER2 therapy at clinically appropriate points for ER+ MBC

Administration and observation times for PHESGO vs PERJETA IV and trastuzumab IV[3]



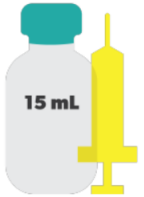
Adapted from Roche. Data on File. M-GB-00002430.

*Observation times of the loading dose of PERJETA IV and trastuzumab IV can range from 300–330 minutes.

†Administration times of the maintenance dose of PERJETA IV and trastuzumab IV can range from 60–90 minutes; Observation times of the maintenance dose of PERJETA IV and trastuzumab IV can range from 120–150 minutes.

‡The total percentage time saving achieved between PHESGO and PERJETA IV and trastuzumab IV can range from 89% to 92%.

Loading (initial) dose

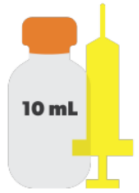


1200 mg pertuzumab, 600 mg trastuzumab, 30,000 units hyaluronidase per 15 mL supplied in a **single-dose, ready-to-use vial**

Administer subcutaneously over approximately **8 minutes** at a rate of no more than 2 mL/min

Observe for hypersensitivity or administration-related reactions: **minimum of 30 minutes***

Maintenance dose



600 mg pertuzumab, 600 mg trastuzumab, 20,000 units hyaluronidase per 10 mL supplied in a **single-dose, ready-to-use vial**

Administer subcutaneously over approximately **5 minutes** at a rate of no more than 2 mL/min

Observe for hypersensitivity or administration-related reactions: **minimum of 15 minutes***

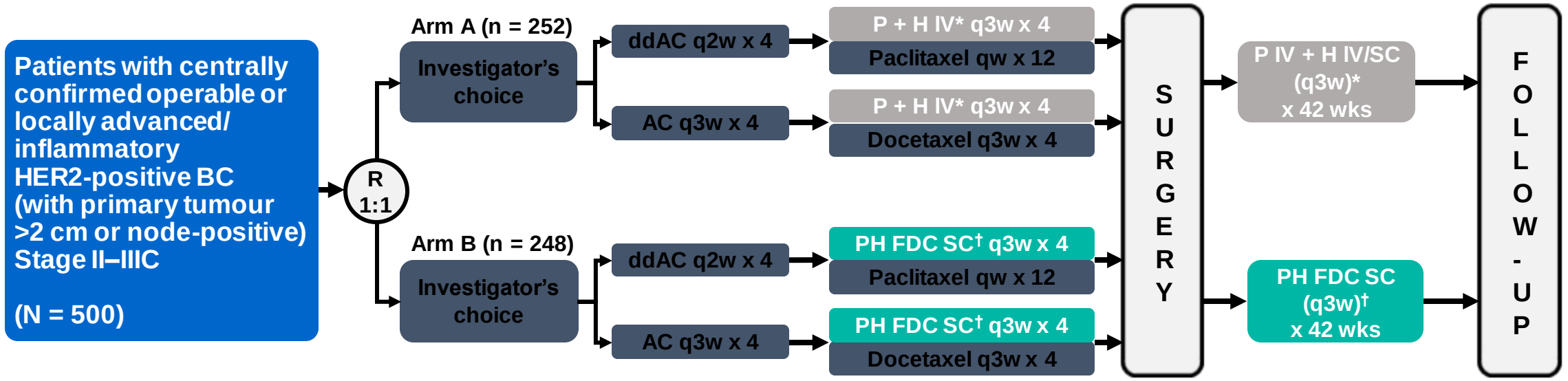
What are the differences between PH FDC SC and Herceptin SC?

	Herceptin SC	PH FDC SC
Pharmaceutical form	Ready-to-use vial for manual injection[1–3]	
Delivery excipient	rHuPH20 (2000 U/mL)[1,2]	
Loading dose*	Fixed dose: 600 mg Herceptin SC (5 mL)[1]	Fixed dose: 1200 mg pertuzumab and 600 mg trastuzumab (15 mL) SC[2,3]
Administration time	Less than 5 minutes[1]	8 minutes
Observation time	6 hours	30 minutes
Maintenance dose*	Fixed dose: 600 mg Herceptin SC (5 mL)[1]	Fixed dose: 600 mg pertuzumab and 600 mg trastuzumab (10 mL) SC[2,3]
Administration time	Less than 5 minutes[1]	5 minutes
Observation time	2 hours	15 minutes
Key trials	HannaH,[4] PrefHer,[5] SafeHer,[6] MetaPHER[7]	BO30185,[8] FeDeriCa,[3] PHranceSCa[9]

* Administration/observation times vary according to local labels.
PH FDC SC, PERJETA–Herceptin fixed-dose combination for subcutaneous use; rHUPH20, recombinant human hyaluronidase; q3w, every 3 weeks; SC, subcutaneous.

