Transform the journey for your HER2+ Breast Cancer patients

Dr Renu Mishra

Disclaimers

- The Content in this presentation is intended for healthcare professionals in India only. The medical information in this presentation is provided as an information resource only and is not to be used or relied on for any diagnostic or treatment purposes
- Roche India does not promote or support the use of medications manufactured by it in off label indications. For specific information regarding various therapeutic agents, including Roche products, please refer to the approved full prescribing information
- If a patient becomes pregnant while receiving pertuzumab and/or trastuzumab / phesgo, or within 7 months following the last dose of pertuzumab and/or trastuzumab, please report this immediately to your local Roche Adverse Event Line
- Additional information will be requested during a pertuzumab- and/or trastuzumab-exposed pregnancy and the first year of the infant's life. This will enable Roche to better understand the safety of pertuzumab and trastuzumab and to provide appropriate information to health authorities, healthcare providers and patients
- All suspected Adverse Event / Special Situations and Other Case Type Reports* / Product Complaints associated with the use of a Roche medicinal product please report the same to india.drugsafety@roche.com

PERJETA–Herceptin has transformed the treatment landscape and is the standard of care for patients with HER2-positive BC

Setting	Neoadjuvant (eBC at high risk of recurrence)[1,2]	Adjuvant (eBC at high risk of recurrence)[1,2]	Metastatic (1L mBC)[1,2]
Pivotal study	NeoSphere[3]	APHINITY[7]	CLEOPATRA[10,11]
Key findings	• Addition of P to H + chemo significantly improved bpCR rates from 31% to 49% compared with H + chemo alone[3]	• Addition of P to H + chemo reduced the risk of recurrence or death by 23% compared with H + chemo + pla[7] • In patients with N-positive eBC, PH + chemo reduced risk of recurrence or death by 28% vs. H + chemo + pla[8]	• Addition of P to H + chemo significantly increased median PFS from 12.4 months to 18.5 months vs. H + chemo + pla[10] • Median OS was also significantly increased in the PH + chemo arm (56.5 months) vs. H + chemo + pla arm (40.8)[11]
Additional supporting studies	TRYPHAENA,[4] BERENICE,[5] PEONY[6]	BERENICE[9*]	PUFFIN,[12] PERUSE[13]

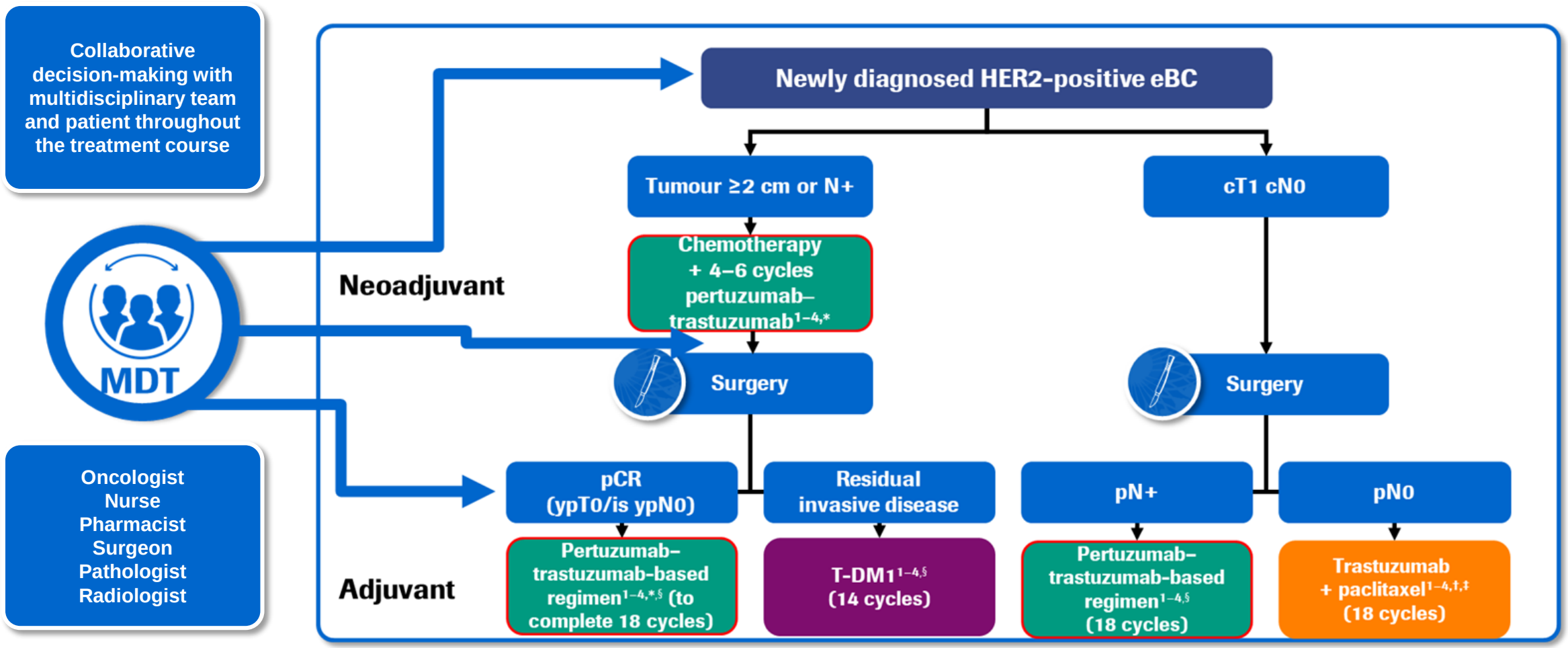
PERJETA–Herceptin + chemotherapy is approved[1,2] and recognised by international guidelines[14–18] as the standard of care for patients with HER2-positive BC

* No BERENICE data yet available. 1L, first-line; BC, breast cancer; bpCR, breast pathological complete response (ypT0/is); chemo, chemotherapy; eBC, early breast cancer; H, Herceptin; mBC, metastatic breast cancer; N, node; P, PERJETA; pla, placebo; PFS, progression-free survival; OS, overall survival.

1. PERJETA SmPC 2019; 2. PERJETA PI 2019; 3. Gianni L, *et al*. *Lancet Oncol* 2012;**13**:25–32; 4. Schneeweiss A, *et al*. *Ann Oncol* 2013; **24**:2278–2284; 5. Swain SM, *et al*. *Ann Oncol* 2018; **29**:646–653; 6. Shao Z, *et al*. *JAMA Oncol* 2019 [Epub ahead of print]; 7. von Minckwitz G, *et al*. *N Engl J Med* 2017; **377**:122–131 (suppl info); 8. Piccart M, *et al*. SABCS 2019 (Abstract GS1-04); 9. Dang C, *et al*. SABCS 2017 (Abstract P5-20-04); 10. Baselga J, *et al*. *N Engl J Med* 2012; **366**:109–119; 11. Swain SM, *et al*. *N Engl J Med* 2015; **372**:724–734; 12. Xu B, *et al*. ASCO 2019 (Abstract 1026); 13. Bachelot *et al* . *Ann Oncol* 2019; **30**:766–773; 14. AGO Breast Cancer Guidelines 2019; 15. NCCN Breast Cancer Guidelines – Version 5. 2020; 16. Cardoso F, *et al*. *Ann Oncol* 2018; **29**:1634–1657; 17. Cardoso F, *et al*. *Ann Oncol* 2019; **30**:1194–1220; 18. Burstein HJ, *et al*. *Ann Oncol* 2019; **30:**1541–1557.

PHESGO™
PERTUZUMAB-TRASTUZUMAB

HER2-positive eBC: Pertuzumab–trastuzumab + chemotherapy is neoadjuvant SoC and adjuvant SoC in patients without residual disease after surgery



* AGO and ESMO guidelines: (neo)adjuvant PH is only recommended for the treatment of patients with node-positive disease.
† In the eBC setting, trastuzumab is approved for the adjuvant treatment of patients with HER2-positive eBC, following adjuvant chemotherapy with doxorubicin and cyclophosphamide in combination with paclitaxel or docetaxel, or in combination with docetaxel and carboplatin.[5,6] Guideline recommendations (NCCN, AGO, ESMO, St. Gallen) for the adjuvant use of trastuzumab with paclitaxel alone represent off-label use in this setting.[1–4]
‡ AGO and ESMO guidelines do not recommend the use of trastuzumab + paclitaxel for the treatment of patients with Stage T1mic or T1a disease.[2,3] St. Gallen guidelines state that the use of trastuzumab + paclitaxel can be considered in patients with Stage T1a disease only on a case-by-case basis, and do not recommend its use in patients with Stage T1mic disease.[4]
§ Post-adjuvant therapy with neratinib following adjuvant trastuzumab-based treatment can be considered in high-risk patients with HER2-positive, hormone receptor-positive disease. It is not known if patients who have previously received pertuzumab–trastuzumab or T-DM1 will benefit from post-adjuvant therapy with neratinib.[1–3]

Abbreviations in slide notes.
1. NCCN Breast Cancer Guidelines – Version 4. 2021;
2. AGO Breast Cancer Guidelines March 2021;
3. Cardoso F, *et al*. *Ann Oncol* 2019; **30:**1194-1220;
4. Burstein HJ, *et al*. *Ann Oncol* 2019; **30:**1541-1557;
5. Herceptin SmPC 2021; 6. Herceptin US PI 2021.

IV infusion of pertuzumab and trastuzumab is well established, but can present challenges to patients and healthcare systems

Long infusion and observation time/ congestion at clinics & hospitals

- Pertuzumab is infused over 30–60 minutes, followed by observation for 30–60 minutes (for maintenance and loading doses, respectively)[1]
- Trastuzumab is infused over 30–90 minutes; observation for 2–6 hours (for maintenance and loading doses, respectively)[2]

Challenge of improving resource utilisation

- IV preparation time is longer than for SC, and requires more associated resources[3,4]

Placement and maintenance of indwelling venous access

- Indwelling venous access can have increased risk of infection, thrombosis and discomfort[3,5–7]

Challenge of venous access in some patients

- Establishing IV access can be particularly burdensome for patients with poor venous access[7]

1. Perjeta SmPC June 2020; 2. Herceptin IV SmPC August 2020; 3. De Cock E, *et al. Cancer Med* 2016; **5**:389–397; 4. De Cock E, *et al*. St. Gallen 2013 (Abstract 209); 5. Shivakumar SP, *et al*. *J Clin Oncol* 2009; **27**:4858–4864; 6. Jackisch C, *et al*. *Geburtshilfe Frauenheilkd* 2014; **74**:343–349; 7. Fallowfield L, *et al*. *The Breast* 2015; **24**:166–170.

