European Journal of Cancer 178 (2023) 70–81

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Incidence and severity of anaphylaxis and hypersensitivity in trials of intravenous pertuzumab plus trastuzumab or the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection for HER2-positive breast cancer

Sandra M. Swain [a,*], Antoinette R. Tan [b], Luca Gianni [c], Sherko Kuemmel [d], Chau T. Dang [e], Andreas Schneeweiss [f], Joyce O'Shaughnessy [g], Haiying Liu [h], Christian Aguila [i], Sarah Heeson [j], Harrison Macharia [k], Ke Yang [l], Eleonora Restuccia [i], Sibylle Loibl [m]

[a] *Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Medstar Health, 20057 - Washington, USA*
[b] *Solid Tumor and Investigational Therapeutics, Levine Cancer Institute, Atrium Health, 28204 - Charlotte, USA*
[c] *Medical Oncology, Fondazione Michelangelo, 20154 - Milan, Italy*
[d] *Breast Unit, Kliniken Essen Mitte, 45136 - Essen/DE and Department of Gynecology with Breast Center, Charité - University Medicine Berlin, 10117 - Berlin, Germany*
[e] *Department of Medicine, Memorial Sloan Kettering Cancer Center, 10065 - New York, USA*
[f] *National Center for Tumor Diseases, University Hospital and German Cancer Research Center, 69120 - Heidelberg, Germany*
[g] *Baylor University Medical Center, Texas Oncology, US Oncology, 75246 - Dallas, USA*
[h] *Product Development Oncology, Genentech, Inc., 94080 - South San Francisco, USA*
[i] *Product Development Oncology, F. Hoffmann-La Roche Ltd, 4058 - Basel, Switzerland*
[j] *Product Development Oncology, Roche Products Limited, AL7 1TW - Welwyn, UK*
[k] *Data Sciences, F. Hoffmann-La Roche Ltd, 4058 - Basel, Switzerland*
[l] *Portfolio Clinical Safety, F. Hoffmann-La Roche Ltd, 010, Beijing, China*
[m] *German Breast Group (GBG), C/o GBG Forschungs GmbH 63263 - Neu-Isenberg/DE and Centre for Haematology and Oncology Bethanien, Frankfurt, Germany*

Received 29 July 2022; accepted 23 September 2022
Available online 7 October 2022

* *Corresponding author*: Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Medstar Health, 20057, Washington, USA.
E-mail address: sms248@georgetown.edu (S.M. Swain).

https://doi.org/10.1016/j.ejca.2022.09.024

KEYWORDS
Pertuzumab;
Intravenous;
Fixed-dose combination;
Subcutaneous;
Hypersensitivity;
Anaphylaxis

Abstract ***Aim:*** To characterise risk of anaphylaxis/hypersensitivity with intravenous pertuzumab plus trastuzumab (PH IV), the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection (PH FDC SC) or concomitant chemotherapy to support potential administration of PH FDC SC by healthcare professionals outside clinics.
Methods: A cumulative search for anaphylaxis/hypersensitivity (Roche Standard Adverse Event Group Terms) was performed for all pivotal trials cited in the current EMA P IV/PH FDC SC summaries of product characteristics: MBC: NCT00567190, NCT02402712; EBC: NCT01358877, NCT00545688, NCT00976989, NCT02132949, NCT03493854 and NCT03674112. Occurrence, incidence and severity of events were analysed and a time–trend analysis (by cycle) was performed.
Results: This analysis includes 4772 patients who received PH IV and/or PH FDC SC. Incidence of all-grade (grade ≥3) anaphylaxis/hypersensitivity events: 3–11% (≤2%) for PH IV MBC trials; 1–13% (0–3%) for PH IV EBC trials; and 2–3% (<1%; not related to PH FDC SC) for PH FDC SC EBC trials. Discontinuations due to anaphylaxis/hypersensitivity were rare for PH IV (generally <1% except two arms of TRYPHAENA: 1% and 3%); no discontinuations of PH FDC SC have been recorded so far. Time–trend analysis showed that most events were reported during the first 6–8 cycles with concurrent chemotherapy, with a decrease in later cycles (except MetaPHER).
Conclusion: PH IV and PH FDC SC were well tolerated, with few grade ≥3 anaphylaxis/hypersensitivity events reported with PH IV and no grade ≥3 related events with PH FDC SC. Most events occurred during chemotherapy.

