Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection (PH FDC SC) plus chemotherapy in HER2-positive early breast cancer (EBC): Safety results from the adjuvant phase of the randomised, open-label, multicentre phase 3 (neo)adjuvant FeDeriCa study

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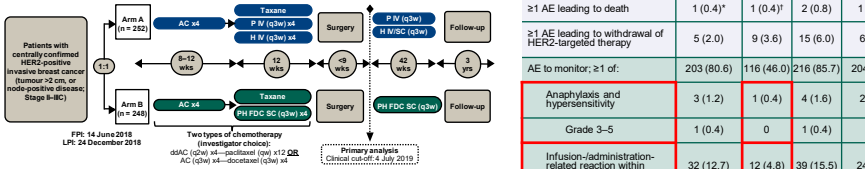
Background

- In the primary analysis of the neoadjuvant phase of the FeDeriCa study (NCT03493854),[1] PH FDC SC cycle 7 P + H serum trough concentrations were non-inferior to intravenous (IV) P + H, with comparable total pathological complete response rates and safety profiles.
  - This led to PH FDC SC approval in the US (including at-home administration) and in Europe.[2,3]
- We present updated descriptive safety data that span the adjuvant phase of the study, with an additional 12 months beyond the primary analysis (clinical cut-off 10 July 2020; including updated data from the neoadjuvant phase compared with the primary analysis).

Methods[1]



Randomisation was stratified by hormone receptor status, stage at presentation and type of chemotherapy.
Study dosing: PH FDC SC q3w: 1200 mg P SC/600 mg H SC loading dose in 15 mL, 600 mg each maintenance in 10 mL; P IV q3w: 840 mg loading dose, 420 mg maintenance; H IV q3w: 8 mg/kg loading dose, 6 mg/kg maintenance; H SC q3w: 600 mg; ddAC q2w: 60 mg/m^2 A/600 mg/m^2 C; paclitaxel qw: 80 mg/m^2; docetaxel q3w: 75 mg/m^2, escalating to 100 mg/m^2 if tolerated; AC q3w, same doses as ddAC. (dd)AC, (dose-dense) doxorubicin + cyclophosphamide; FPI, first patient in; LPI, last patient in; P + H IV, intravenous pertuzumab plus trastuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; qw, every week; q2w, every 2 weeks; q3w, every 3 weeks. Reprinted from *Lancet Oncology* **22**, Tan AR, *et al*, Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection plus chemotherapy in HER2-positive early breast cancer (FeDeriCa): a randomised, open-label, multicentre, non-inferiority, phase 3 study, p85–97, Copyright (2021), with permission from Elsevier.

Results

- An adverse event (AE) overview is shown in Table 1. Most grade 3–5 AEs were grade 3 or 4 (except the deaths mentioned in the footnotes); mostly occurring during chemotherapy.
- During the adjuvant phase:
  - Infusion-/administration-related reactions within 24 hours were higher with PH FDC SC (17.3%) than with P + H IV (4.8%) (Table 1); all were grade 1/2 and mostly due to local injection site reactions associated with SC administration.
  - No grade 3–5 anaphylaxis or hypersensitivity was reported in either arm (Table 1).
    - All grade 1 or 2 events had an onset within 24 hours of treatment.
    - All patients recovered/all events resolved.
  - The most common AEs were diarrhoea (21.0% with P + H IV and 17.3% with PH FDC SC), radiation skin injury (21.0% and 20.2%, respectively) and arthralgia (20.6% and 18.1%, respectively).
  - Selected AE incidence rates by body weight quartile are shown in Table 2.
- In the updated cardiac safety analysis (Table 3), one patient died from heart failure (New York Heart Association [NYHA] class III/IV) and a significant left ventricular ejection fraction (LVEF) decline in the P + H IV arm, and one event resolved. There was one instance of cardiac death (definite or probable) in this arm, which was recorded as "cardiac failure suspected to be caused by P + H IV." In the PH FDC SC arm, two of the three heart failure (NYHA class III/IV) and significant LVEF decline events resolved, and the cardiac death (definite or probable) was due to acute myocardial infarction which was not related to HER2 treatment (it occurred after cycle 2; hence, prior to the start of PH FDC SC).