1. Herceptin SC SmPC 2019; 2. Roche, Data on file. WO40324 Protocol Version 2 – 2018; 3. Tan AR, *et al*. SABCS 2019 (Abstract PD4-07); 4. Ismael G, *et al*. *Lancet Oncol* 2012; **13**:869–878; 5. Pivot X, *et al*. *Ann Oncol* 2014; **25**:1979–1987; 6. Gligorov J, *et al*. *Eur J Cancer* 2017; **82**:237–246; 7. Kümmel S, *et al*. ESMO 2018 (Abstract 323P and poster presentation); 8. Kirschbrown WP, *et al*. *J Clin Pharmacol* 2019; **59**:702–716; 9. https://clinicaltrials.gov/ct2/show/NCT03674112 (Accessed December 2019).

FeDeriCa is a Phase III study assessing the PK, efficacy, and safety of PH FDC SC vs. P + H IV



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

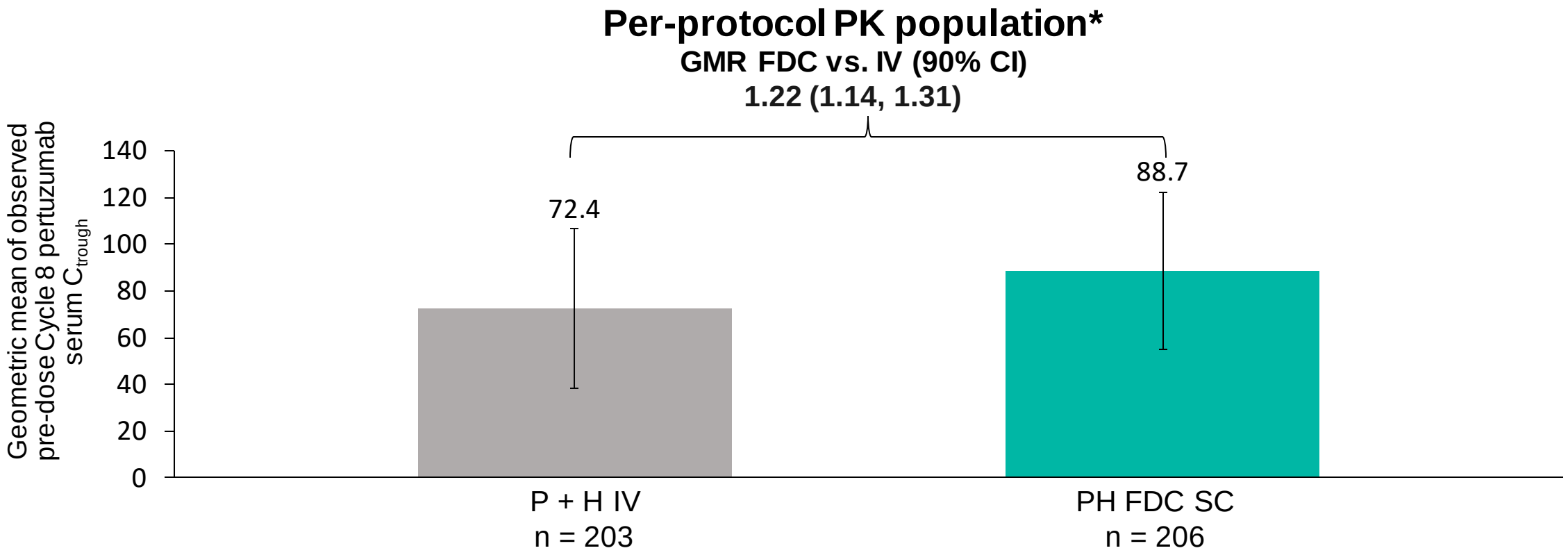
Primary endpoint: Non-inferiority of Cycle 7 (pre-dose Cycle 8) pertuzumab serum C_{trough}

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.
† PH FDC SC 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; PH FDC SC, PERJETA–Herceptin fixed-dose combination for subcutaneous use; PK, pharmacokinetics; qw, every week; qxw, every x weeks; SC, subcutaneous; tpCR, total pathological complete response (ypT0/is ypN0).

