Transform the journey for your HER2+ Breast Cancer patients

M-IN-00002517

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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

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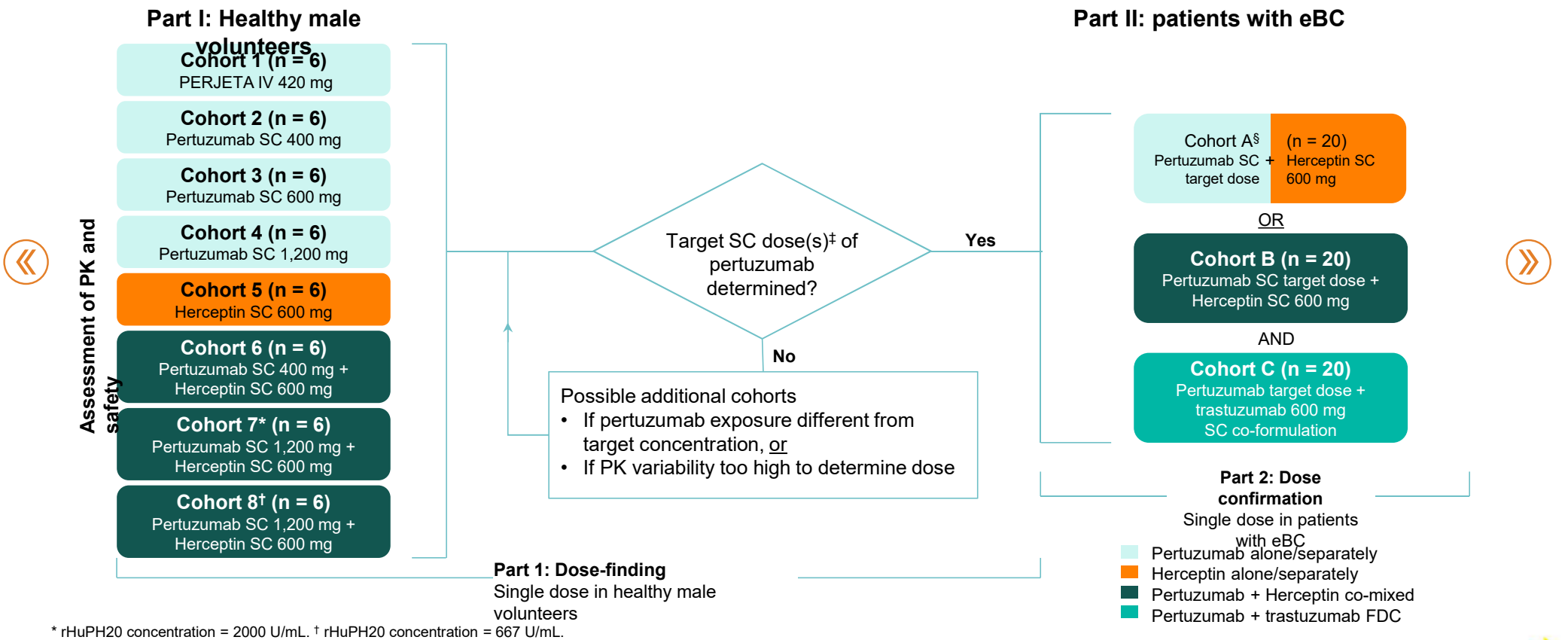
BO30185: Phase Ib dose-finding study was used to select the dose of pertuzumab for PHESGO



* 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.

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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.

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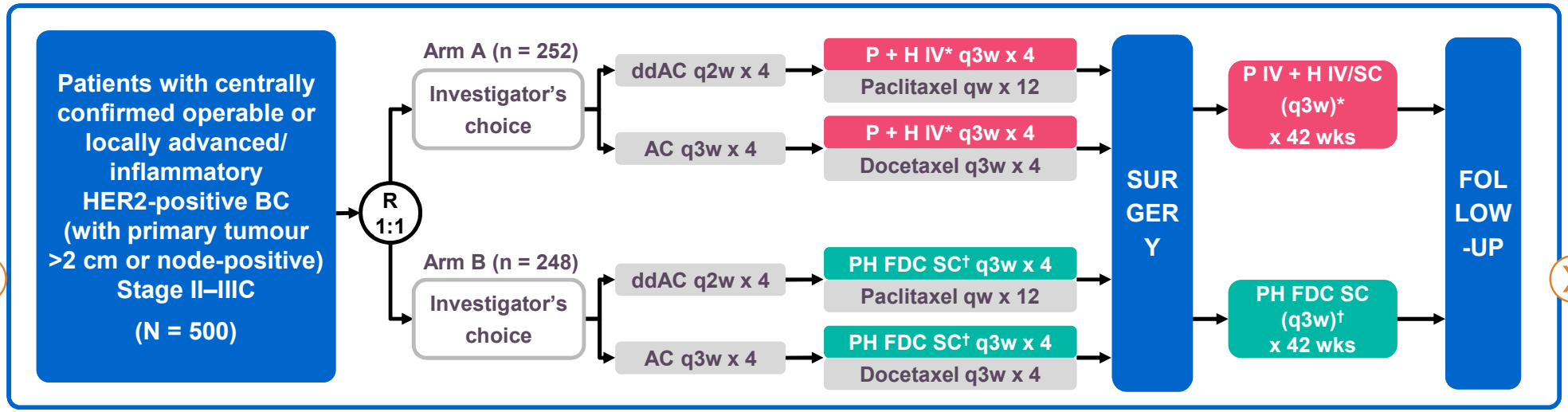
FeDeriCa: Phase III non-inferiority study assessing the PK, efficacy and safety of PH FDC SC vs. P + H IV