1. Introduction

Pertuzumab–trastuzumab (PH) is standard of care in first line HER2-positive metastatic breast cancer (MBC) and high-risk HER2-positive early breast cancer (EBC) [1–4]. PH can be administered intravenously (PH IV) or as a fixed-dose combination for subcutaneous injection (PH FDC SC), which is approved for the same indications as PH IV [5,6].

PH IV and PH FDC SC are usually given with chemotherapy for the first 3–8 treatment cycles, all of which can trigger anaphylaxis/hypersensitivity [7–12]. These events are often a concern with monoclonal antibodies [7,8]. Anaphylaxis is an acute, potentially fatal systemic allergic reaction with varied mechanisms and clinical presentations. The most common symptoms are cutaneous reactions, including urticaria, angio-oedema, erythema and pruritus [13]. Anaphylactic reactions typically begin within 15 min of exposure to the allergen. Symptoms range from mild to severe/life-threatening; each person usually has the same symptoms each time. Like other allergic reactions, an anaphylactic reaction does not usually occur after first exposure to the antigen but may occur after a later exposure to the allergen [14]. Events that trigger anaphylaxis are anaphylactic (immunoglobulin E immunologically mediated) or anaphylactoid (non-immunoglobulin mediated), although usually multiple pathways are involved [15]. Hypersensitivity is broadly defined as 'objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects, and may be caused by immunologic (allergic) and non-immunologic mechanisms' [16]. Drug-induced hypersensitivity reactions can encompass a spectrum of immunologically mediated hypersensitivity reactions with varying mechanisms and clinical presentations, accounting for ~5–10% of all adverse drug reactions [17]. Factors associated with increased risk of allergic reaction include age (higher in young/middle-aged adults vs. infants or the elderly), sex (higher in females), genetic polymorphisms in the human leucocyte antigen region, certain viral infections (e.g. HIV, herpes, Epstein–Barr virus-related mononucleosis) and drug-related factors (e.g. frequency of exposure [more frequent results in higher risk], route of administration [higher with topical vs. parenteral or oral], molecular weight [high molecular weight compounds and/or hapten-forming drugs are more immunogenic]) [17,18].

In the US, once concomitant chemotherapy has been completed, PH FDC SC has the potential to be administered by healthcare professionals (HCPs) in patients' homes [5]. Therefore, there is a need to provide a broader characterisation of the anaphylaxis/hypersensitivity with PH-based regimens and supportive guidance, particularly for those who would like to opt for PH FDC SC home administration.

This exploratory analysis was performed to assess the occurrence, incidence and severity of anaphylaxis/hypersensitivity events with PH IV or PH FDC SC in pivotal clinical trials in HER2-positive BC. A time–trend analysis (by cycle) was also carried out.

2. Materials and methods

2.1. Studies

A cumulative search for anaphylaxis/hypersensitivity events (Roche Standard Adverse Event [AE] Group Terms and Medical Dictionary for Regulatory Activities [MedDRA] v22.1; see preferred terms in Appendix 1) from 11/9/2001 (date of authorization to conduct a clinical trial in any country) to 31/12/2019 (cut-off date) was conducted for patients treated with PH IV or PH FDC SC across pivotal trials in HER2-positive BC (Table 1).

2.2. Databases

Searches were performed on the European database of suspected adverse drug reaction reports with the substance 'pertuzumab' and the product 'Phesgo', and on the U.S. Food and Drug Administration (FDA) AE Reporting System with the terms 'pertuzumab', 'perjeta', 'pertuzumab＼trastuzumab', 'hyaluronidase-zzxf＼pertuzumab＼trastuzumab' and 'Phesgo' on 9/6/2022 [27,28]. These databases include publicly available data submitted to the European Medicines Agency (EMA) and FDA by drug manufacturers, HCPs and consumers. The top three most prevalent events from the preferred terms list (Appendix 1) are reported.