IV, intravenous; SC, subcutaneous.

PHESGO™
PERTUZUMAB-TRASTUZUMAB

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 pertuzumab and trastuzumab, 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)[1–3]

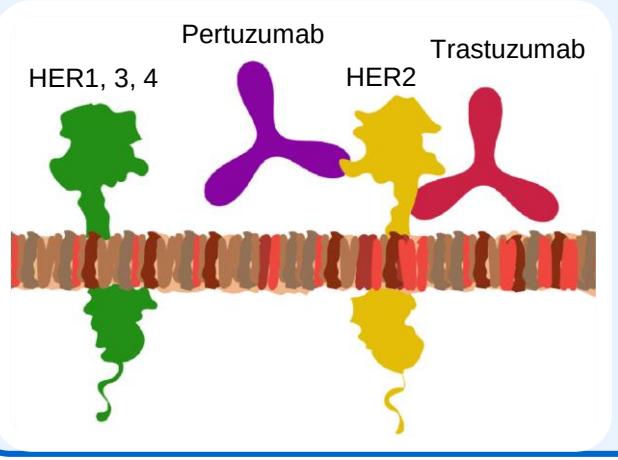
Is a ready-to-use fixed-dose formulation, administered by a SC injection in the thigh over approximately 5–8 minutes[2]

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

1. Tan *et al. Lancet Oncol* 2021; **22**:85–97;
2. PHESGO Indian prescribing information 3. Locke, K *et al. Drug Deliv*. 2019; 26(1):98–106.

PHESGO™
PERTUZUMAB-TRASTUZUMAB

Mechanism of action of pertuzumab and trastuzumab fixed-dose combination for SC use



Pertuzumab and trastuzumab fixed-dose combination for SC use combines pertuzumab and trastuzumab, two monoclonal antibodies, with recombinant human hyaluronidase[1]

- Pertuzumab is designed to work with trastuzumab for a dual-HER2 blockade
- In preclinical models, pertuzumab targeted a different subdomain on the HER2 receptor than trastuzumab, to block dimerisation with HER1 and HER3 receptors and provide a dual blockade of HER2-driven signalling pathways[4]

Hyaluronidase is an endoglycosidase used to increase dispersion and absorption of co-administered drugs when administered subcutaneously[2,3]

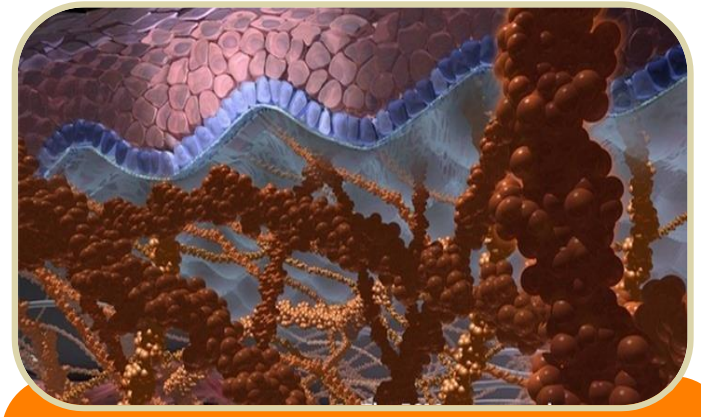
- Hyaluronidase allows subcutaneous delivery of larger drug volumes[2,3]
- Hyaluronidase increases permeability of the subcutaneous tissue by depolymerising hyaluronan, based on preclinical studies[2,3]
- The effects of hyaluronidase are reversible, and permeability of the subcutaneous tissue is restored within 24 to 48 hours[2,3]

SC, subcutaneous.

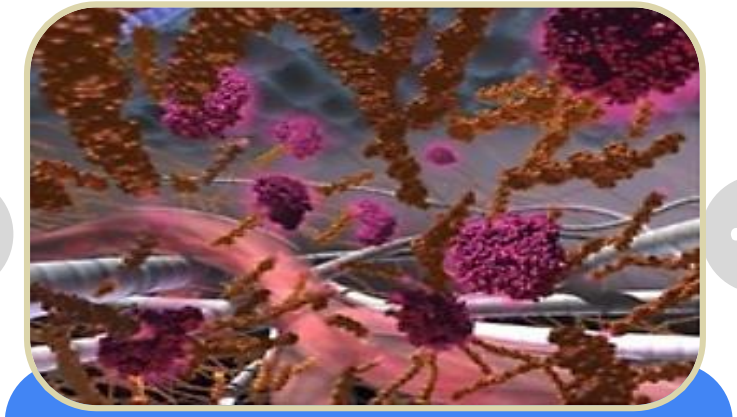
1. PHESGO Indian PI;
2. Locke K, *et al. Drug Delivery* 2019; **26:**98–10;
3. Thomas J, *et al. J Palliat Med* 2007; **10:**1312–1320;
4. Scheuer W, *et al. Cancer Res* 2009; **69:**9330–9336;

PHESGO™
PERTUZUMAB-TRASTUZUMAB

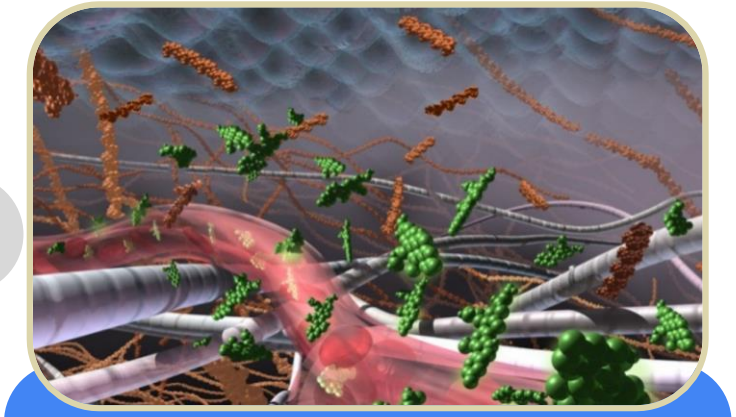
Impact of rHuPH20 on the SC injection of large fluid volumes



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, >1mL

rHuPH20, recombinant human hyaluronidase; SC, subcutaneous.

1. Jackisch C, *et al*. *Geburtshilfe Frauenheilkd* 2014; **74**:343–349; 2. Roche. Data on file (FeDeriCa trial protocol); 3. Frost GI. *Expert Opin Drug Deliv* 2007; **4**:427–440. Images courtesy of Halozyme Therapeutics.

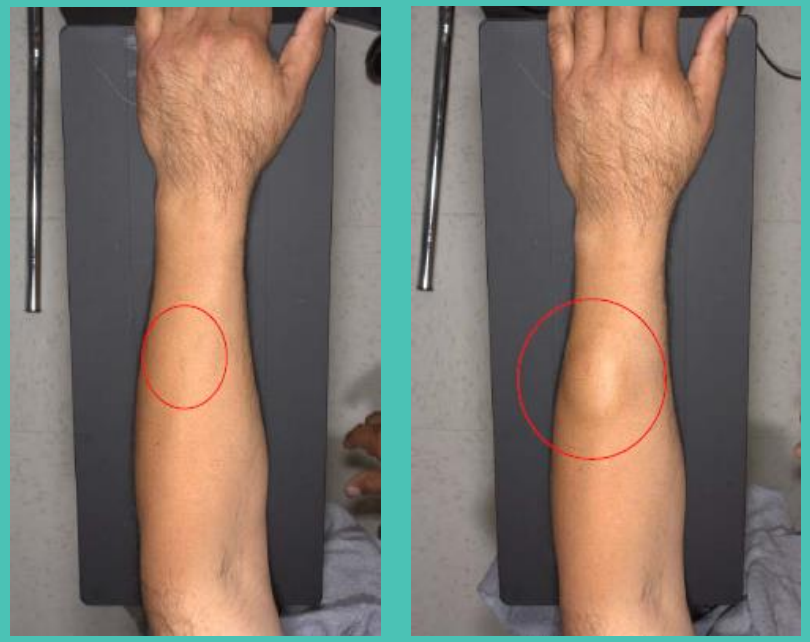
PHESGO™
PERTUZUMAB-TRASTUZUMAB

rHuPH20 allows SC administration of volumes larger than 1 mL

Bolus injection of 10 mL 10% IgG solution

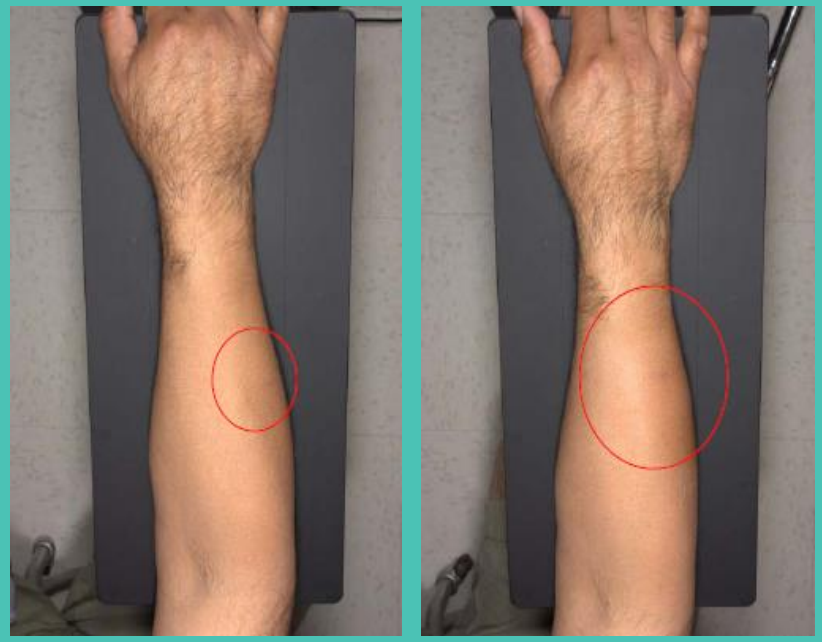
Without rHuPH20

Before infusion **Immediately post-infusion**



With 2000 U/mL rHuPH20

Before infusion **Immediately post-infusion**



IgG, immunoglobulin G; rHUPH20, recombinant human hyaluronidase; SC, subcutaneous.

Shpilberg O & Jackisch C. *Br J Cancer* 2013; **109**:1556–1561.