Table 1. Summary of AEs and AEs to monitor by treatment regimen (safety population)

	P + H IV (n = 252)			PH FDC SC (n = 248)		
	Phase			Phase		
No. patients (%)	Neoadjuvant	Adjuvant	Overall	Neoadjuvant	Adjuvant	Overall
≥1 AE (any grade)	249 (98.8)	218 (86.5)	251 (99.6)	248 (100)	221 (89.1)	248 (100)
Related (HER2-targeted therapy)	152 (60.3)	118 (46.8)	183 (72.6)	144 (58.1)	149 (60.1)	188 (75.8)
≥1 grade 3–5 AE	131 (52.0)	37 (14.7)	149 (59.1)	124 (50.0)	28 (11.3)	133 (53.6)
Related (HER2-targeted therapy)	29 (11.5)	15 (6.0)	42 (16.7)	25 (10.1)	9 (3.6)	31 (12.5)
≥1 serious AE	43 (17.1)	8 (3.2)	50 (19.8)	39 (15.7)	10 (4.0)	47 (19.0)
≥1 AE leading to death	1 (0.4)*	1 (0.4)†	2 (0.8)	1 (0.4)‡	1 (0.4)§	2 (0.8)
≥1 AE leading to withdrawal of HER2-targeted therapy	5 (2.0)	9 (3.6)	15 (6.0)	6 (2.4)	5 (2.0)	12 (4.8)
AE to monitor; ≥1 of:	203 (80.6)	116 (46.0)	216 (85.7)	204 (82.3)	111 (44.8)	220 (88.7)
Anaphylaxis and hypersensitivity	3 (1.2)	1 (0.4)	4 (1.6)	2 (0.8)	2 (0.8)	4 (1.6)
Grade 3–5	1 (0.4)	0	1 (0.4)	0	0	0
Infusion-/administration-related reaction within 24 hours	32 (12.7)	12 (4.8)	39 (15.5)	24 (9.7)	43 (17.3)	55 (22.2)
Grade 3–5	3 (1.2)	0	3 (1.2)	0	0	0
Serious rash/skin reaction	0	0	0	0	1 (0.4)	1 (0.4)
Grade 3–5	0	0	0	0	0	0
Diarrhoea	138 (54.8)	53 (21.0)	149 (59.1)	148 (59.7)	43 (17.3)	153 (61.7)
Grade 3–5	10 (4.0)	3 (1.2)	13 (5.2)	18 (7.3)	0	18 (7.3)
Cardiac dysfunction	36 (14.3)	33 (13.1)	66 (26.2)	33 (13.3)	20 (8.1)	53 (21.4)
Grade 3–5	3 (1.2)	8 (3.2)	12 (4.8)	1 (0.4)	2 (0.8)	3 (1.2)
Interstitial lung disease	2 (0.8)	1 (0.4)	3 (1.2)	2 (0.8)	3 (1.2)	5 (2.0)
Grade 3–5	0	0	0	0	0	0
Neutropenia/ febrile neutropenia	131 (52.0)	49 (19.4)	142 (56.3)	118 (47.6)	31 (12.5)	123 (49.6)
Grade 3–5	88 (34.9)	9 (3.6)	92 (36.5)	79 (31.9)	10 (4.0)	82 (33.1)
Serious mucositis	4 (1.6)	0	4 (1.6)	3 (1.2)	0	3 (1.2)
Grade 3–5	4 (1.6)	0	4 (1.6)	2 (0.8)	0	2 (0.8)
Pregnancy- and neonatal-related‖	4 (1.6)	4 (1.6)	8 (3.2)	3 (1.2)	2 (0.8)	5 (2.0)
Grade 3–5	2 (0.8)	1 (0.4)	3 (1.2)	0	1 (0.4)	1 (0.4)

* Urosepsis. † Related cardiac failure. ‡ Acute myocardial infarction. § Unexplained. ‖ Includes exposure during pregnancy, exposure during breastfeeding, pregnancy complications, oligohydramnios and congenital abnormalities.
AE, adverse event; P + H IV, intravenous pertuzumab plus trastuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection.

Table 2. Summary of AEs by treatment regimen and body weight quartile (safety population)