2.3. Treatment

2.3.1. Clinical trials

Study drugs were administered per protocol guidance. In MBC, PH was administered with docetaxel (D) until disease progression or unmanageable toxicity [7]. PH was continued if D was discontinued. Unlike CLEOPATRA, in MetaPHER the combination of endocrine

Table 1
Overview of clinical trials included in the analysis.[a]

		Patients (n)	Chemotherapy	Anti-HER2 therapy
MBC	**CLEOPATRA** (Phase III; NCT00567190) [19]			
	Placebo + H + D	397	≥6 cycles	Administered until
	PH IV + D	407	(median 8 cycles)	disease progression
	MetaPHER (Phase IIIb; NCT02402712) [20]			
	H SC + P IV + D	412	≥6 cycles (median 8 cycles)	Administered until disease progression
EBC	**APHINITY** (Adjuvant, phase III; NCT01358877) [21]			
	PH IV + chemo	2364	6–8 cycles	18 cycles
	Placebo + H IV + chemo	2405		
	NeoSphere (Neoadjuvant, phase II; NCT00545688) [22]			
	Arm A (H IV + D)	107	3–7 cycles	13–17 cycles[b]
	Arm B (PH IV + D)	107		
	Arm C (PH IV)	108		
	Arm D (P IV + D)	94		
	TRYPHAENA (Neoadjuvant, phase II; NCT00976989) [23]			
	Arm A (FEC + PH IV → PH IV + D)	72	6 cycles	18 cycles[b]
	Arm B (FEC→ PH IV + D)	75		
	Arm C (PH IV + C + D)	76		
	BERENICE (Neoadjuvant, phase II; NCT02132949) [24]		8 cycles	17 cycles
	Cohort A (ddAC + PH IV + T)	199		
	Cohort B (FEC + PH IV + D)	198		
EBC	**FeDeriCa** (Neoadjuvant, phase III; NCT03493854) [25]			
	PH IV + chemo	252	8 cycles	18 cycles
	PH FDC SC + chemo	248		
	PHranceSCa (Adjuvant, phase II; NCT03674112) [26]			
	PH IV → PH FDC SC crossover	80	Physician discretion[c]	6 cycles
	PH FDC SC →PH IV crossover	80		6 cycles
	PH IV continuation	21		To complete 18 cycles[d]
	PH FDC SC continuation	137		To complete 18 cycles[d]

Chemo, chemotherapy; D, docetaxel; ddAC, dose-dense doxorubicin plus cyclophosphamide; EBC, early breast cancer; FEC, fluorouracil, epirubicin and cyclophosphamide; H IV, intravenous trastuzumab; H SC, subcutaneous trastuzumab; MBC, metastatic breast cancer; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; PH IV, intravenous pertuzumab plus trastuzumab; P IV, intravenous pertuzumab; T, paclitaxel.

[a] Doses of HER2-targeted therapy: P: 840 mg loading dose; 420 mg maintenance; H: 8 mg/kg loading; 6 mg/kg maintenance.

[b] In NeoSphere and TRYPHAENA, PH IV was administered during neoadjuvant treatment. After surgery, patients received adjuvant H only.

[c] In PHranceSCa, chemotherapy was administered in the neoadjuvant setting, before trial enrolment. Most patients (90.6%) received ≥4 cycles of neoadjuvant PH IV.

[d] Eighteen cycles of HER2 therapy in PHranceSCa includes those administered during the neoadjuvant period, before study enrolment.

therapy with PH after chemotherapy was allowed at investigator's discretion [20] per clinical practice and international guidelines [1,3].

In EBC, patients received PH for 3–6 cycles in the neoadjuvant setting with chemotherapy. In the adjuvant setting, PH was administered for a total of 1 year (maximum 18 cycles or until disease recurrence, or unmanageable toxicity; whichever occurred first), as part of a complete regimen for EBC, including standard anthracycline- and/or taxane-based chemotherapy. In BERENICE, FeDeriCa and PHranceSCa, patients received PH across the neoadjuvant and adjuvant settings to complete 1 year (maximum 18 cycles).

