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116P Time and motion randomised study of a subcutaneous (SC) pertuzumab and trastuzumab fixed-dose combination (PH FDC) for the treatment of HER2-positive early breast cancer (HER2 EBC): PHaTiMa

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Background

- Human epidermal growth factor receptor-2 (HER2) is a tyrosine kinase receptor involved in cell proliferation, survival and differentiation, frequently overexpressed in breast cancer and associated with worse prognosis.
- Trastuzumab and pertuzumab are humanised monoclonal antibodies blocking HER2, and their combination exerts synergistic activity due to their complementary mode of action.
- The pivotal FeDeriCa study (randomised, open-label, multicentre, non-inferiority, phase III: NCT03493854) demonstrated that the subcutaneous fixed-dose combination of pertuzumab and trastuzumab (PH-FDC-SC) provided non-inferior cycle 7 pertuzumab serum C_{trough} concentrations to intravenous pertuzumab plus trastuzumab (P-IV+H-IV), both administered every 3 weeks with chemotherapy in HER2-positive breast cancer (HER2 BC), with comparable total pathological complete response rates and that safety was similar between treatment groups, and in line with other pertuzumab, trastuzumab and chemotherapy trials.[1]
- The PHranceSCa study (randomised, crossover, open-label, phase II: NCT03674112) showed that patients with HER2 BC strongly preferred PH-FDC-SC over PH-IV, and that PH-FDC-SC was generally well tolerated, with no new safety signals (even when switching from P-IV+H-IV to PH-FDC-SC or vice versa).[2]
- Time and motion sub-analyses of the prospective, observational PrefHer study (NCT01401166) have found that for trastuzumab, H-SC versus H-IV significantly saved patient chair and active HCP times and reduced health care costs in patients with HER2 BC.[3,4] This and other studies have shown that in oncologic monotherapy, SC compared to IV route brings advantages like patients' and healthcare professionals (HCP) preference and improved healthcare efficiency, thanks to reductions of both time and use of resources. It would be interesting to assess whether, in dual therapies, the advantages of the SC route compared to IV are added to those of the fixed-dose combination compared to the separate administration of drugs.
- PHaTiMa is a time and motion study evaluating dual blockade with combined P+H treatment in patients with HER2 BC. The objectives were to assess time saved by patients and HCP and what resources were used with PH-FDC-SC versus P-IV+H-IV or P-IV+H-SC.

Methods

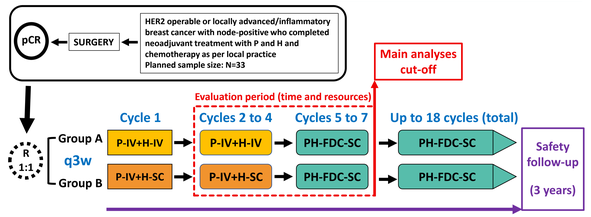
Clinical trial identification: EudraCT 2020-004241-36.

This is a national (performed in Spain), multicentre, interventional, randomised, open label, Phase IIIb clinical trial assessing time and resources during adjuvant treatment of HER2 early breast cancer (EBC) with pathologic complete response (pCR) after neoadjuvant dual blockade and chemotherapy.

From cycles 1 to 4, patients were randomly treated with pertuzumab (Perjeta® or P) IV and trastuzumab (Herceptin® or H) either IV or SC (P-IV+H-IV or P-IV+H-SC) every 3 weeks, and later with subsequent PH-FDC-SC (Phesgo®) every 3 weeks from cycle 5 up to a total of 18 cycles (neoadjuvant + adjuvant) unless they decided to switch back to IV formulations. Trained observers measured with stopwatches the time used and recorded the resource utilization (consumables and drug wastage) for cycles 2 to 7 (Figure 1). For patients the time spent in the treatment room and chair was measured and for HCP the active time used preparing and administering study treatments

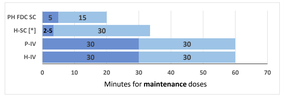
Cycle 1 was excluded for the primary and secondary analyses to avoid variability if some patients required loading doses since they require longer times for both infusion/injection and for observation post-treatment periods (Figure 2). Nonetheless, time and resources were also recorded and assessed during cycle 1, respectively serving as a training experience and to be analysed as exploratory endpoints.