PHESGO™
PERTUZUMAB-TRASTUZUMAB

Does PH FDC SC have the same pharmacokinetics, efficacy and safety as P + H IV?

PHESGO clinical development programme

Finding and confirming the dose of pertuzumab within PHESGO*

BO30185
Phase Ib in HMV and eBC
(completed May 2018)

PHESGO recommended doses

PHESGO loading dose:
1200 mg pertuzumab/
600 mg trastuzumab

PHESGO maintenance dose:
600 mg pertuzumab/
600 mg trastuzumab

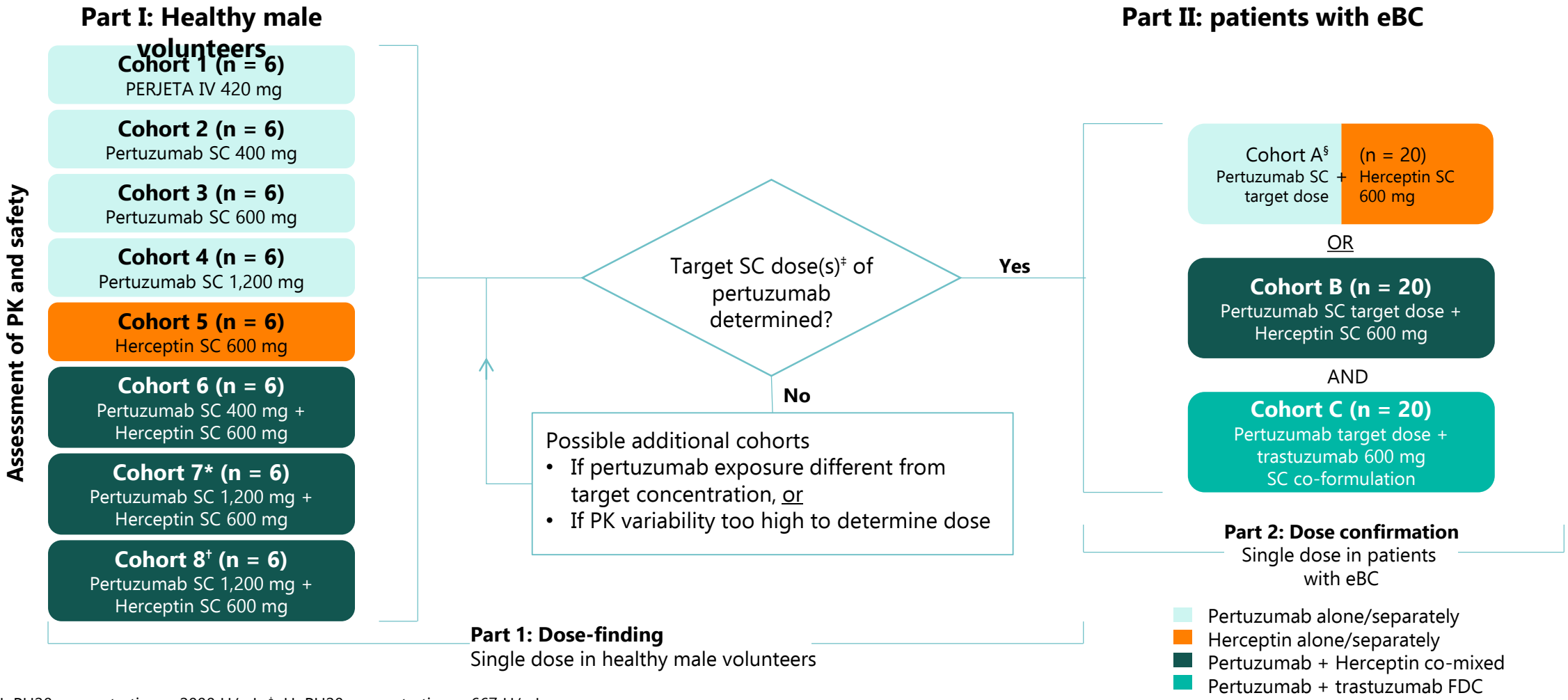
PK/efficacy/safety/preference

FeDeriCa (WO40324)
Phase III in eBC
(ongoing)
Primary analysis: SABCS 2019

PHranceSCa (MO40628)
Phase II in eBC
(ongoing)
Primary analysis: ESMO 2020

PHESGO™
PERTUZUMAB-TRASTUZUMAB

BO30185: Phase Ib dose-finding study was used to select the dose of pertuzumab for PHESGO



* rHuPH20 concentration = 2000 U/mL. † rHuPH20 concentration = 667 U/mL.
‡ Calculated to deliver a similar exposure to a 420 mg IV dose. § Only if co-formulated PH FDC is not feasible.
eBC, early breast cancer; FDC, fixed-dose combination; IV, intravenous;
PK, pharmacokinetic; SC, subcutaneous.

Kirschbrown WP, *et al. J Clin Pharmacol* 2019; **59**:702–716.

PHESGO™
PERTUZUMAB-TRASTUZUMAB

BO30185: Summary

PK & dose finding

- **BO30185 selected a loading dose of 1200 mg pertuzumab SC and a maintenance dose of 600 mg pertuzumab SC to be used in PHESGO**
- PK data in healthy male volunteers and patients with early breast cancer predicted these doses will result in an equivalent pertuzumab serum exposure to that of PERJETA IV 840 mg and 420 mg, respectively
- The **dose-finding processes used to find the subcutaneous dose of pertuzumab were similar** to those used successfully in the development of both Herceptin SC and MabThera SC

Safety

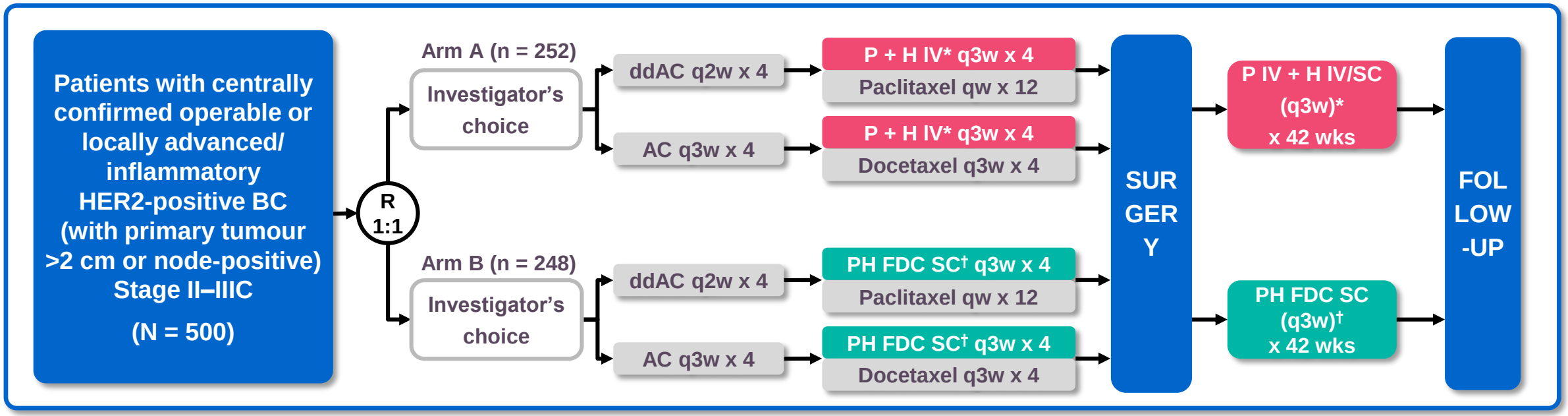
- There were **no new safety signals observed for pertuzumab SC** alone, or when co-mixed or co-formulated with Herceptin SC
- The **PK and safety results** of BO30185 **supported further development of PHESGO**

PK, pharmacokinetics; SC, subcutaneous.

Kirschbrown WP, *et al*. *J Clin Pharmacol* 2019; **59**:702–716.

PHESGO™
PERTUZUMAB-TRASTUZUMAB

FeDeriCa: Phase III non-inferiority 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) P serum C_{trough}

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

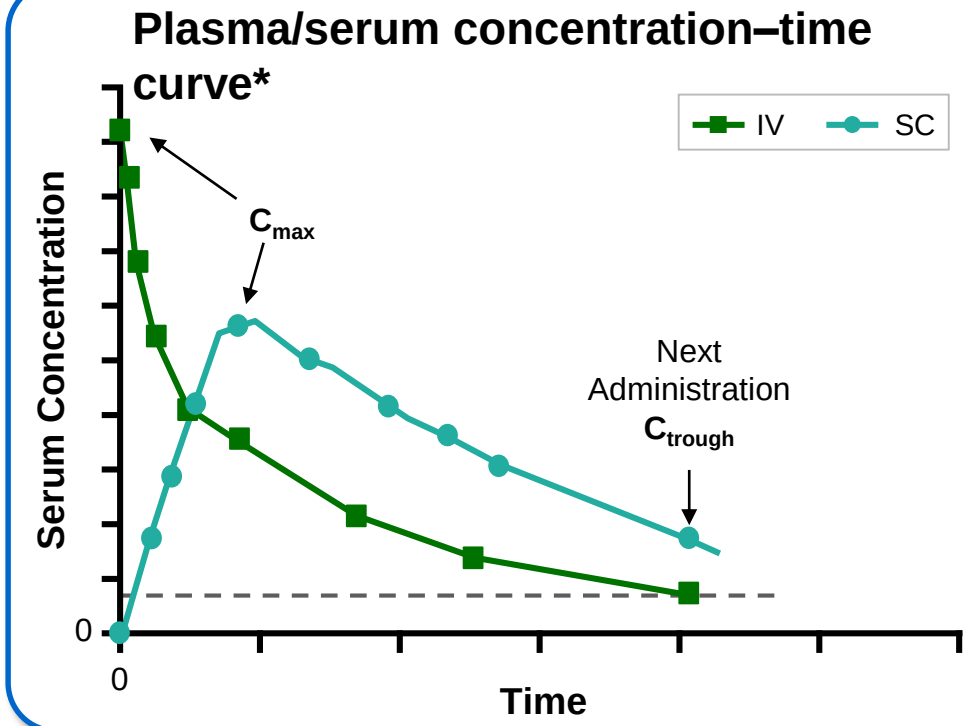
* P IV (fixed dose) loading dose: 840 mg; maintenance: 420 mg. H IV (fixed dose) loading dose: 8 mg/kg; maintenance: 6 mg/kg IV. H SC is given as a fixed dose of 600 mg.
† PH FDC SC (fixed dose): P 1200 mg/H 600 mg in 15 mL; maintenance: P 600 mg/H 600 mg in 10 mL.
C_{trough}, serum trough concentration; ddAC, dose-dense doxorubicin + cyclophosphamide; DRFI, disease recurrence-free interval; EFS, event-free survival; IDFS, invasive disease-free survival; OS, overall survival; PK, pharmacokinetics; qw, every week; qxw, every x weeks; R, randomised; tpCR, total pathological complete response rate; wks, weeks.