For PH IV, the initial P dose (840 mg) was administered as a 60-min IV infusion, followed once every 3 weeks (q3w) by 420 mg over 30–60 min [7,8]. An observation period (30–60 min) was recommended after each P infusion prior to subsequent H infusions. The initial H IV dose (8 mg/kg body weight) was administered as an IV infusion over approximately 90 min, followed by an observation period of up to 360 min in the EU [9,10]. This was followed q3w by 6 mg/kg body weight over 30 min with up to 120 min of observation in the EU. H SC was given as a 600 mg fixed dose over 2–5 min q3w. Observation times were 30 min for loading doses and 15 min for maintenance doses [29]. For PH FDC SC, the loading dose was 1200 mg P and 600 mg H in 15 ml of solution in a single-dose vial [11,12]. The maintenance dose was 600 mg P and 600 mg H in 10 ml of solution in a single-dose vial. Observation times were up to 30 min for loading doses and 15 min for maintenance doses [11,12].

2.3.2. Clinical practice

For the European database of suspected adverse drug reaction reports and the FDA AE Reporting System, it was assumed that P, H and PH FDC SC were used in line with prescribing information [7,8] and international guidelines [1–4,8].

3. Results

3.1. Patients

This analysis includes 4772 patients from the safety populations of eight pivotal Roche-sponsored trials. Baseline demographics and disease characteristics in the intention-to-treat populations have been published [19–26].

3.2. Incidence, severity and timing of anaphylaxis/hypersensitivity events

Incidence of all-grade and grade ≥3 anaphylaxis/hypersensitivity events are shown in Table 2.

3.3. MBC

3.3.1. CLEOPATRA

The proportion of patients experiencing anaphylaxis/hypersensitivity AEs was balanced between arms. No fatal events were reported. In the PH IV arm, the outcome was 'recovered/resolved with sequelae' for one event (hypersensitivity) and 'recovered/resolved' for remaining events. 4/407 patients (1.0%) in the PH IV arm discontinued treatment due to an anaphylaxis/hypersensitivity event. These were deemed to be study medication-related; three patients received treatment (Appendix 2). Incidence of all-grade and grade ≥3 anaphylaxis/hypersensitivity events in CLEOPATRA was highest during the initial cycles when patients were receiving D, then decreased in later cycles (Fig. 1a). The vast majority of grade ≥3 events occurred during the chemotherapy phase; only one grade 3 hypersensitivity event (which led to drug discontinuation) occurred later, in cycle 18.

3.3.2. MetaPHER

One patient (0.2%) discontinued treatment due to an anaphylaxis/hypersensitivity event: grade 3 anaphylaxis during cycle 2 when the patient was receiving D (Fig. 1b). This was deemed to be P-related (Appendix 2) and the patient received treatment. No fatal events anaphylaxis/hypersensitivity events were reported. All events recovered/resolved.

3.4. Adjuvant EBC

3.4.1. APHINITY

6/2364 patients (0.3%) in the P IV arm discontinued treatment due to an anaphylaxis/hypersensitivity event. Of those, four experienced events that were deemed to be anti-HER2 therapy-related (Appendix 2). No fatal events were reported. All anaphylaxis/hypersensitivity events reported in the P IV arm recovered/resolved. Incidence of all-grade and grade ≥3 events was highest during the initial cycles and decreased in later cycles (Fig. 1c). The vast majority of grade ≥3 events occurred during the chemotherapy phase.

3.4.2. PHranceSCa

Four patients experienced anaphylaxis/hypersensitivity events that were reported as injection-related reactions. All were non-serious, grade 1 or 2 in intensity and subsequently resolved. Among these, three events occurred during PH FDC SC treatment during the crossover period that were PH FDC SC-related. No patients discontinued treatment due to anaphylaxis/hypersensitivity during crossover; the continuation period is ongoing [26].

Table 2
Incidence and severity of anaphylaxis/hypersensitivity events in pivotal clinical trials of PH IV and PH FDC SC.