Figure 1. Study design.



FDC: fixed-dose combination; H: trastuzumab; IV: intravenous; P: pertuzumab; pCR: pathologic complete response; q3w: 3-week cycles; R: randomization; SC: subcutaneous.

Figure 2. Protocol time instructions for loading and maintenance doses of the study treatments.
Patients could be observed for longer periods at the discretion of the investigator or if necessary.



Doses
PH-FDC-SC: fixed dose (non-weight based), either a 15 mL loading dose (1200 mg pertuzumab and 600 mg trastuzumab) or a 10 mL maintenance dose (600 mg pertuzumab and 600 mg trastuzumab).
H-SC: 5 mL (600 mg) fixed dose (non-weight based). No loading dose required.
P-IV: 840 mg (loading dose) and 420 mg (maintenance dose). It should be administered before H-IV or H-SC.
H-IV: 8 mg/kg (loading dose) and 6 mg/kg (maintenance dose).

[*] According to its summary of product characteristics (SmPC), the observation period for H-SC was 30 minutes. After this study had started, the observation period was reduce to 15 minutes in the SmPC (but in this study all patients were observed at least during 30 minutes after H-SC administration).

Selection criteria

Adults with node-positive HER2 EBC:

- Who had locally advanced, inflammatory, or early-stage, unilateral, with hormone receptor status either positive or negative, and histologically confirmed node-positive invasive breast cancer with initial diagnosis TNM staging any T (except T0) plus N+ and M0.
- Who have been previously treated with P, H and chemotherapy in routine clinical practice in the neoadjuvant setting, have undergone surgery and have achieved a total pathologic complete response. The study treatment must be initiated 2-8 weeks after surgery.

Study objectives

Primary objectives:

Time savings for HCP and patients with PH-FDC-SC vs P-IV+H-IV and P-IV+H-SC in the adjuvant treatment of HER2-positive EBC patients.

- Difference of HCP active time for PH-FDC-SC (adjuvant cycles 5 to 7) vs P-IV+H-IV or P-IV+H-SC (adjuvant cycles 2 to 4).
- Difference of patient time (chair and treatment room) for PH-FDC-SC (adjuvant cycles 5 to 7) vs P-IV+H-IV or P-IV+H-SC (adjuvant cycles 2 to 4).

Secondary objectives:

- Resource utilization reduction (consumables and drug wastage during the preparation and administration of study treatments) related to the different administration routes.
- Describe the safety and tolerability of the study treatments over the entire adjuvant treatment period.

Statistical analyses

- The results were analysed with paired *t*-test, comparing PH-FDC-SC versus P-IV+H-IV and P-IV+H-SC; for patients, the times spent to receive the study treatments and for HCP, the active times used to prepare and administer the study treatments.
- In the sensitivity analyses, the *t*-test for two independent samples was used to compare PH-FDC-SC versus P-IV+H-IV and P-IV+H-SC.

This is an intermediate analysis assessing the final results of the primary and secondary objectives. However, the safety results are preliminary, because the 3-year safety follow-up is expected until April 4, 2025 (or until the last visit of the last patient).

Results

Baseline characteristics

In 10 Spanish centres, 34 women were randomised (n=17 in Groups A and B).

Baseline demographic characteristics were similar between the patients in the two study treatment groups. The mean (SD) age was 52.47 (12.48) years. Most of them had less than 65 years (30 patients: 88.24%) and were white (33: 97.06%). The mean (SD) value for weight was 63.46 (10.64) kg (ranging from 49 to 97 kg) and for body mass index (BMI) was 24.83 (4.30) kg/m^2 (ranging from 20 to 39 kg/m^2) and most of them were not obese (BMI<25 kg/cm^2: 21 patients [63.64%]).

Most patients had Eastern Cooperative Oncology Group (ECOG) performance status graded 0 (31: 91.18%).

All tumours were positive to HER2 test, slightly higher number of them were hormone positive: 20 (58.82%; mainly in Group A: 12 [70.59%] and fewer in Group B: 8 [47.06%]) versus 14 (41.18%) that were hormone negative and were mainly classified as T2 (24: 70.59%) or T3 (7: 20.59%), and only 1 (2.94%, in Group A) was classified T4. Lymphatic nodes were classified N1 (23: 67.65%) or N2 (10: 29.41%), and only 1 (2.94%, in Group A) was classified N3. No patients had metastasis.