1. Tan AR, *et al. Lancet Oncology* 2021; **22:**P85–97.

PHESGO™
PERTUZUMAB-TRASTUZUMAB

Pharmacokinetic (PK) parameters are important for understanding bioequivalence between IV and SC formulations

PK endpoints are a key focus of the PH FDC SC clinical development programme and are used to assess bioequivalence



- **C_{trough}** = Trough plasma/serum drug concentration; the concentration measured at the end of a dosing interval
  - Related to mode of action
  - Associated with clinical outcomes[1–6]
- **AUC** = Area under the plasma/serum concentration–time curve;
  - Provides exposure information over the course of the treatment cycle (how much of a drug stays in the body and for how long)
  - May correlate with C_{trough}
- **C_{max}** = Maximum (peak) plasma/serum drug concentration
  - C_{max} after IV is not subject to distribution and elimination effects, compared with C_{max} after SC which requires time for absorption and is subject to elimination effects before reaching the bloodstream
  - Not clearly correlated with clinical outcomes[1,3]

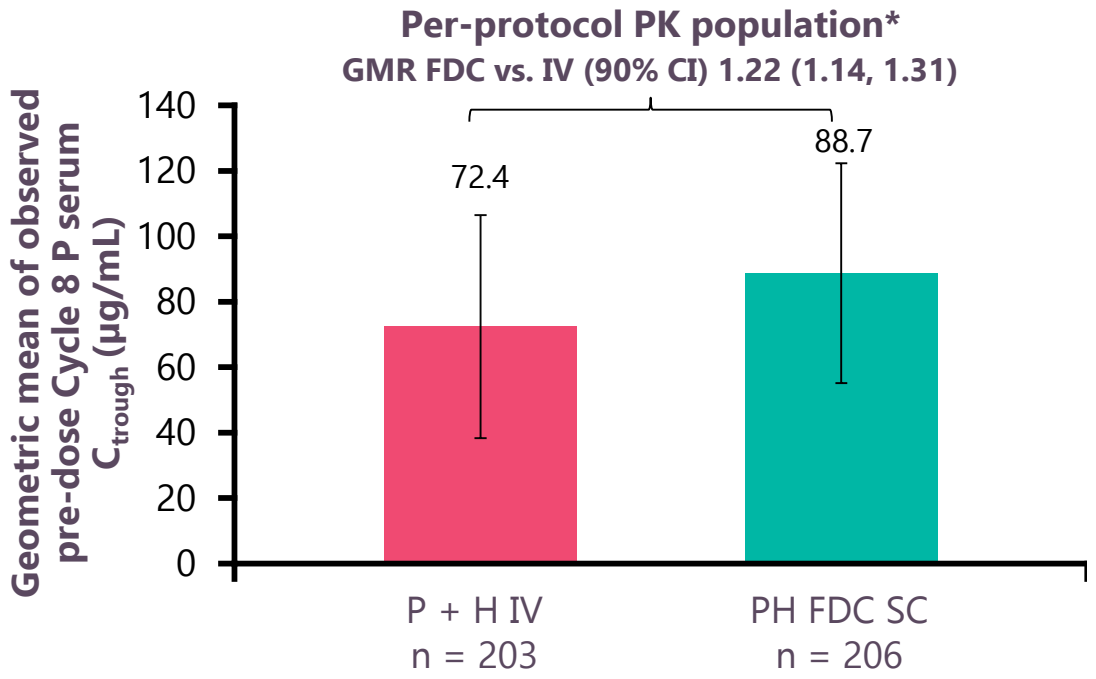
* Figure for Illustration purposes only. Not based on measured data.
AUC, area under the plasma/serum concentration–time curve;
$C_{max,}$ maximum serum concentration; $C_{trough,}$ serum trough concentration; IV, intravenous; SC, subcutaneous.

1. Berinstein NL, *et al*. *Ann Oncol* 1998; **9**:995–1001; 2. Yin A, *et al*. *J Clin Oncol* 2010 **28**:e13108;
3. Tobinai K, *et al*. *Ann Oncol* 2004;**15**:821–830; 4. Jäger U, *et al*. *Haematologica* 2012; **97**:1431–1438; 5. Maloney DG, *et al*. *Blood* 1997; **90**:2188–2195; 6. Igarashi T, *et al*. *Ann Oncol* 2002; **13**:928–943.

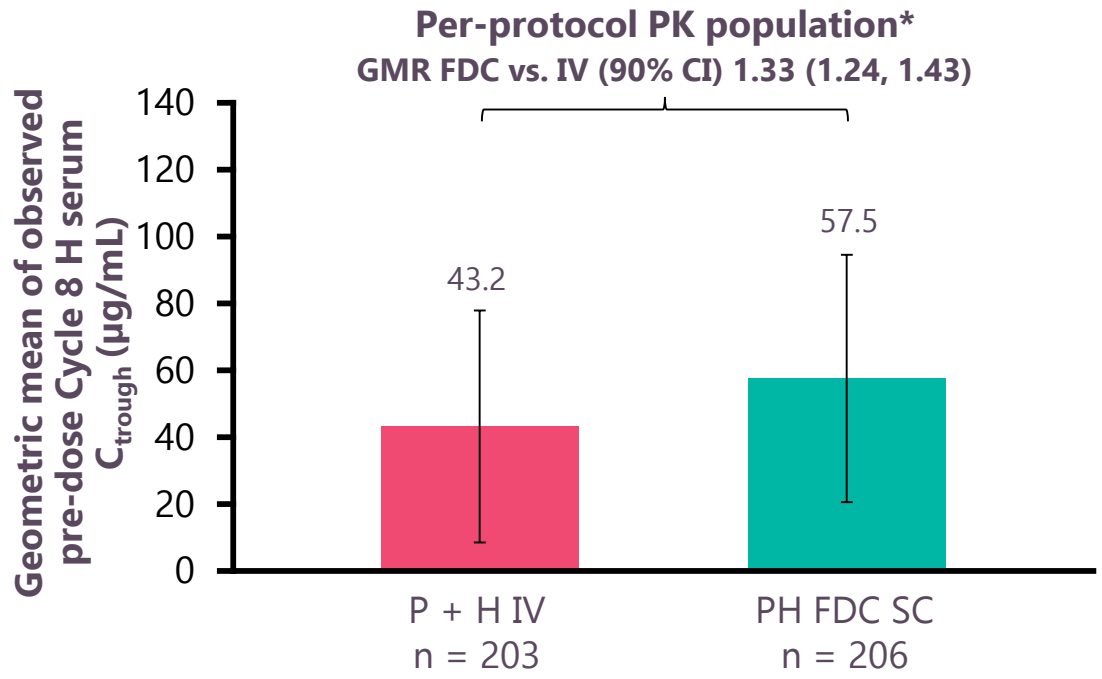
PHESGO™
PERTUZUMAB-TRASTUZUMAB

FeDeriCa: PH FDC SC was non-inferior to P + H IV, based on Cycle 7 (pre-dose Cycle 8) P and H serum C_{trough} concentrations

Primary endpoint: P serum C_{trough}



Secondary endpoint: H serum C_{trough}



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

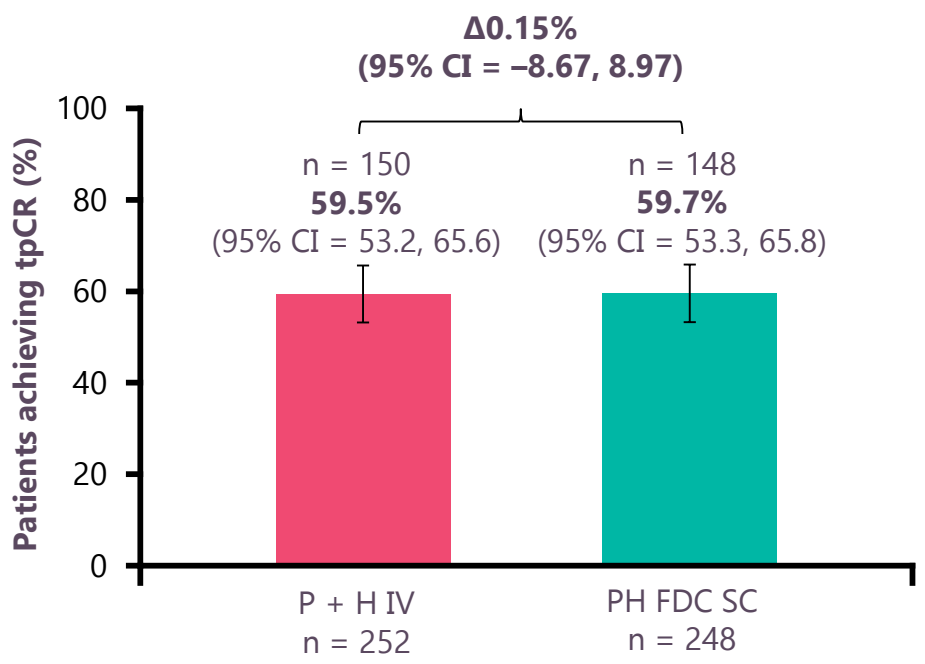
* This population includes only patients who adhered to the pre-specified criteria for the schedule of PK assessments.
C_{trough}, serum trough concentration; CI, confidence interval; GMR; geometric mean ratio; H, trastuzumab; P, pertuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; PK, pharmacokinetics.

Tan AR, *et al. Lancet Oncol* 2021.