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.

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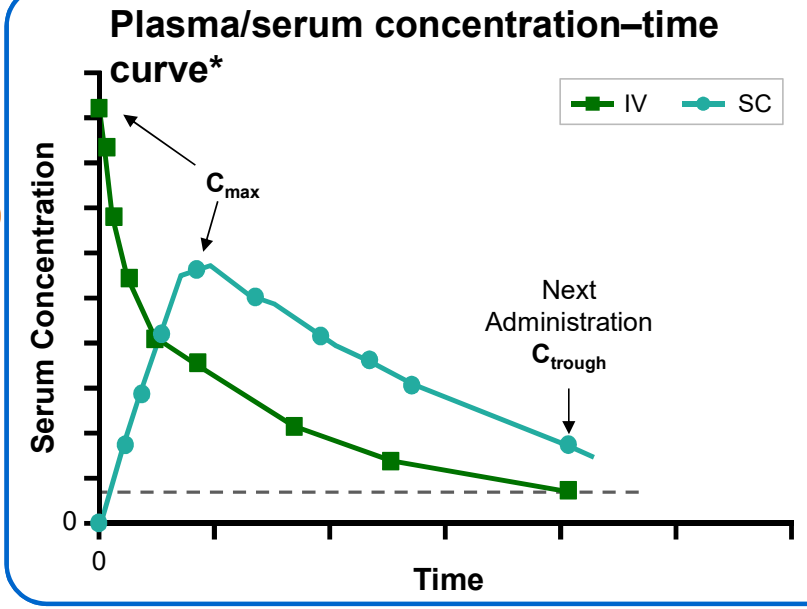
Pharmacokinetic (PK) parameters are important for understanding bioequivalence between IV and SC formulations

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.