		Patients (n)	Incidence of anaphylaxis/hypersensitivity, patients, n (%)		P[a] discontinuation rate due to anaphylaxis/hypersensitivity events, patients, n (%)
			All grades	Grade ≥3	
PH IV clinical trials					
MBC	**CLEOPATRA** (NCT00567190) [19]				
	Placebo + H + D	397	36 (9.1)	10 (2.5)	N/A[b]
	PH IV + D	407	44 (10.8)	8 (2.0)	4 (1.0)
	MetaPHER (NCT02402712) [20]				
	H SC + P IV + D	412	14 (3.4)	1 (0.2)	1 (0.2)
EBC	**APHINITY** (NCT01358877) [21]				
	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[b]
	NeoSphere[c] (NCT00545688) [22]				
	Arm A (H IV + D)	107	2 (1.9)	0	N/A[b]
	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[c] (NCT00976989) [23]				
	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[c] (NCT02132949) [24]				
	Cohort A (ddAC + PH IV + T)	199	7 (3.5)	0	0
	Cohort B (FEC + PH IV + D)	198	5 (2.5)	2 (1.0)	0
PH FDC SC clinical trials					
EBC	**FeDeriCa**[c] (NCT03493854) [25]				
	PH IV + chemo	252	5 (2.0)	1 (0.4)	1 (0.4)
	PH FDC SC + chemo	248	4 (1.6)	0	0
	PHranceSCa (NCT03674112) [26]				
	PH IV crossover	160	0	0	0
	PH FDC SC crossover	160	3 (1.9)	0	0
	PH IV continuation	21	0	0	0
	PH FDC SC continuation	137	2 (1.5)	0	0

Chemo, chemotherapy; D, docetaxel; ddAC, dose-dense doxorubicin plus cyclophosphamide; EBC, early breast cancer; FEC, fluorouracil, epirubicin and cyclophosphamide; H IV, intravenous trastuzumab; H SC, subcutaneous trastuzumab; MBC, metastatic breast cancer; N/A, not applicable; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; PH IV, intravenous pertuzumab plus trastuzumab; P IV, intravenous pertuzumab; T, paclitaxel.
[a] Discontinuation of PH IV or PH FDC SC.
[b] No PH IV or PH FDC SC were administered in these arms so there is no P discontinuation rate.
[c] Data reported for the neoadjuvant period only.

3.5. Neoadjuvant EBC

3.5.1. NeoSphere

All anaphylaxis/hypersensitivity events were reported as 'drug hypersensitivity', with the exception of one grade 2 anaphylaxis event (Arm D), following which the D dosage was modified. This event resolved on the same day, without sequelae. In Arms B and D, the majority of hypersensitivity reactions were specifically attributed to D, whereas in Arm C the majority were attributed to P IV. The reported events occurred in up to three cycles across the four arms and the outcome was reported as 'recovered-no sequelae' for all. One patient (0.9%) in each of Arm B (n = 107) and Arm C (n = 108) discontinued treatment due to drug hypersensitivity. Only one of the events leading to discontinuation was deemed to be anti-HER2 therapy-related (Appendix 2).

3.5.2. TRYPHAENA

All but two anaphylaxis/hypersensitivity events were reported as 'drug hypersensitivity'. The outcome was 'resolved-no sequelae' for all. 1/72 in Arm A (1.4%) and 2/76 in Arm C (2.6%) had grade ≥3 events (drug hypersensitivity), which led to study treatment discontinuation. One of these events was deemed to be D-related; all patients who discontinued received treatment for the hypersensitivity event (Appendix 2). One patient