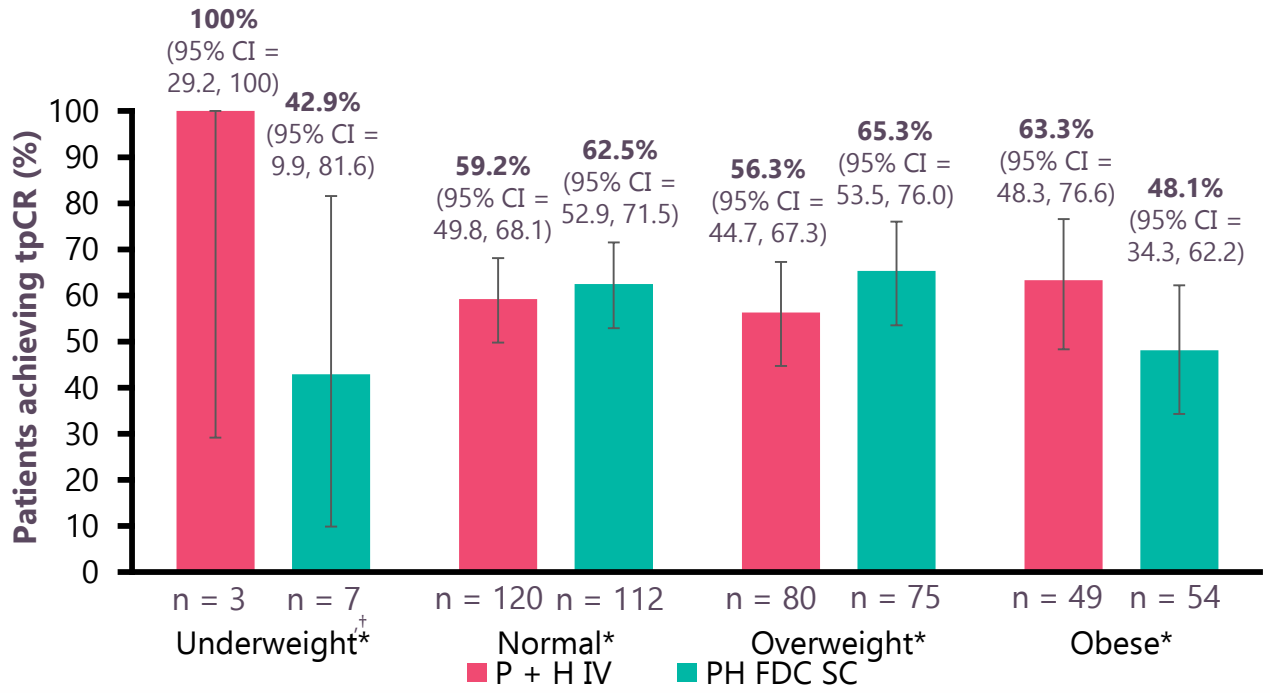
PHESGO™
PERTUZUMAB-TRASTUZUMAB

FeDeriCa: PH FDC SC had almost identical tpCR rates to P + H IV[1]

tpCR in ITT population



tpCR by body mass index



tpCR rates in the ITT population are in keeping with data from previous studies of P–H IV + chemotherapy in the neoadjuvant setting[2–5]

IV, intravenous; ITT, intention-to-treat; H, trastuzumab; P, pertuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; tpCR, total pathological complete response rate .
* Underweight <18.5 kg/m²; Normal 18.5–<25.0 kg/m²; Overweight 25.0–<30.0 kg/m²; Obese ≥30 kg/m². † Patient numbers in the underweight subgroup were low.

1 . Tan AR, *et al. Lancet Oncol* 2021; 2. Schneeweiss A, *et al. Ann Oncol* 2013; 3. Loibl S, *et al. Ann Oncol* 2017; 4. Hurvitz SA, *et al. Lancet Oncol* 2018; 5. Swain SM, *et al. Ann Oncol* 2018.

PHESGO™
PERTUZUMAB-TRASTUZUMAB

Safety profile of PH FDC SC was comparable to P + H IV formulations

No. of patients, n (%)	P + H IV n = 252	PH FDC SC n = 248
Any AE[1]	251 (99.6)	248 (100)
Grade ≥3 AEs[1]	133 (52.8)	121 (48.8)
Serious AE[1]	45 (17.9)	40 (16.1)
Death[1]	1 (0.4)*	1 (0.4)†
Discontinued randomised treatment due to AE[2]	26 (10.3)	17 (6.9)

The rates of treatment discontinuations due to AEs were similar between arms[2]

1. Tan AR, *et al.* SABCS 2019 (Abstract PD4-07);
2. Roche, Data on file (CSR 11/09/2019).

* Death was unrelated to HER2 treatment. The cause of death was reported as urosepsis.
† The cause of death was reported as acute myocardial infarction and occurred after cycle 2; hence, it occurred prior to the start of anti-HER2 treatment with PH FDC SC.
AE, adverse event; H, trastuzumab; IV, intravenous; P, pertuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection .

PHESGO™
PERTUZUMAB-TRASTUZUMAB

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)

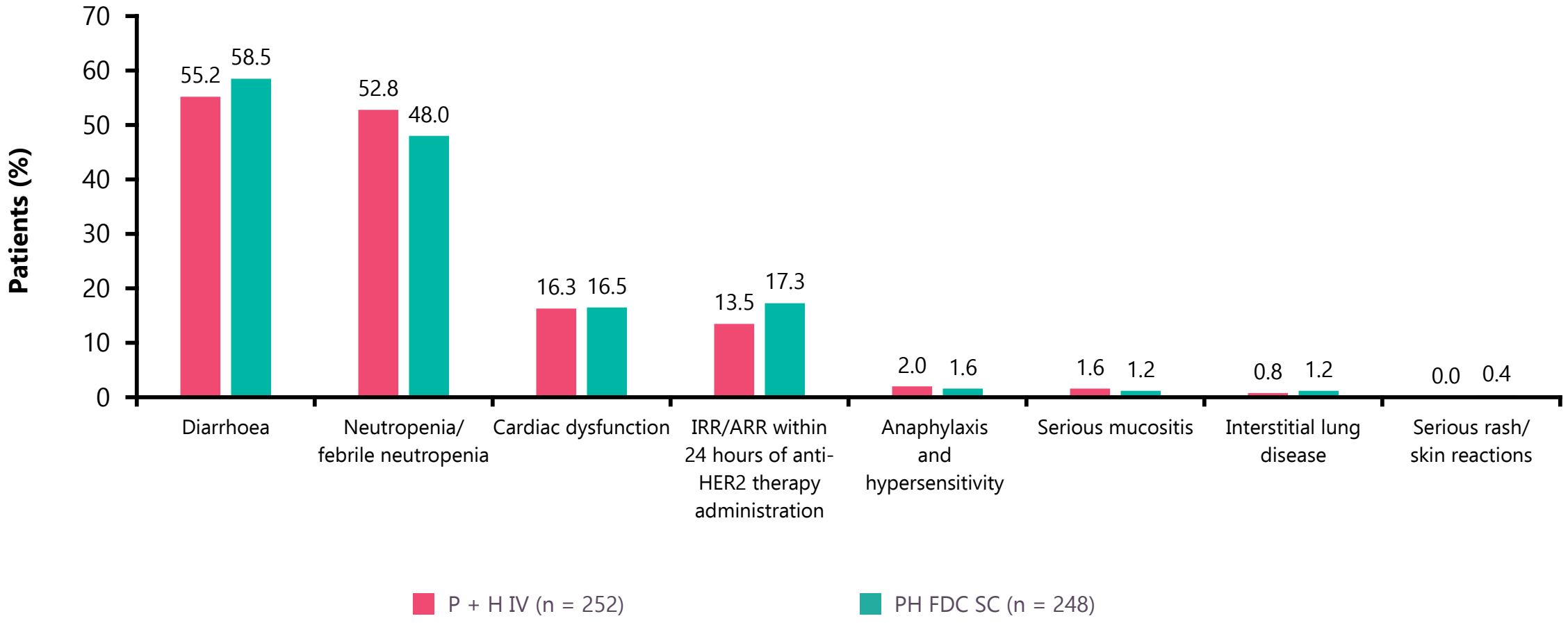
Incidences of AEs were consistent with other studies that included P-H IV + chemotherapy[2–4]

1. Tan AR, *et al.* SABCS 2019 (Abstract PD4-07); 2. Gianni L, *et al. Lancet Oncol* 2012;
3. Schneeweiss A, *et al. Ann Oncol* 2013; 4. Swain SM, *et al. Ann Oncol* 2018..

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

PHESGO™
PERTUZUMAB-TRASTUZUMAB

FeDeriCa: Incidence of AEs of interest, including cardiac dysfunction, IRR/ARRs and hypersensitivity, was comparable between treatment arms*



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

* One pregnancy-/neonatal-related AE of epidermolysis under standardised MedDRA queries "Pregnancy and neonatal topics (wide)" occurred in each treatment arm (0.4% incidence).
AE, adverse event; ARR, administration-related reaction; IRR, infusion-related reaction; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection.

PHESGO™
PERTUZUMAB-TRASTUZUMAB

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)

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

* 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, pertuzumab.

PHESGO™
PERTUZUMAB-TRASTUZUMAB

PH FDC SC showed non-inferior PK vs. pertuzumab + trastuzumab IV, with comparable efficacy and safety

PH FDC SC was non-inferior to pertuzumab + trastuzumab IV, based on Cycle 7 (pre-dose Cycle 8) pertuzumab and trastuzumab serum C_{trough} concentrations[1]

The tpCR rate of PH FDC SC (59.7%) was nearly identical to that of pertuzumab + trastuzumab IV (59.5%)[1] and consistent with previous data from trials with pertuzumab + trastuzumab IV + chemotherapy[2–5]

The safety profile of PH FDC SC was comparable to that of pertuzumab + trastuzumab IV[1] and was consistent with previous pertuzumab + trastuzumab IV + chemotherapy trials; no new safety signals identified, including when switching formulations[2,3,6,7]

PK, pharmacokinetics; tpCR., total pathological complete response.