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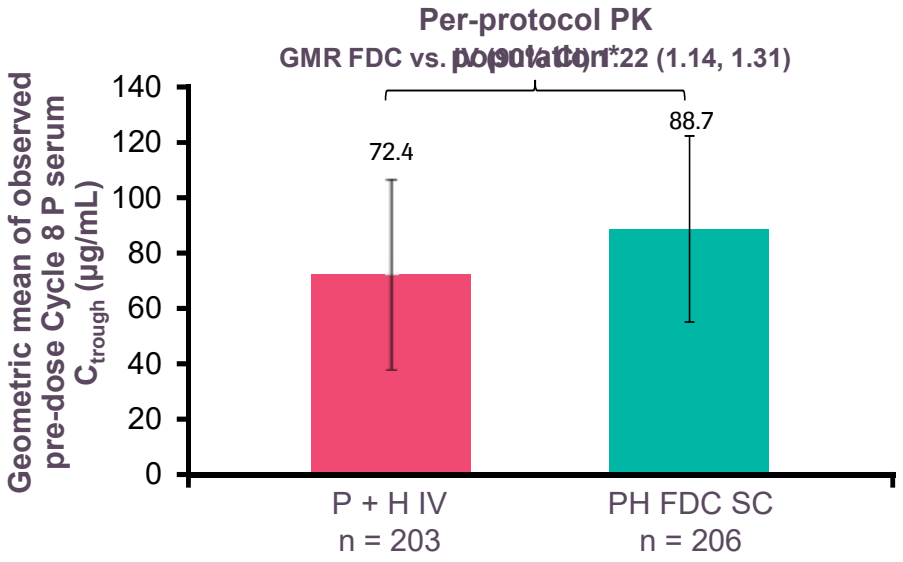
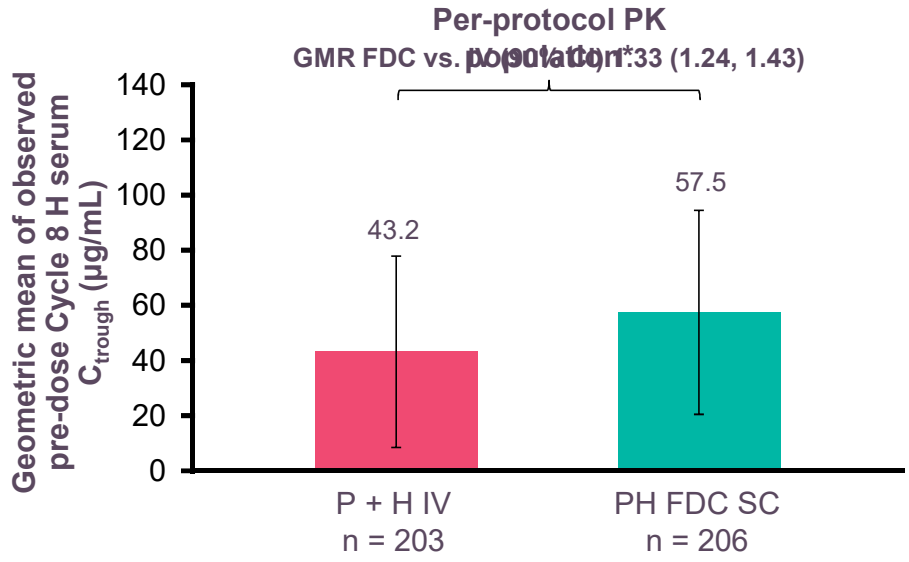
FeDeriCa: PH FDC SC was non-inferior to P + H IV, based on Cycle 7 (pre-dose Cycle 8) P and H serum C_{trough} concentrations

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.

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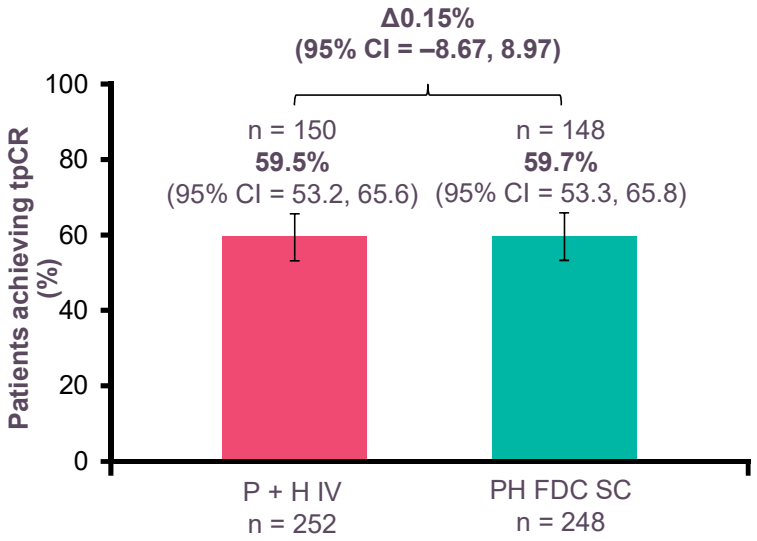
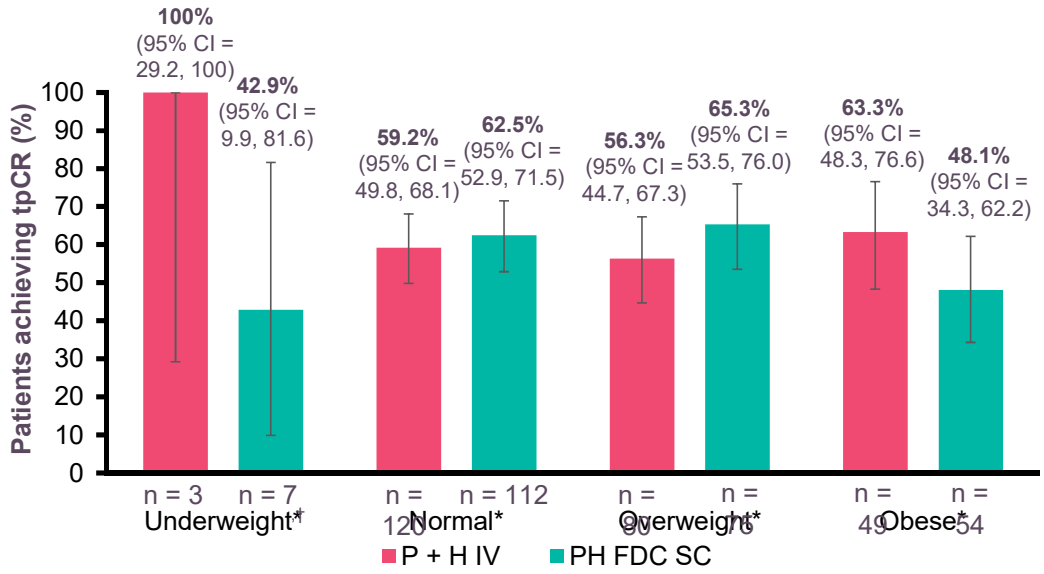
FeDeriCa: PH FDC SC had almost identical tpCR rates to P + H IV[1]