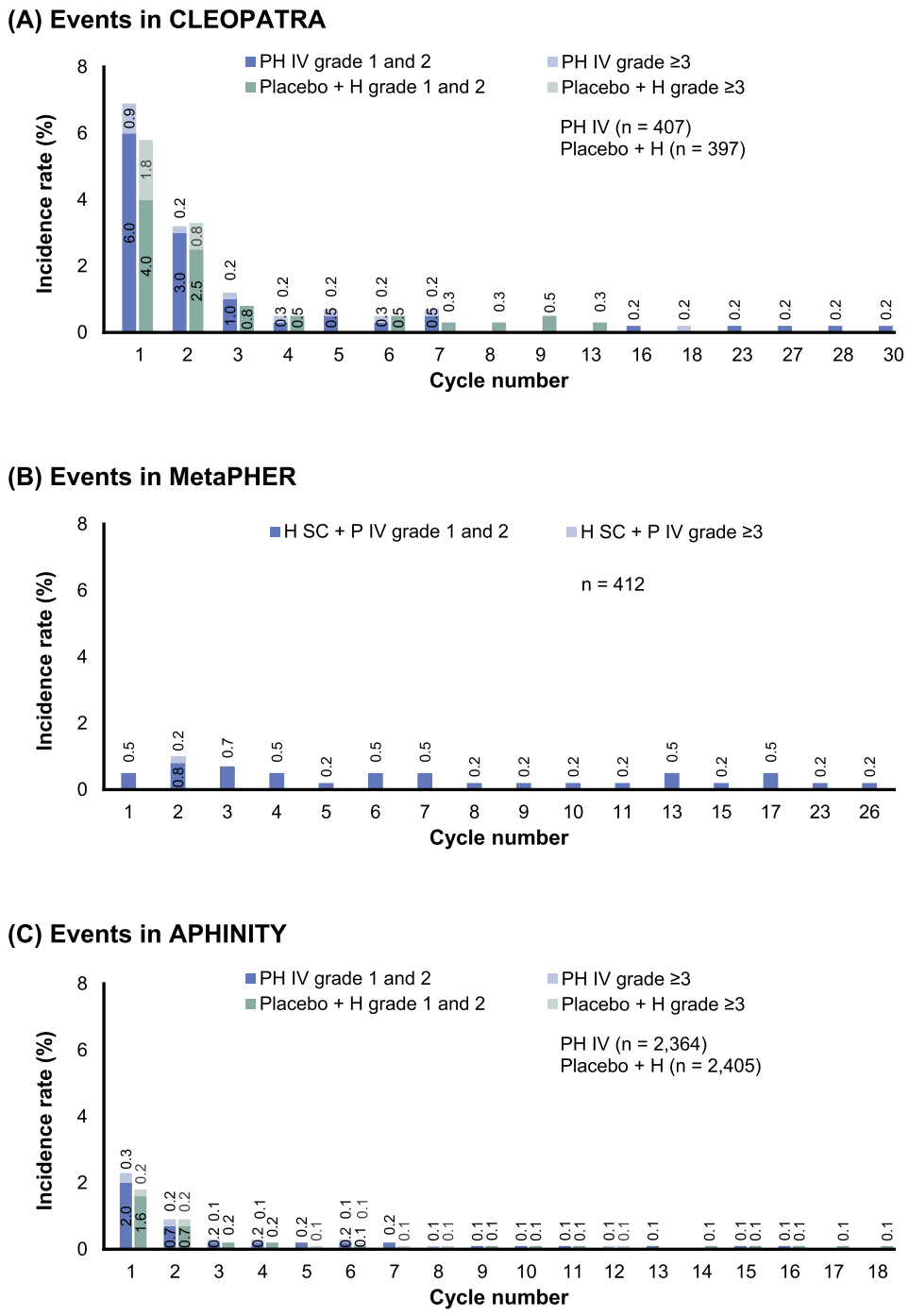

Fig. 1. Incidence of anaphylaxis/hypersensitivity events during HER2-targeted therapy by cycle.*
Similar figures have not been included for NeoSphere and TRYPHAENA as patients received H only after surgery.
* Graphs represent number of anaphylaxis/hypersensitivity events observed.
D, docetaxel; ddAC, 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.

experienced a grade 1 circulatory collapse, which was unrelated to study treatment and resolved without sequelae. Three out of the four grade ≥3 events were reported at cycle 1; the remaining event, at cycle 5 when patients were receiving chemotherapy.