Results of primary objectives

Per cycle, PH FDC SC significantly saved patients' time in treatment room and in chair compared with P-IV+H-IV and P-IV+H-SC, respectively (Figure 3).

HCP total active time was significantly reduced, including preparation and administration times for PH FDC SC compared with P-IV+H-IV and P-IV+H-SC, respectively (Figure 4) .

Active times were reduced both for pharmacy staff (pharmacists and pharmacists' assistants) and nursing staff (nurses and nurses' assistants) for PH-FDC-SC compared with P-IV+H-IV and P-IV+H-SC, respectively (Figure 5).

Results of secondary objectives

PH-FDC-SC reduced use of several consumables. Table 1 shows the consumables whose use has greater differences with PH-FDC-SC compared to the other two treatments of the study.

Pre-medication was administered in more cycles for P-IV+H-IV (21: 43.75%), followed by P-IV+H-SC (18: 35.29%) and in fewer cycles for PH-FDC-SC (13: 13.13%).

After the reconstitution of H-IV the leftover amounts are discarded. This drug waste is avoided with the P-IV+H-SC and PH-FDC-SC treatments (Table 2).

Safety data up to cycle 7 (in 2025 ends 3-year follow-up) reported a total of 130 treatment-emergent adverse events (TEAE) in 33 (97.06%) of 34 randomised patients. A total of 38 of these TEAE (reported in 20 patients) were related to study treatments, with only 2 Grade 3: diarrhoea and a serious (SAE) drug hypersensitivity (Table 3) . This was the only SAE reported.

Only one patient presented an adverse event of special interest (AESI). It was a symptomatic decline in left ventricular ejection fraction (LVEF) of >10 percentage points from baseline to a LVEF of <50%, and was rated as grade 2. This AESI (decreased ejection fraction) and the SAE (drug hypersensitivity) were the 2 TEAE leading to treatment discontinuation.

No TEAE led to death. No grade 3 and grade 4 TEAE occurred during the reported follow-up period.

Figure 3. Mean time (minutes) per cycle spent by patients to receive study treatments (ITT population).

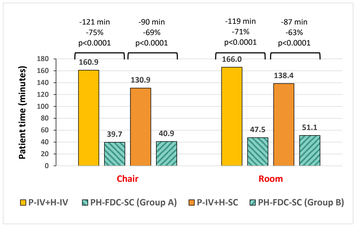


Figure 4. Active HCP mean time (minutes) per cycle for total and for preparation/administration of study treatments (ITT population).

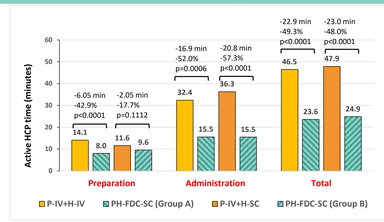
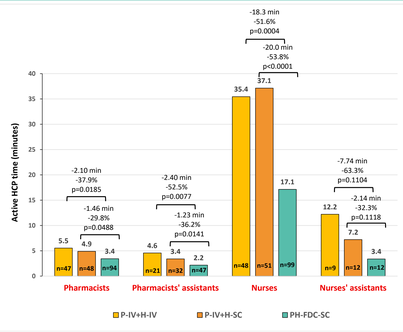


Figure 5. Total active mean time (minutes) per cycle used by pharmacy and nursing staff. Sensitivity analyses (ITT population).



n: number of observations without missing values for each treatment.
Total observations correspond to the total number of patients for all cycles (number of patients **x** number of cycles):
For P-IV+H-IV: 17 patients / 51 observations. For P-IV+H-SC : 17 patients / 51 observations. For PH-FDC-SC: 34 patients / 102 observations.

Table 1. Consumables used during the evaluation period (ITT population).
Only the results with differences with PH-FDC-SC compared with the other treatments are shown.