Tan AR, *et al*. SABCS 2019 (Abstract PD4-07).

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

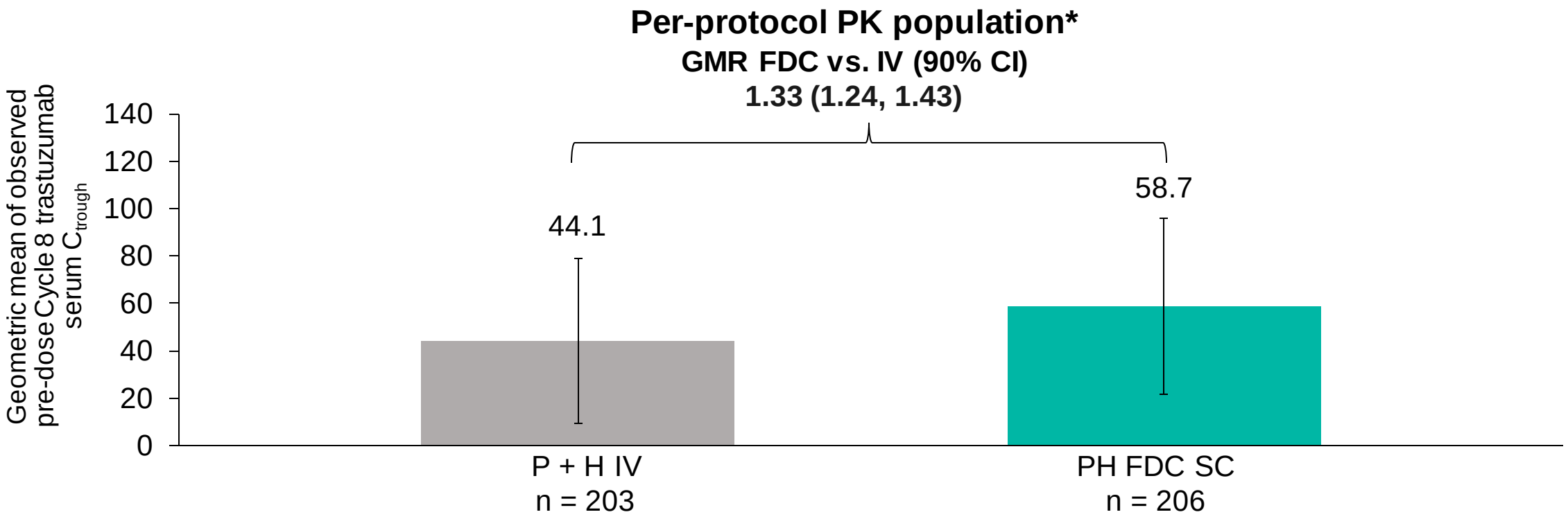


Lower limit of the 90% CI for pertuzumab serum C_{trough} GMR exceeded the non-inferiority margin of 0.8

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

Tan AR, *et al*. SABCS 2019 (Abstract PD4-07).