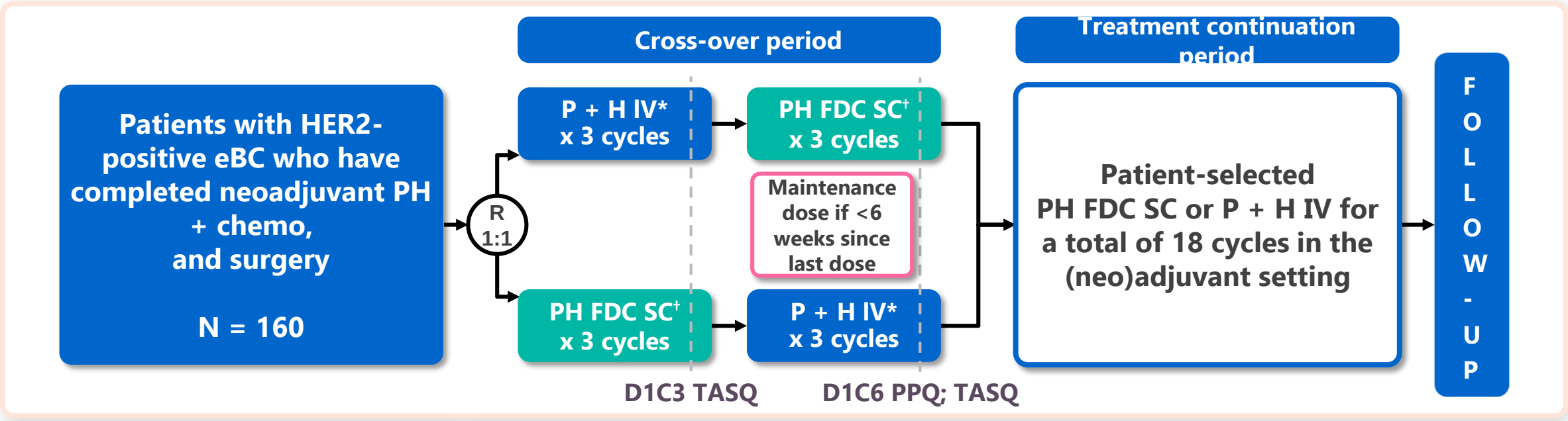
1. Tan AR, *et al.* Lancet Oncol 2021; 2. Schneeweiss A, *et al. Ann Oncol* 2013;
3. Swain SM, *et al. Ann Oncol* 2018; 4. Loibl S, *et al. Ann Oncol* 2017;
5. Hurvitz SA, *et al. Lancet Oncol* 2018; 6. Gianni L, *et al. Lancet Oncol* 2012.
7. O'Shaughnessy J, et al. ESMO 2020 (Abstract 165MO)

PHESGO™
PERTUZUMAB-TRASTUZUMAB

Do patients prefer PH FDC SC to P + H IV?

PHESGO™
PERTUZUMAB-TRASTUZUMAB

PHranceSCa: Phase II study assessing patient preference for PH FDC SC vs. P + H IV[1,2]



Stratification factors:

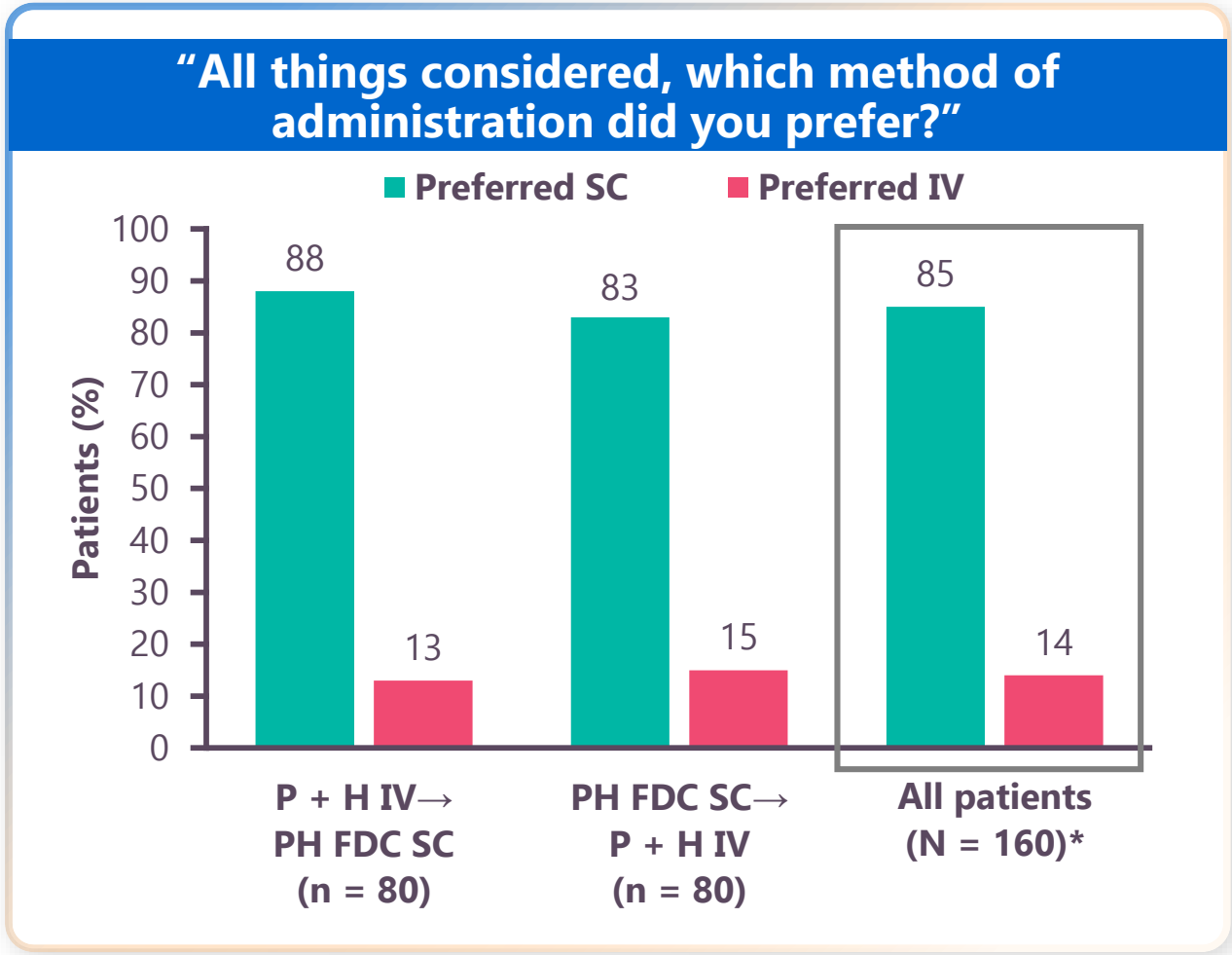
- NACT regimen
- pCR vs. no pCR
- HR status

Primary objective: Patient preference of PH FDC SC
Key secondary objectives: Patient satisfaction, patients' choice of formulation for the continuation period, health-related quality of life, HCP perception on time/resource at each cycle during the treatment cross-over period, 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. Adjuvant hormone therapy and radiotherapy for breast cancer were permitted.
* 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.
DXCX, Day X, Cycle X; HCP, healthcare profession; HR, hormone receptor; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; PPQ, Patient Preference Questionnaire; q3w, every 3 weeks; SC, subcutaneous; TASQ, Therapy Administration Satisfaction Questionnaire.

1. O'Shaughnessy J, *et al.* ESMO Virtual Congress 2020 (Abstract 165MO and oral presentation);
2. https://clinicaltrials.gov/ct2/show/NCT03674112 (Accessed May 2021).

PHranceSCa: Phase II study assessing patient preference for PH FDC SC vs. P + H IV[1,2]



- Preference for PH FDC SC was very or fairly strong for the majority of patients (93%)
- Main reasons for SC preference:
  - "Less time in clinic" (42%)
  - "More comfortable during administration" (26%)
- 87% chose PH FDC SC to continue treatment

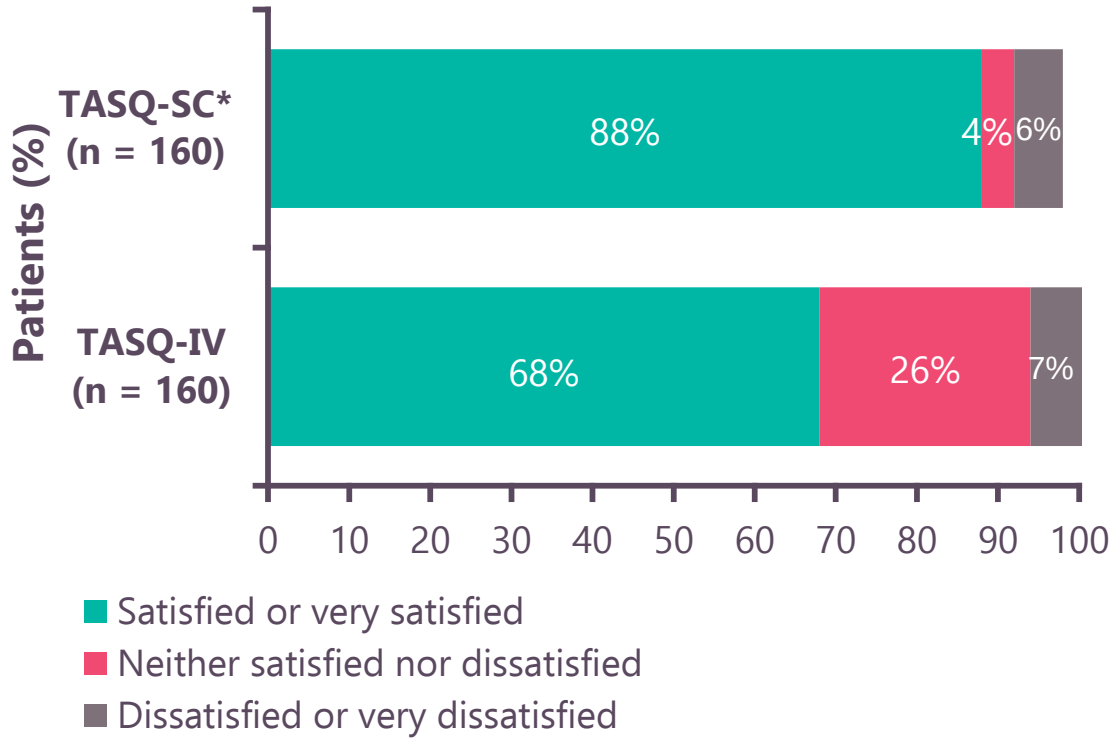
Clinical cut-off: 24 February 2020.
* Two patients stated "no preference." 95% CI for PH FDC SC preference: 79–90.
CI, confidence interval; H, trastuzumab; IV, intravenous; P, pertuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; PPQ, Patient Preference Questionnaire; SC, subcutaneous.

O'Shaughnessy J, *et al.* ESMO Virtual Congress 2020 (Abstract 165MO and oral presentation).

PHESGO™
PERTUZUMAB-TRASTUZUMAB

PHranceSCa: More patients were “very satisfied” or “satisfied” with PH FDC SC vs. P + H IV (88% vs. 68%)

“How satisfied or dissatisfied were you with the SC injection or IV infusion?”



- **Treatment had no impact on patient–HCP speaking time:**
  - **PH FDC SC: 85%**
  - **P + H IV: 79%**
- **Most patients had more than enough time to talk to their HCP during treatment:**
  - **PH FDC SC: 90%**
  - **P + H IV: 83%**

* Two patients did not answer the question.
H, trastuzumab; HCP, healthcare professional (nurse or doctor); IV, intravenous; P, pertuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; SC, subcutaneous.