3.5.3. BERENICE

During neoadjuvant treatment, the incidence of anaphylaxis/hypersensitivity events was low in both cohorts. Two grade ≥3 events occurred during the neoadjuvant period in Cohort B: hypersensitivity and

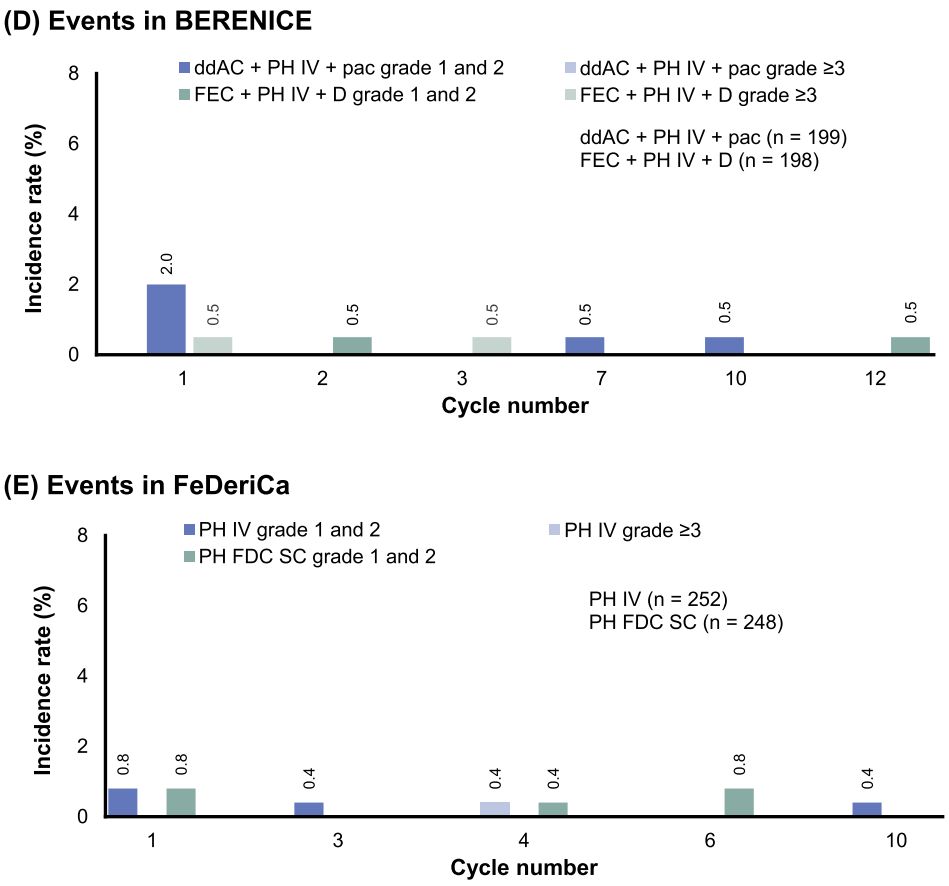

Fig. 1. (*continued*)

anaphylactic reaction. The PH IV dose was not altered in response to the events for these two patients and the outcome was reported as recovered. No patients discontinued P due to anaphylaxis/hypersensitivity (Appendix 2). Most events occurred during the neoadjuvant phase, where the first four cycles of HER2-targeted therapy were given in combination with chemotherapy.

3.5.4. FeDeriCa

Anaphylaxis/hypersensitivity events occurred with low and comparable incidence across treatment arms. All events related to HER2-targeted therapy were grade 1 (two patients in the PH IV arm and three in the PH FDC SC arm) or grade 2 (one patient per arm). One grade 3 event (in the PH IV arm) was considered related to concomitant levofloxacin. Most events occurred during the neoadjuvant phase, where the first four cycles of HER2-targeted therapy were given in combination with chemotherapy (Fig. 1e). One patient (0.4%) in the PH IV arm discontinued treatment due to anaphylaxis/hypersensitivity (grade 2 paclitaxel-related, infusion-related reaction [Appendix 2]); none discontinued in the PH FDC SC arm.