	P + H IV (n = 252)			PH FDC SC (n = 248)		
	Phase			Phase		
No. patients (%)	Neoadjuvant	Adjuvant	Overall	Neoadjuvant	Adjuvant	Overall
≥1 treatment-emergent serious AE*						
Q1: <58.0 kg	8 (3.2)	2 (0.8)	10 (4.0)	8 (3.2)	3 (1.2)	12 (4.8)
Q2: 58.0–65.0 kg	8 (3.2)	1 (0.4)	9 (3.6)	6 (2.4)	4 (1.6)	9 (3.6)
Q3: 65.0–77.0 kg	14 (5.6)	3 (1.2)	16 (6.3)	7 (2.8)	3 (1.2)	8 (3.2)
Q4: >77.0 kg	13 (5.2)	2 (0.8)	15 (6.0)	18 (7.3)	0	18 (7.3)
Total	43 (17.1)	8 (3.2)	50 (19.8)	39 (15.7)	10 (4.0)	47 (19.0)
≥1 cardiac dysfunction†						
Q1: <58.0 kg	11 (4.4)	9 (3.6)	19 (7.5)	8 (3.2)	7 (2.8)	15 (6.0)
Q2: 58.0–65.0 kg	5 (2.0)	6 (2.4)	11 (4.4)	5 (2.0)	4 (1.6)	9 (3.6)
Q3: 65.0–77.0 kg	12 (4.8)	13 (5.2)	22 (8.7)	6 (2.4)	3 (1.2)	8 (3.2)
Q4: >77.0 kg	8 (3.2)	5 (2.0)	14 (5.6)	14 (5.6)	6 (2.4)	21 (8.5)
Total	36 (14.3)	33 (13.1)	66 (26.2)	33 (13.3)	20 (8.1)	53 (21.4)
≥1 significant LVEF decline‡						
Q1: <58.0 kg	1 (0.4)	6 (2.4)	6 (2.4)	0	3 (1.2)	3 (1.2)
Q2: 58.0–65.0 kg	0	3 (1.2)	3 (1.2)	0	1 (0.4)	1 (0.4)
Q3: 65.0–77.0 kg	3 (1.2)	5 (2.0)	6 (2.4)	0	2 (0.8)	2 (0.8)
Q4: >77.0 kg	0	2 (0.8)	2 (0.8)	3 (1.2)	4 (1.6)	7 (2.8)
Total	4 (1.6)	16 (6.3)	17 (6.7)	3 (1.2)	10 (4.0)	13 (5.2)
≥1 AE leading to withdrawal of HER2-targeted therapy						
Q1: <58.0 kg	1 (0.4)	2 (0.8)	3 (1.2)	1 (0.4)	1 (0.4)	2 (0.8)
Q2: 58.0–65.0 kg	1 (0.4)	3 (1.2)	4 (1.6)	1 (0.4)	2 (0.8)	3 (1.2)
Q3: 65.0–77.0 kg	3 (1.2)	3 (1.2)	6 (2.4)	1 (0.4)	1 (0.4)	3 (1.2)
Q4: >77.0 kg	0	1 (0.4)	2 (0.8)	3 (1.2)	1 (0.4)	4 (1.6)
Total	5 (2.0)	9 (3.6)	15 (6.0)	6 (2.4)	5 (2.0)	12 (4.8)

*Overall" includes AEs from post-screening, neoadjuvant, adjuvant and follow-up phases. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient. † Occurring on the day or after first administration of study drug until 28 days after last study drug administration. ‡ Cardiac failure (wide Standardised MedDRA queries). § LVEF drop of ≥10% points from baseline and to <50%.
AE, adverse event; P + H IV, intravenous pertuzumab plus trastuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; Q, quartile.

Table 3. Cardiac events at primary and updated analyses (safety population)

	P + H IV (n = 252)		PH FDC SC (n = 248)	
No. patients (%)	Primary analysis (4 July 2019)[1]	Updated analysis (10 July 2020)	Primary analysis (4 July 2019)[1]	Updated analysis (10 July 2020)
Primary event	0	2 (0.8)	2 (0.8)	4 (1.6)
Heart failure (NYHA class III/IV) and significant LVEF decline*	0	2 (0.8)	1 (0.4)†	3 (1.2)
Cardiac death (definite/probable)	0	1 (0.4)	1 (0.4)‡	1 (0.4)
Secondary event§	2 (0.8)	10 (4.0)	1 (0.4)	2 (0.8)

* LVEF drop of ≥10% points from baseline and to <50%. † Not resolved. ‡ Acute myocardial infarction, not related to HER2 treatment (occurred after cycle 2; hence, occurred prior to the start of PH FDC SC). § Asymptomatic or mildly symptomatic left ventricular systolic dysfunction (ejection fraction decreased) of NYHA Functional Classification Class II, following the LVEF definition above, confirmed by a second assessment within ~3 weeks; only counted for patients not experiencing primary cardiac events.
AE, adverse event; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; P + H IV, intravenous pertuzumab plus trastuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection.

Conclusions

- **Overall safety and tolerability, including cardiac safety, of PH FDC SC in the adjuvant phase of FeDeriCa remained comparable to those of P + H IV, with the exception of AEs associated with the different routes of administration.**
- **Results are in line with the expectation that most AEs with PH FDC SC or P + H IV are observed during concomitant chemotherapy.**
- **AE incidence rates were balanced across body weight quartiles, both within and between treatment arms and including the lowest quartile, which was consistent with the overall safety profile.**
- **PH FDC SC offers a faster, more convenient and less invasive treatment option for HER2-positive BC than standard P + H IV.[1]**

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Conflicts of interest

S-AI reports advisory/consultancy roles for AstraZeneca, Amgen, Eisai, Hanmi, GSK, Lilly, MSD, Novartis, Roche and Pfizer; investigator-initiated clinical trial research grants through her institution from AstraZeneca, Eisai, Daewoong Pharm, Roche and Pfizer; and medical writing support from F. Hoffmann-La Roche Ltd. For disclosures of co-authors, please see abstract. This study was funded by F. Hoffmann-La Roche Ltd and Genentech, Inc.