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



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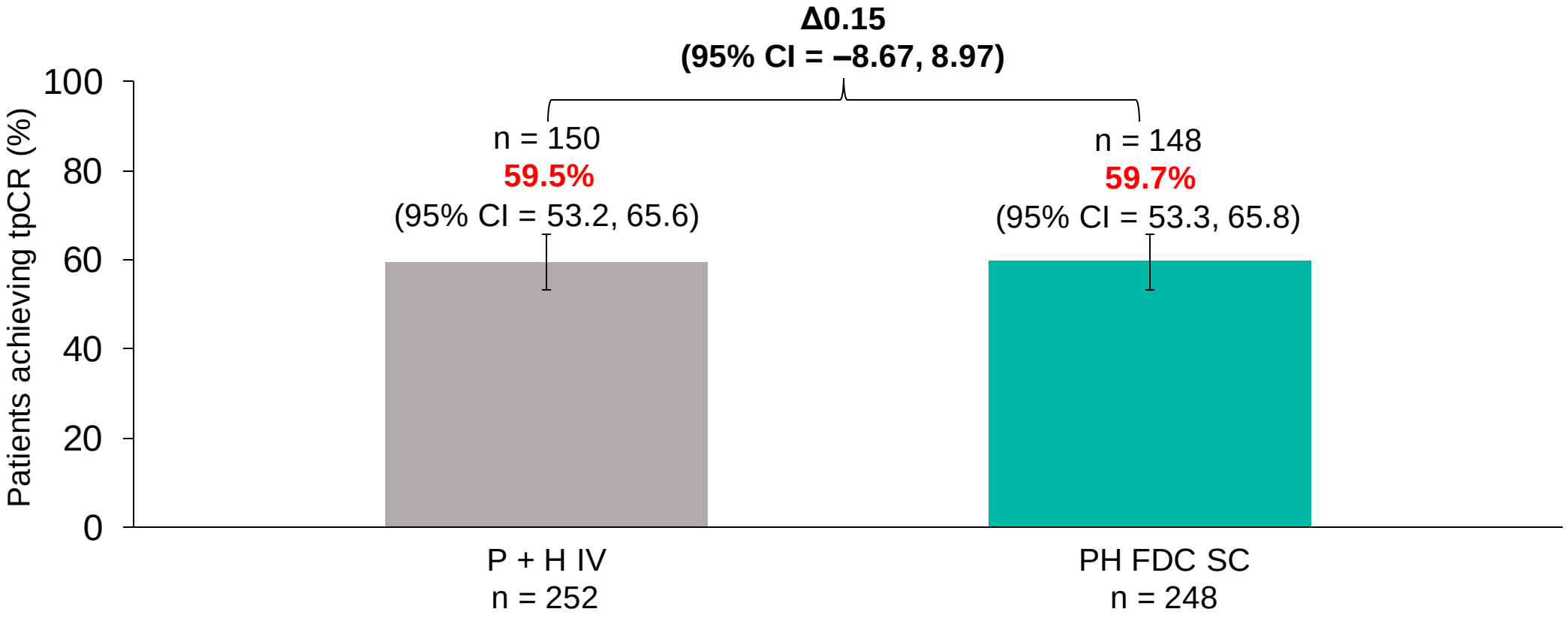
Tan AR, *et al*. SABCS 2019 (Abstract PD4-07).

PH FDC SC 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]

H, Herceptin; IV, intravenous; P, PERJETA;
PH FDC SC, PERJETA–Herceptin fixed-dose combination for subcutaneous use;
tpCR, total pathological complete response (ypT0/isypN0).

1. Tan AR, *et al*. SABCS 2019 (Abstract PD4-07);
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.

Most common AEs were balanced between treatment arms[1]

AEs (occurring in ≥30% of patients) No. of patients, n (%)*	P + H IV n = 252	PH FDC SC n = 248
Alopecia	177 (70.2)	191 (77.0)
Nausea	152 (60.3)	146 (58.9)
Diarrhoea	139 (55.2)	145 (58.5)
Anaemia	103 (40.9)	84 (33.9)
Asthenia	76 (30.2)	70 (28.2)

Incidences of AEs were consistent with other studies that included PERJETA–Herceptin + chemotherapy[2–4]

* Multiple occurrences of the same AE in an individual are counted only once.
AE, adverse event; H, Herceptin; IV, intravenous; P, PERJETA;
PH FDC SC, PERJETA–Herceptin fixed-dose combination for subcutaneous use.

1. Tan AR, *et al*. SABCS 2019 (Abstract PD4-07); 2. Gianni L, *et al*. *Lancet Oncol* 2012; **13**:25–32;
3. Schneeweiss A, *et al*. *Ann Oncol* 2013; **24**:2278–2284; 4. Swain SM, *et al*. *Ann Oncol* 2018; **29**:646–653.