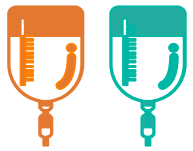
O'Shaughnessy J, *et al.* ESMO Virtual Congress 2020 (Abstract 165MO and oral presentation).

PHESGO™
PERTUZUMAB-TRASTUZUMAB

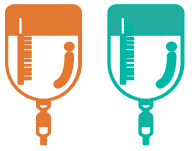
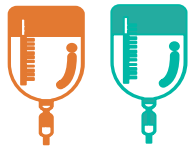
PHranceSCa: Majority of HCPs felt that switching from IV to SC would save time and resources

Drug preparation room*

HCP estimate of total time in drug preparation room

P + H IV	PH FDC SC
	
15–20 mins	5 mins

Treatment room†

HCP estimate of patient time in the treatment room		HCP estimate of treatment administration time	
P + H IV	PH FDC SC	P + H IV	PH FDC SC
			
130–300 mins	33–50 mins	60–150 mins	7–8 mins

- 88% of HCPs thought that **PH FDC SC was the quickest** from start of preparation to completion of administration
- 87% of HCPs felt that **PH FDC SC required less resource usage** for preparation and administration
- 77% of HCPs agreed or strongly agreed that ready-to-use **PH FDC SC resulted in less drug wastage**

Time ranges (median) refer to the various cycles during the treatment cross-over period.
* The vast majority of HCPs in the drug preparation room completed at least one question of the HCPQ during the treatment cross-over period (957/960 HCPQs, 99.7%).
† The vast majority of HCPs in the treatment room completed at least one question from the HCPQ during the treatment cross-over period (950/960 HCPQs, 99%).
H, trastuzumab; HCP, healthcare professional; HCPQ, healthcare professional questionnaire; IV, intravenous; P, pertuzumab;
PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; SC, subcutaneous.

O'Shaughnessy J, *et al.* ESMO Virtual Congress 2020 (Abstract 165MO and oral presentation).

PHranceSCa: AE rates before and after switching were similar, with no new safety signals[1,2]

	P + H IV → PH FDC SC		PH FDC SC → P + H IV		
	P + H IV Cycles 1–3 (n = 80)	PH FDC SC Cycles 4–6 (n = 80)	PH FDC SC Cycles 1–3 (n = 80)	P + H IV Cycles 4–6 (n = 80)	All patients (N = 160)
AEs	62 (77.5)	58 (72.5)	62 (77.5)	51 (63.8)	140 (87.5)
Five most common AEs (in ≥5% of patients), n (%)					
Radiation skin injury	17 (21.3)	7 (8.8)	10 (12.5)	10 (12.5)	43 (26.9)
Injection site reaction	0	12 (15.0)	24 (30.0)	0	36 (22.5)
Diarrhoea	12 (15.0)	7 (8.8)	6 (7.5)	4 (5.0)	25 (15.6)
Fatigue	5 (6.3)	4 (5.0)	5 (6.3)	4 (5.0)	15 (9.4)
Hot flush	6 (7.5)	4 (5.0)	5 (6.3)	0	15 (9.4)

Patients could be counted in multiple study periods but once in the "All patients" column.
AE, adverse event; H, trastuzumab; IV, intravenous; P, pertuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; SAE, serious adverse event; SC, subcutaneous.

1. O'Shaughnessy J, *et al.* ESMO Virtual Congress 2020 (Abstract 165MO and oral presentation); 2. Roche. Data on file.

PHranceSCa: 85% of patients (136/160; 95% CI: 79–90%) preferred PH FDC SC; 14% (22/160) preferred P + H IV*

Main reasons for PH FDC SC preference:

"Less time in clinic"

"More comfortable during administration"

Patient satisfaction

- More patients were "very satisfied" or "satisfied" with PH FDC SC vs. P + H IV
- Most patients indicated that treatment had no impact on the amount of time they had to talk to their nurse/doctor, and that while receiving treatment they had more than enough time to talk to their nurse/doctor

HCP perception on time/resource impact

- HCPs indicated PH FDC SC had marked time savings and required fewer resources compared with P + H IV

Safety

- PH FDC SC was generally well tolerated, with a safety profile in line with previous studies using P + H IV[1,2]
- No new safety signals were observed, including when switching from IV to SC and vice-versa
- Safety results support those seen with PH FDC SC in the FeDeriCa study[3]

* Two patients stated "no preference."
H, trastuzumab; HCP, healthcare professional; IV, intravenous; P, pertuzumab;
PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; SC, subcutaneous.

1. von Minckwitz G, *et al. N Engl J Med* 2017; 2. Baselga J, *et al. N Engl J Med* 2012;
3. Tan AR, *et al. Lancet Oncol* 2021.

What are the practical considerations for using PH FDC SC in the real world?

Administering pertuzumab and trastuzumab fixed-dose combination for SC use: Tips to ensure comfortable drug delivery

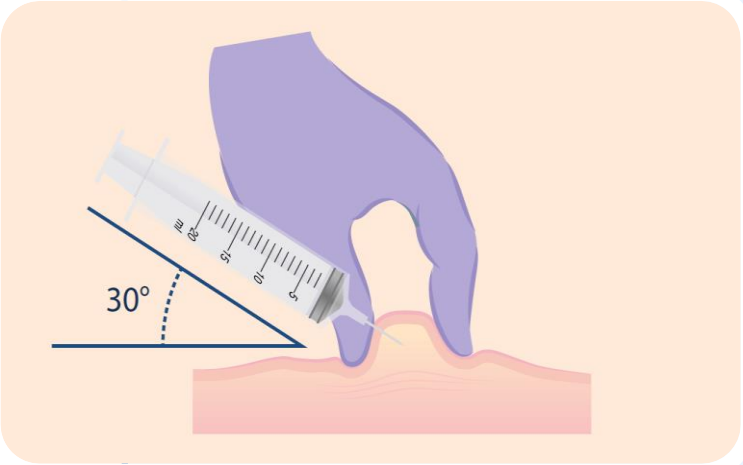
- Ask the patient to sit back in a reclining chair or bed and to make the thigh area accessible
- Be sure to arrange your chair at the right level, so that your feet are flat on the floor and you are able sit up straight without twisting, bending, or reaching to administer the injection
- Ensure that your hands are in good position and resting; this will reduce any unnecessary movement during the injection that might cause discomfort for the patient

- The injection site should be alternated between the left and right thigh only. **It is never administered in the abdomen**
- **Do not split the dose between two syringes or between the two sites of administration -** even with very slim patients, pertuzumab and trastuzumab fixed-dose combination for SC use is safe and comfortable to use on one site
- Each new injection should be given at least 2.5 cm (1 inch) from the previous site
- Choose an area of healthy skin that is not red, bruised, tattooed, tender or hard
- Record the used site to the patient's notes

SC, subcutaneous.

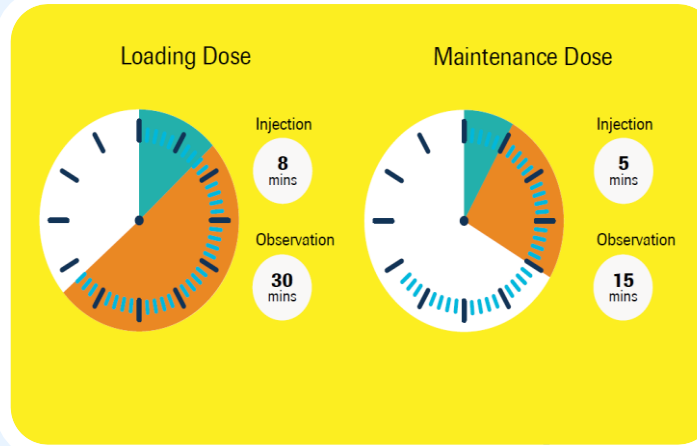
PHESGO™
PERTUZUMAB-TRASTUZUMAB

Administering pertuzumab and trastuzumab fixed-dose combination for SC use: Administering the injection



- To administer the injection, pinch the skin of the thigh with one hand to create a fold; this makes it easier to get the injection into the subcutaneous tissue and not into the muscle tissue
- Inject and maintain the needle at an angle of about 30 degrees
  - Note that the injection can feel difficult at the start because of the thickness of the solution
  - Using a butterfly needle makes administration easier
- If at any point during the injection the patient feels pain or discomfort, ease off the injection before continuing
- Keep the needle in place and check to make sure that the needle is at the right 30-degree angle of injection

- The injection should be slowed or paused if the patient experiences a significant injection-related reaction
- The injection should be discontinued immediately if the patient experiences a serious hypersensitivity reaction such as anaphylaxis
- Make sure that medication to treat reactions, as well as emergency equipment, is available for immediate use
- After the loading dose, the patient should be observed for a minimum of 30 minutes, for signs of hypersensitivity symptoms or administration-related reactions
- After the maintenance dose, the patient should be observed for a minimum of 15 minutes



SC, subcutaneous.

Best practice: Setting aside hospital space for administration of pertuzumab and trastuzumab fixed-dose combination for SC use

- Depending on the hospital's outpatient settings, the doses can be administered on a dedicated date
- Having a single room for administration and observation gives patients enough physical privacy, but also enables them to talk more freely about physical and psychosocial challenges

- **If the drug is administered in the chemotherapy day unit, curtains or other shades are required to ensure patient privacy**
- **A blanket on top of the patient's lower abdomen and pelvis may make them feel less exposed**
- **To ensure patient comfort during administration, a bed or reclining chair is required**
- **Nurses should have a comfortable chair and a removable drug table to ensure quality and safety of administration**

SC, subcutaneous.

PHESGO™
PERTUZUMAB-TRASTUZUMAB

What could PHESGO mean for patients and HCPs?

HCP, healthcare professional.

PHESGO™
PERTUZUMAB-TRASTUZUMAB

PHESGO provides benefits in cost, time and reduction of patient/HCP burden

- Shorter administration time (5–8 minutes) and observation period (15–30 minutes) of PHESGO reduces the burden on patients, carers and providers[1,2]
- PHESGO has a less invasive administration (single SC injection) vs. IV (two separate IV infusions), freeing patients from the burden of IV-related pain, bruising and irritation[3]
- Fixed-dose formulation may help reduce risk of dosing errors, reduce drug wastage and increase availability of nursing / pharmacy staff for other tasks[2,4]
- Reduced time required for drug preparation and administration with PHESGO vs. IV has the potential to relieve strain on infusion centres [2,5]
- No new safety signals have been observed when switching from IV to PHESGO and vice versa[6]

IV, intravenous; SC, subcutaneous.