Mean (units or mL) per cycle	Group A 17 patients / 51 observations		Group B 17 patients / 51 observations	
	P-IV+H-IV	PH-FDC-SC	P-IV+H-SC	PH-FDC-SC
3-Way valve (units)	n=31	X	n=33	n=3
Mean	1.13		1.12	1.00
Port-a-cath or peripheral IV catheter (units) [*]	n=48	n=1	n=50	n=3
Mean	1.08	1.00	1.08	1.00
Heparinized solution (3 mL units)	n=12	n=1	n=14	n=3
Mean	2.25	1.00	2.00	1.00
Injectable water (mL)	n=25	X	n=11	X
Mean	23.92	---	11.45	---
Perfusion pump kit (units)	n=46	X	n=48	X
Mean	1.00		1.04	---
Pump adaptor with spike (units)	n=25	X	n=20	X
Mean	1.56	---	1.00	---
Saline solution (mL)	n=48	n=11	n=51	n=11
Mean	526.67	10.64	300.80	8.09
Transfusion extension tube (units)	n=25	X	n=32	X
Mean	1.20	---	1.19	---
Vented spike (units)	n=25	n=3	n=21	n=3
Mean	2.20	1.00	1.24	1.00

[*] Port-a-cath was used by 5 patients in Group A and 4 patients in Group B.
n: number of observations without missing values regarding the use of each consumable; X: consumables not used.
Total observations correspond to the total number of patients for all cycles (number of patients **x** number of cycles).

Table 2. Discarded trastuzumab from reconstituted vials of intravenous formulation (H-IV). ITT population.

	Mean (SD) per patient and cycle	Percent discarded from 150 mg vials
Cycle 1 [*]	83.1 (45.3) mg	55.4%
Cycles 2-4	86.3 (41.2) mg	57.5%

[*] In **cycle 1**, less trastuzumab is discarded because in some patients a **loading dose** will have to be used that is twice the maintenance dose (8 mg/kg body weight versus 6 mg/kg body weight). However, in the other cycles, the maintenance dose is used. Then in cycle 1 it is more frequent that a larger amount (mean of 86.3 mg) will be discarded.

This **drug waste** is **avoided** with the **P-IV+H-SC** and **PH-FDC-SC** treatments.

Table 3. Treatment-emergent adverse events (TEAE) related to study treatments (safety population).
Preliminary safety data up to cycle 7 (see study design in Figure 1).

Treatment-emergent adverse events (TEAE) related to the study treatments					
Patients	Related TEAE	(n/N) %: For P-IV and PH-FDC-SC, the percentages are calculated with respect to the 34 patients in the safety population, and for H-IV and H-SC with respect to 17 patients in the safety population respectively for Group A or Group B (because only half of the safety population received one of these treatments).			
		P-IV	H-IV	H-SC	PH-FDC-SC
N=20	n=38	17/10 (29.41%)	9/5 (29.41%)	11/6 (35.29%)	16/12 (35.29%)
Preferred terms and relevant classifications of TEAE related to study treatment					
N=3			Drug hypersensitivity **(1/1)**: G3, SAE, discontinuation		
			Diarrhea **(1/1)**: G3		
					Ejection fraction decreased **(1/1)**: G2, SAE, EASI, discontinuation

N: number of patients; **n:** number of events; **discontinuation:** adverse event leading to treatment discontinuation.
AESI: adverse events of special interest; **FDC:** fixed-dose combination; **G2:** severity grade 2; **G3:** severity grade 3; **H:** trastuzumab; **IV:** intravenous; **P:** pertuzumab; **SAE:** serious adverse event; **SC:** subcutaneous.

Conclusions

- PH-FDC-SC was a more efficient option for health care centres:
  - Significantly saved time to HCP.
  - Significantly reduced use of healthcare resources and consumables.
  - Avoided drug waste.
- PH-FDC-SC improved quality of health care assistance to patients:
  - Significantly saved time to patients receiving treatment in the hospital.
- Preliminary safety data indicated that the study treatments were well tolerated, and consistent with known safety profiles.
- These results support that in dual therapies the advantages of the SC versus IV route are added to those of fixed dose combination versus separate administration of drugs.
- Together with previous findings showing comparable efficacy and safety profiles and patients' preference of PH-FDC-SC versus P-IV+H-IV, these results encourage the use of PH-FDC-SC for dual blockade treatment of HER2 BC.

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Disclosures of first and presenting author

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