Anaphylaxis and hypersensitivity in trials of intravenous pertuzumab + trastuzumab (PH IV) or the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection (PH FDC SC) for HER2-positive breast cancer (BC)

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Background

- PH is the standard of care for previously untreated HER2-positive metastatic BC (MBC) and high-risk HER2-positive early BC (EBC).[1–3]
- PH can be administered either as two sequential IV administrations[4] or as a PH FDC SC.[5]
- PH IV and PH FDC SC are usually given with chemotherapy, all of which can trigger anaphylaxis/hypersensitivity that may be life-threatening.[4,5] Hypersensitivity and administration-related reactions may include dizziness, nausea, chills, fever, vomiting, diarrhoea, urticaria, angio-oedema, breathing problems or chest pain.[5]
- In the US, PH FDC SC can be administered by healthcare professionals in patients' homes.[6] Therefore, there is a need to provide a broader characterisation of the incidence and severity of anaphylaxis/hypersensitivity with PH-based regimens.

Methods

- This exploratory analysis was designed to assess the occurrence, incidence and severity of anaphylaxis/hypersensitivity events with PH IV or PH FDC SC in pivotal Roche clinical trials. A time-trend analysis (by cycle) was performed for these studies, excluding those with neoadjuvant use only of PH IV.
- A cumulative search for anaphylaxis/hypersensitivity events (Roche Standard Adverse Event Group Terms and Medical Dictionary for Regulatory Activities v22.1; see preferred terms in supplement) from 11 September 2001 to 25 August 2020 was conducted for patients treated with PH IV or PH FDC SC across all pivotal trials assessed by the European Medicines Agency to support the current P IV and PH FDC SC labels.
- Trials included in this analysis were MBC: CLEOPATRA,[7] MetaPHER;[8] EBC: APHINITY,[9] NeoSphere,[10] TRYPHAENA,[11] BERENICE,[12] FeDeriCa,[13] PHranceSCa[14] (see Table).
- Patients received PH IV or PH FDC SC according to protocol guidance (see supplementary material).

Results

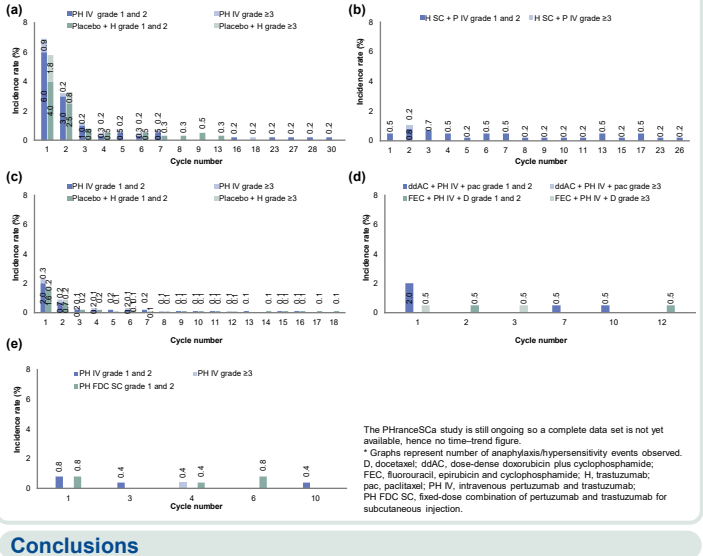
- This analysis includes 4772 patients.[7–14]
- Incidence of grade ≥3 anaphylaxis/hypersensitivity events was generally low (0.2–2.0% for MBC studies, 0–0.8% in the adjuvant EBC setting and 0–2.8% in the neoadjuvant EBC setting) (Table).
- Anaphylaxis/hypersensitivity events were managed by modifying or discontinuing either chemotherapy, anti-HER2 treatment or both; no fatal events due to anaphylaxis/hypersensitivity were reported.
- Time–trend analyses showed that most all-grade and grade ≥3 anaphylaxis/hypersensitivity events occurred during the first 6–8 cycles of treatment, when PH was administered in combination with chemotherapy (Figures).
- Discontinuations due to anaphylaxis/hypersensitivity were rare for PH IV (generally ≤1% except for one arm in TRYPHAENA, which was 3%); no discontinuations of PH FDC SC had been recorded up until 25 August 2020.

Table. Incidence and severity of anaphylaxis/hypersensitivity events in pivotal Roche trials of PH IV and PH FDC SC