1. PHESGO PI 2020; 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. FDA approval press release (accessed July 2020); 6. Roche, data on file (PHranceSCa primary analysis CSR).

PHESGO™
PERTUZUMAB-TRASTUZUMAB

Overall summary

- **Phesgo is the first formulation in oncology to combine two mAbs, P and H, in one vial for SC injection, and offers a faster and less invasive method of administration compared with P + H IV**
- **Phesgo had Cycle 7 (pre-dose Cycle 8) P and H serum C_{trough} concentrations and incidence of adverse events comparable to those seen with P + H IV, even when switching formulations[1,2]**
- **tpCR rates were almost identical between Phesgo and P + H IV in the ITT population, and were not impacted by body mass index[1]**

1. Tan AR, *et al. Lancet Oncol* 2021;
2. O'Shaughnessy J, *et al.* ESMO Virtual Congress 2020 (Abstract 165MO and oral presentation).

PHESGO™
PERTUZUMAB-TRASTUZUMAB

Overall summary (cont'd)

- Majority of patients (85%) preferred Phesgo vs. P + H IV, regardless of sequencing, and felt that PH FDC SC had no impact on patient–HCP speaking **time**[1]
- Majority of HCPs (88–89%) thought that switching from IV infusions to SC injections would save time and resources during preparation and treatment[1]
- **Phesgo is now FDA- and EMA-approved for the same indications as P + H IV (HER2-positive eBC and mBC, with or without concomitant IV chemotherapy)**[2,3]

1. O'Shaughnessy J, *et al.* ESMO Virtual Congress 2020 (Abstract 165MO and oral presentation);
2. PHESGO Indian PI

PHESGO™
PERTUZUMAB-TRASTUZUMAB

Thank you

WARNING: To be sold by retail on the prescription of a "Registered Oncologist Only"

ABRIDGED PRESCRIBING INFORMATION

(Phesgo ®) SUMMARY OF PRESCRIBING INFORMATION:

Generic Name: Pertuzumab-Trastuzumab Injection

Brand Name: Phesgo ®

Composition: *Active ingredient(s):* Pertuzumab, Trastuzumab. Phesgo is a clear to opalescent solution, colourless to slightly brownish solution supplied in sterile, preservative-free, non-pyrogenic single-dose vials. Single dose vials contain:1200 mg pertuzumab/600 mg trastuzumab/15 mL solution in a 20 cc vial 600 mg pertuzumab/600 mg trastuzumab/10 mL solution in a 15 cc vial *Excipients:* rHuPH20, L-Histidine, L-Histidine Hydrochloride Monohydrate, α,α-Trehalose Dihydrate, Sucrose, Polysorbate 20, L-Methionine, Water for Injection. Phesgo contains vorhyaluronidase alfa (recombinant human hyaluronidase rHuPH20), an enzyme used to increase the dispersion and absorption of co-formulated drugs when administered subcutaneously. **Indications: 1. Early Breast Cancer (EBC)** Phesgo is indicated for use in combination with chemotherapy for: • The neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. • The adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence. **2. Metastatic Breast Cancer (MBC)** Phesgo is indicated for use in combination with docetaxel for the treatment of adult patients with HER2- positive metastatic breast cancer who have not received prior anti HER2 therapy or chemotherapy for metastatic disease. **Type of dosage form:** Solution for subcutaneous injection **Dosage and Administration:** Phesgo therapy should only be administered under the supervision of a healthcare professional experienced in the treatment of cancer patients. Patients currently receiving intravenous pertuzumab and trastuzumab can switch to Phesgo. Phesgo is for subcutaneous (SC) use in the thigh only. Do not administer intravenously.

	Dose (irrespective of body weight)	Approximate duration of SC injection	Observation time ab
Loading dose	1200 mg pertuzumab/ 600 mg trastuzumab	8 minutes	30 minutes
Maintenance dose (every 3 weeks)	600 mg pertuzumab/ 600 mg trastuzumab	5 minutes	15 minutes

In patients receiving intravenous pertuzumab and trastuzumab with < 6 weeks since their last dose, Phesgo should be administered as a maintenance dose of 600 mg pertuzumab/600 mg trastuzumab and every 3 weeks for subsequent administrations. In patients receiving intravenous pertuzumab and trastuzumab with ≥ 6 weeks since their last dose, Phesgo should be administered as a loading dose of 1200 mg pertuzumab/600 mg trastuzumab, followed by a maintenance dose of 600 mg pertuzumab/600 mg trastuzumab every 3 weeks for subsequent administrations. **Contraindications:** Phesgo is contraindicated in patients with a known hypersensitivity to pertuzumab, trastuzumab or any of the excipients. **Warnings and Precautions**: *Left ventricular dysfunction*: Decreases in LVEF have been reported with drugs that block HER2 activity, including pertuzumab and trastuzumab. The incidence of symptomatic left ventricular systolic dysfunction (LVD [congestive heart failure]) was higher in patients treated with pertuzumab in combination with trastuzumab and chemotherapy compared to trastuzumab and chemotherapy**.** *Injection-related reactions (IRRs):* Phesgo has been associated with injection-related reactions. Injection-related reactions were defined as any systemic reaction with symptoms such as fever, chills, headache, likely due to a release of cytokines occurring within 24 hours of administration of Phesgo. *Hypersensitivity reactions/anaphylaxis:* Patients should be observed closely for hypersensitivity reactions. Although severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have not been observed in patients treated with Phesgo, caution should be exercised as these have been associated with intravenous pertuzumab in combination with trastuzumab and chemotherapy. *Use in Special population: Fertility:* No specific fertility studies in animals have been performed to evaluate the effects of Phesgo. No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. No adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies of pertuzumab for up to six month duration in cynomolgus monkeys. Reproduction studies conducted in cynomologus monkeys with trastuzumab revealed no evidence of impaired fertility in female cynomologus monkeys. *Contraception:* Women of childbearing potential including those who are partners of male patients should use effective contraception during treatment with Phesgo and for 7 months following the last dose of Phesgo. *Pregnancy:* Phesgo should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus. No clinical studies of Phesgo in pregnant women have been performed. Pertuzumab administered intravenously to cynomolgus monkeys during organogenesis led to oligohydramnios, delayed renal development and embryo fetal death. In the post-marketing setting for trastuzumab, cases of fetal renal growth and/or function impairment in association with oligohydramnios, some of which resulted in fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women. Based on the aforementioned animal studies and post-marketing data, Phesgo has the potential to cause fetal harm when administered to a pregnant woman. Women who become pregnant should be advised of the possibility of harm to the fetus. If a pregnant woman is treated with Phesgo, or if a patient becomes pregnant while receiving Phesgo or within 7 months following the last dose of Phesgo, close monitoring by a multidisciplinary team is desirable. *Labor and Delivery:* The safe use of Phesgo during labor and delivery has not been established. *Lactation:* As human IgG is excreted in human milk, and the potential for absorption and harm to the infant is unknown, women should be advised to discontinue nursing during Phesgo therapy and for 7 months after the last dose of Phesgo. *Pediatric use:* The safety and efficacy of Phesgo in pediatric patients below 18 years of age have not been established. *Geriatric use:* No overall differences in efficacy and safety of Phesgo was observed in patients ≥65 (n=26) and <65 years of age (n=222). However, with intravenous pertuzumab in combination with trastuzumab, the incidence of the following all grade adverse events were at least 5% higher in patients ≥65 years of age (n=418) compared to patients <65 years of age (n=2926): decreased appetite, anemia, weight decreased, asthenia, dysgeusia, neuropathy peripheral, hypomagnesemia and diarrhea. **Undesirable Effects:** This is not the complete list. The very commonly reported Adverse Events (AEs) with Phesgo includes Neutropenia, Anemia, Febrile neutropenia, Leukopenia, Lacrimation increased, Diarrhea, Nausea, Vomiting, Stomatitis, Constipation, Dyspepsia, Abdominal pain, Fatigue, Mucosal inflammation, Asthenia, Pyrexia, Edema peripheral, Injection site reactions, Nasopharyngitis, Decreased appetite, Arthralgia, Myalgia, Pain in extremity, Dysgeusia, Headache, Peripheral sensory neuropathy, Neuropathy peripheral, Dizziness, Paraesthesia, Insomnia, Epistaxis, Cough, Dyspnea, Alopecia, Rash, Nail disorder, Pruritus, Dry skin, Hot flush. **Interactions with other medicinal products and other forms of interaction:** No formal drug-drug interaction studies have been performed. **Overdose:** There is no experience with overdose of Phesgo in human clinical trials. The highest Phesgo dose tested is 1200 mg pertuzumab/600 mg trastuzumab. **Storage:** Vials: - Store in a refrigerator at 2°C - 8°C. Keep vial in the outer carton in order to protect from light. DO NOT FREEZE. This medicine should not be used after the Expiry Date shown on the pack. The 1200 mg pertuzumab/600 mg trastuzumab and 600 mg pertuzumab/600 mg trastuzumab solution are ready to use solutions for injection which does not need to be mixed with other drugs or diluted. Once transferred from the vial to the syringe, the medicinal product is physically and chemically stable for 28 days at 2°C - 8°C or 24 hours at 9°C - 30°C *Shelf-life:* 18 Months Please read full prescribing information before usage. **Details of Permission or License Number with date:** Permission No. IMP/BIO/21/000082 dated 01-Oct-2021 **Date of Revision:** Current at January 2022, Version 2.0

Disclaimer:

® = Registered Trade Mark F. Hoffmann - La Roche Limited, Basel, Switzerland.
For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.
Full prescribing information available on request.
For scientific information on Roche Medicinal Product please write to india.medinfo@roche.com
For all Adverse Events/Special Situation Reports with Roche Medicinal Product please report the same to india.drugsafety@roche.com within one business day/24 hours.
This promotional input is not valid after 4/3/2023 or any update

Marketed in India by:
Roche Products (India) Pvt. Ltd.
146-B, 166 A, Unit No. 7, 8, 9v8th Floor, R City Office, R City MallvLal Bahadur Shastri MargvGhatkopar, Mumbai - 400 086
Maharashtra;vTel No. +91 22 50457300;vFax No. +91 22 50457301

M-IN-00001397

PHESGO™
PERTUZUMAB-TRASTUZUMAB