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/m^2; Normal 18.5–<25.0 kg/m^2; Overweight 25.0–<30.0 kg/m^2; Obese ≥30 kg/m^2. † 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.

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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 .

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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.

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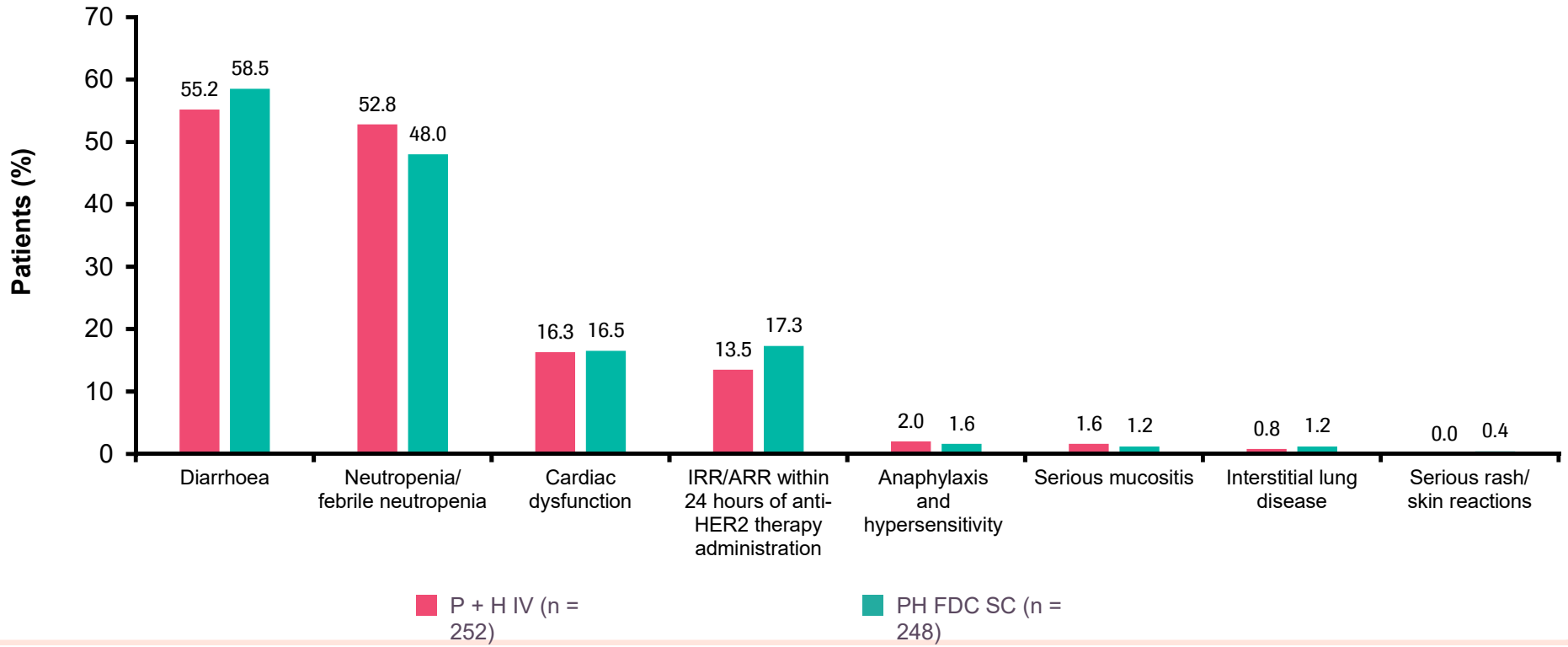
FeDeriCa: Incidence of AEs of interest, including cardiac dysfunction, IRR/ARRs and hypersensitivity, was comparable between treatment arms*



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.

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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.

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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)

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Maharashtra; Tel No. +91 22 50457300; Fax No. +91 22 50457301

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