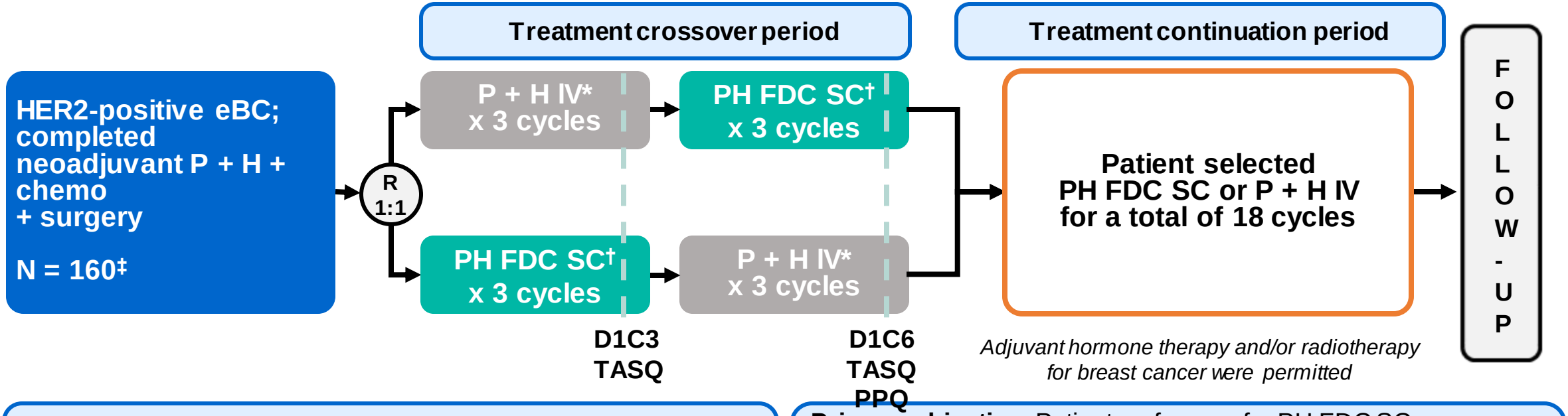
There was no meaningful difference in cardiac safety between treatment arms

No. patients, n (%)	P + H IV n = 252	PH FDC SC n = 248
Primary cardiac event[1]	0	2 (0.8)
Heart failure (NYHA III/IV) and significant LVEF decline*	0	1 (0.4)
Cardiac death (definite or probable)	0	1 (0.4)[§]
Secondary cardiac event[†,1]	9 (3.6)	4 (1.6)
Identified by initial LVEF assessments	9 (3.6)	4 (1.6)
Confirmed by second LVEF assessment	2 (0.8)	1 (0.4)
LVEF declines[2]		
≥1 LVEF significant LVEF drop[‡]	7 (2.8)	5 (2.0)
Asymptomatic LVEF decline requiring treatment or leading to discontinuation of anti-HER2 treatment	10 (4.0)	5 (2.0)

* Significant LVEF decline defined as a drop in LVEF of ≥10 percentage points from baseline and to <50%.
[†] Secondary cardiac events defined as asymptomatic or mildly symptomatic significant LVEF declines by initial assessment or confirmed by second assessment.
[‡] Defined by a drop in LVEF of ≥10 percentage points from baseline and to <50%.
[§] One cardiac death occurred after Cycle 2 (prior to start of anti-HER2 treatment) in an 81-year-old patient.
H, Herceptin; IV, intravenous; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; P, PERJETA; PH FDC SC, PERJETA–Herceptin fixed-dose combination for subcutaneous use.

1. Tan AR, *et al*. SABCS 2019 (Abstract PD4-07);
2. Roche, Data on file (FeDeriCa Primary CSR).

PHranceSCa is a Phase II, open-label, randomised cross-over study evaluating patient preference for PH FDC SC vs. PH IV



Stratification factors:

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

Primary objective: Patient preference for PH FDC SC

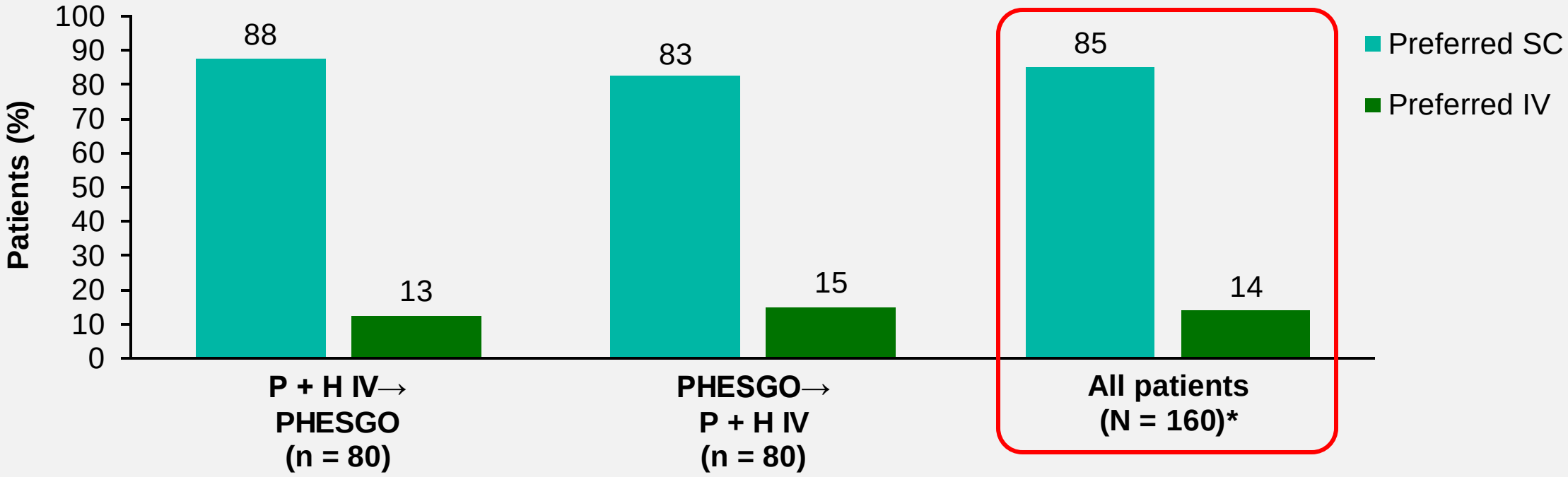
Key secondary objectives: Patient satisfaction; patients' choice of formulation for the continuation period; HRQoL, HCP perception on time/resource, safety and tolerability (including safety of switching from SC to IV formulations and vice-versa), efficacy

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.
† PH FDC SC 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; PH FDC SC, PERJETA–Herceptin fixed-dose combination for subcutaneous use; PPQ, Patient Preference Questionnaire; q3w, every 3 weeks; SC, subcutaneous; TASQ, Therapy Administration Satisfaction Questionnaire.

https://clinicaltrials.gov/ct2/show/NCT03674112 (Accessed December 2019); O'Shaughnessy J, *et al.* ESMO Breast 2020 (Abstract 800).

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. Roche, data on file (PHranceSCa primary analysis CSR);
2. Pivot X, *et al. Ann Oncol* 2014; **25:**1979–1987;
3. Rummel M, *et al. Ann Oncol* 2017; **28:**836–842.

No cardiac safety concerns were identified during the crossover period at the interim analysis[1,2]