			Patients with events, n (%)		PH discontinuation rate due to anaphylaxis/ hypersensitivity,* patients, n (%)
		Patients, n	All grades	Grade ≥3	
PH IV (MBC)	**CLEOPATRA** (NCT00567190)				
	Placebo + H + D	397	36 (9.1)	10 (2.5)	n/a
	PH IV + D	407	44 (10.8)	8 (2.0)	4 (1.0)
	MetaPHER (NCT02402712)				
	H SC + P IV + D	412	14 (3.4)	1 (0.2)	1 (0.2)
PH IV (EBC)	**APHINITY** (NCT01358877)				
	PH IV + chemo	2364	116 (4.9)	18 (0.8)	6 (0.3)
	Placebo + H IV + chemo	2405	86 (3.6)	17 (0.7)	n/a
	NeoSphere†,‡ (NCT00545688)				
	Arm A (H IV + D)	107	2 (1.9)	0	n/a
	Arm B (PH IV + D)	107	6 (5.6)	1 (0.9)	1 (0.9)
	Arm C (PH IV)	108	6 (5.6)	2 (1.9)	1 (0.9)
	Arm D (P IV + D)	94	6 (6.4)	0	0
	TRYPHAENA†,‡ (NCT00976989)				
	Arm A (FEC + PH IV → PH IV + D)	72	7 (9.7)	2 (2.8)	1 (1.4)
	Arm B (FEC → PH IV + D)	75	1 (1.3)	0	0
	Arm C (PH IV + C + D)	76	10 (13.2)	2 (2.6)	2 (2.6)
	BERENICE†,§ (NCT02132949)				
	Cohort A (ddAC + PH IV + pac)	199	7 (3.5)	0	0
	Cohort B (FEC + PH IV + D)	198	5 (2.5)	2 (1.0)	2 (1.0)
PH FDC SC (EBC)	**FeDeriCa** (NCT03493854)				
	PH IV + chemo	252	4 (1.6)	1 (0.4)‖	1 (0.4)
	PH FDC SC + chemo	248	4 (1.6)	0	0
	PHranceSCa (NCT03674112)				
	PH IV → PH FDC SC crossover	80	0	0	0
	PH FDC SC → PH IV crossover	80	3 (1.9)¶	0	0
	PH IV continuation	21**	0	0	0
	PH FDC SC continuation	137**	2 (1.5)	0	0

The control arms (without PH IV or PH FDC SC) are included for comparison. Median number of cycles of P IV or PH FDC SC in each study: CLEOPATRA, 24.0; MetaPHER, 21.5; APHINITY, 18.0; NeoSphere, 4.0 in each arm; TRYPHAENA, 6.0, 3.0 and 6.0 for Arms A, B and C, respectively; BERENICE, 17.0 in each cohort (4.0 neoadjuvant and 13.0 adjuvant); FeDeriCa, 18.0 in each arm (4.0 neoadjuvant and 14.0 adjuvant); PHranceSCa, 16.5 (all patients; total PH IV and PH FDC SC across neoadjuvant [pre-enrolment] and adjuvant periods). * Discontinuation of PH IV or PH FDC SC. † Events reported for the neoadjuvant period only. ‡ In NeoSphere and TRYPHAENA, PH IV was administered during neoadjuvant treatment. After surgery, patients received adjuvant H only. § In the BERENICE adjuvant period, a further two events (1.1%) were recorded in Cohort A (n = 181) and one event (0.5%) in Cohort B (n = 190). ‖ Grade ≥3 event was an allergic reaction to concomitant medication (levofloxacin). ¶ Events were injection-related reactions related to PH FDC SC administration. ** Patients who received treatment during the continuation period of PHranceSCa are a subset of those who received treatment during the crossover period. C, carboplatin; chemo, chemotherapy; D, docetaxel; ddAC, dose-dense doxorubicin plus cyclophosphamide; EBC, early breast cancer; FEC, fluorouracil, epirubicin and cyclophosphamide; H, trastuzumab; MBC, metastatic breast cancer; pac, paclitaxel; PH IV, intravenous pertuzumab and trastuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection.

Figures. Incidence of anaphylaxis/hypersensitivity events during HER2-targeted therapy by cycle.* (a) Events in CLEOPATRA; b) events in MetaPHER; (c) events in APHINITY; (d) events in BERENICE; (e) events in FeDeriCa



The PHranceSCa study is still ongoing so a complete data set is not yet available, hence no time–trend figure.
* Graphs represent number of anaphylaxis/hypersensitivity events observed. D, docetaxel; ddAC, dose-dense doxorubicin plus cyclophosphamide; FEC, fluorouracil, epirubicin and cyclophosphamide; H, trastuzumab; pac, paclitaxel; PH IV, intravenous pertuzumab and trastuzumab; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection.

Conclusions

- **PH IV and PH FDC SC are well tolerated, with few grade ≥3 anaphylaxis/hypersensitivity events reported with PH IV and no grade ≥3 events with PH FDC SC.**
- **The majority of the anaphylaxis/hypersensitivity events were grade 1/2 and occurred within the first 6–8 cycles when PH IV or PH FDC SC were given in combination with chemotherapy.**
- **Patients should be closely monitored during and after PH IV infusions and PH FDC SC injections. If a significant infusion- or injection-related reaction occurs, slow down or pause treatment and administer appropriate medical therapies. Patients should be carefully monitored until complete resolution of symptoms. Permanently discontinue PH IV or PH FDC SC in patients who experience anaphylaxis or severe infusion- or injection-related reactions.[4,5]**

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Conflicts of interest

SMS reports honoraria received for consulting or advisory role from AstraZeneca, Daiichi Sankyo, F. Hoffmann-La Roche Ltd/Genentech, Inc., Exact Sciences (Genomic Health), Molecular Templates, Silverback Therapeutics, Merck, Lilly, Natera, Athenex and Beijing Medical Foundation; advisory board for Inivata; research grants or funding to institution received from F. Hoffmann-La Roche Ltd/Genentech, Inc. and Kailos Genetics; travel/accommodation/expenses from F. Hoffmann-La Roche Ltd/Genentech, Inc., Daiichi Sankyo and Caris Life Sciences. All authors have received support for third-party writing assistance for this ePoster from F. Hoffmann-La Roche Ltd. Please refer to the abstract for all author conflicts of interest. This study was sponsored by F. Hoffmann-La Roche Ltd.

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Supplementary
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