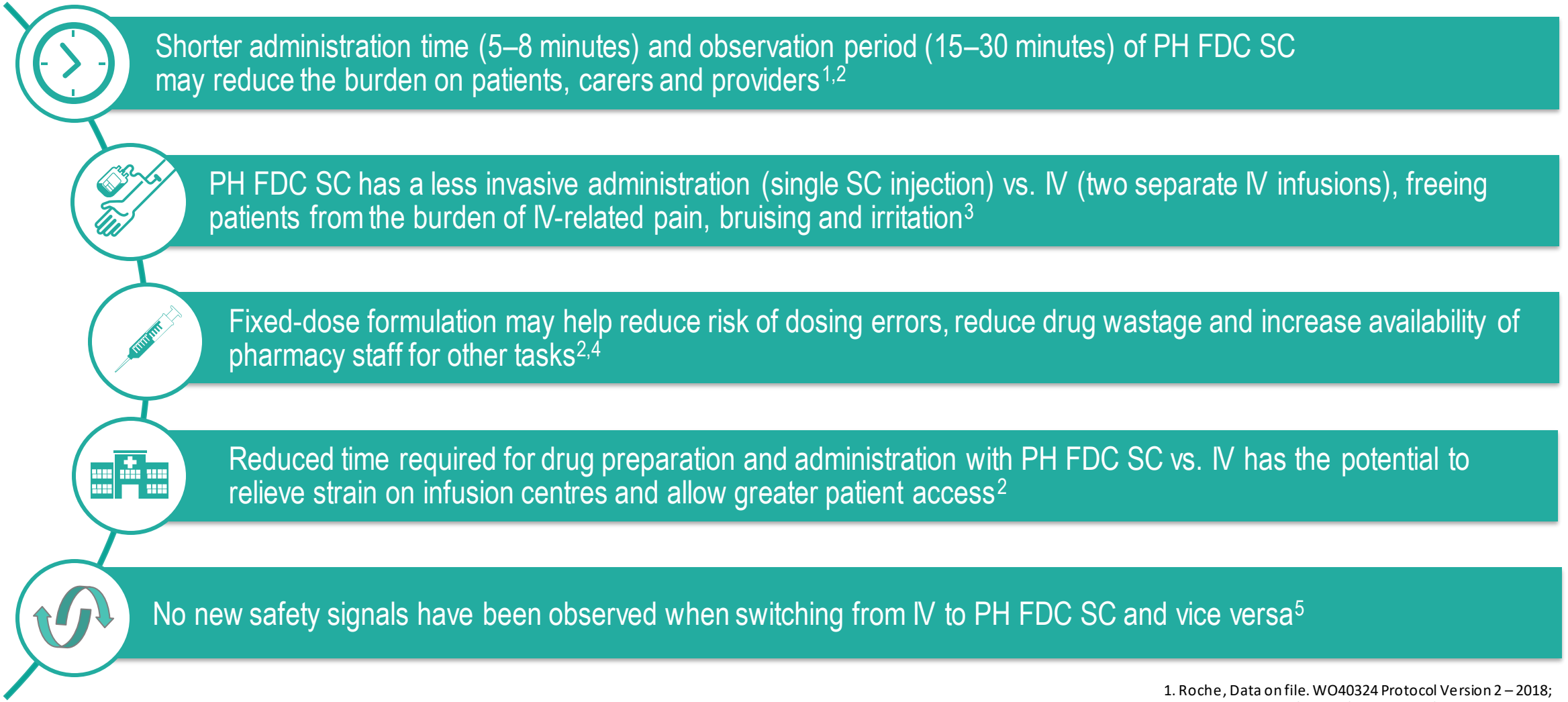
Number of patients n, (%)	P + H IV→ PH FDC SC		PH FDC SC→ P + H IV		All patients (N = 116)
	P + H IV Cycles 1–3 (n = 56)	PH FDC SC Cycles 4–6 (n = 33)	PH FDC SC Cycles 1–3 (n = 60)	P + H IV Cycles 4–6 (n = 32)	
Cardiac disorders					
Total number of patients with at least one	0	1 (3.0)	0	0	1 (0.9)
AE	0	1 (3.0)	0	0	1 (0.9)
Arrythmia	0	1	0	0	1
Total number of events					

- **One grade 1 arrhythmia event occurred during treatment with PH FDC SC in the P + H IV→PH FDC SC arm; this was unrelated to the HER2-directed therapy and did not lead to treatment discontinuation**
- **Four patients experienced symptomatic LVD during the crossover period (1.1% PH FDC SC vs. 3.4% P + H IV)***

* Two Grade 3 events occurred, one during P + H IV treatment and one during PH FDC SC treatment.
AE, adverse event; H, Herceptin; IV, intravenous; LVD, left ventricular disease; P, PERJETA;
PH FDC SC, PERJETA–Herceptin fixed-dose combination for subcutaneous use.

1. O'Shaughnessy J, *et al*. ESMO Breast 2020 (Abstract 80O);
2. Roche, data on file (PHranceSCa interim analysis CSR).

Clinical Value: PH FDC SC could provide benefits in costs, time and reduction of patient/HCP burden



IV, intravenous; PH FDC SC, PERJETA–Herceptin fixed-dose combination for subcutaneous use; SC, subcutaneous.

1. Roche, Data on file. WO40324 Protocol Version 2 – 2018;
2. De Cock E, *et al*. *Cancer Med* 2016; **5**:389–397;
3. Pivot X, *et al*. *Ann Oncol* 2014; **25**:1979–1987;
4. De Cock E, *et al*. EBCC (Abstract 42 and poster 033);
5. O'Shaughnessy J, *et al*. ESMO Breast 2020 (Abstract 80O).

Conclusion

- **Adjuvant anti-HER2 therapy** improves DFS and OS in EBC with HER2 overexpression
- **Dual anti-HER2 blockade** improves DFS in high-risk EBC with HER2 overexpression
- **Dual anti-HER2 blockade** is a standard treatment of 1st line MBC, HER2 overexpression
- **Phesgo SC** supported by clinical evidence is an alternative drug of dual anti HER2 that provides benefits in costs, time, and reduction of patient/HCP burden


THANK YOU