3.6. Databases

The European database of suspected adverse drug reaction reports had 8170 instances for the substance 'pertuzumab' and 68 for the product 'Phesgo'. For 'pertuzumab', 197 were hypersensitivity reactions (2.4%), 93 were anaphylactic reactions (1.1%) and 57 were anaphylactic shock (0.7%). For 'Phesgo', two were anaphylactic reactions (2.9%), one was hypersensitivity (1.5%) and one was drug hypersensitivity (1.5%). The FDA AE Reporting System had 14,221 instances reported for the search terms 'pertuzumab', 'perjeta', 'pertuzumab \ trastuzumab', 'hyaluronidase-zzxf \ pertuzumab \ trastuzumab' and 'Phesgo'. Of those, 190 were hypersensitivity reactions (1.3%), 102 were anaphylactic reactions (0.7%) and 45 were anaphylactic shock (0.3%).

4. Discussion

To our knowledge, this is the first analysis to report the incidence and severity of anaphylaxis/hypersensitivity events involving P-containing regimens in. HER2-positive BC. The incidence of grade ≥3 anaphylaxis/hypersensitivity events was generally low in the Roche-sponsored PH IV and PH FDC SC clinical trials

assessed here (0.2–2.0% for MBC studies, 0–0.8% in the adjuvant EBC setting and 0–2.8% in the neoadjuvant EBC setting), and no fatal events were reported.

Time–trend analysis for PH IV and PH FDC SC studies in MBC and EBC showed that the majority of all-grade and grade ≥3 anaphylaxis/hypersensitivity events occurred during the first 6–8 cycles of treatment, when PH IV or PH FDC SC were administered with chemotherapy. The relatedness could not be determined due to the limited information collected with respect to timing; however, the reported events may well be attributable to the chemotherapy given. The incidence of all-grade and grade ≥3 anaphylaxis/hypersensitivity events in MetaPHER (P IV + H SC) was lower than in the PH IV studies, and the time–trend relationship was less obvious; cross-study comparisons should be made with caution due to possible differences in study populations, treatments and AE reporting requirements.

Within the PH FDC SC studies, only one grade 3 event was reported; this was considered related to a concomitant medication in FeDeriCa (levofloxacin). Discontinuations due to anaphylaxis/hypersensitivity were rare for PH IV (generally ≤1% except for one arm in TRYPHAENA, which was 3%) and PH FDC SC (<1%; notably, this case was related to paclitaxel in FeDeriCa). One limitation of this analysis is that not all events leading to discontinuation were attributed to a specific study treatment so we cannot fully ascertain how many were related to P.

The European database of suspected adverse drug reaction reports and FDA AE Reporting System have some limitations, including the potential for submission of incomplete, inaccurate, untimely, unverified information. No link between the medicine and the observed effect(s) is confirmed, and incidence or prevalence of an event cannot be determined due to possible under reporting. However, it is interesting to note the similarly low incidences of anaphylaxis/hypersensitivity reported in clinical use.

The risk of anaphylaxis/hypersensitivity should be considered when assessing patients' eligibility to be treated at home with PH FDC SC. Risk factors such as patient age, concomitant diseases and concurrent medications should also be taken into account [17,18]. An ongoing expanded access single-arm study is assessing the feasibility of home administration of PH FDC SC after completing concurrent chemotherapy during the COVID-19 pandemic [30,31]. Data for 114 patients were available at a preliminary analysis: no new AEs emerged during home administration and two patients (2.7%) experienced hypersensitivity events (both grade 1).

The overall risk of anaphylaxis or hypersensitivity during PH IV or PH FDC SC treatment is very low. 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, it is recommended that treatment should be slowed down or paused and that appropriate medical therapies should be administered. Patients should be carefully monitored until complete resolution of symptoms. Permanent discontinuation of PH IV or PH FDC SC in patients who experience anaphylaxis or severe infusion- or injection-related reactions is recommended [8,12].

5. Conclusion

Analysis of pivotal clinical trials in HER2-positive EBC and MBC showed that PH IV and PH FDC SC were well tolerated, with few grade ≥3 anaphylaxis/hypersensitivity events reported with PH IV and no grade ≥3-related events with PH FDC SC. The majority of the anaphylaxis/hypersensitivity events were grade 1 and 2 and occurred within the first 6–8 cycles when PH IV or PH FDC SC were given with chemotherapy. The incidence rate of grade ≥3 events after the chemotherapy cycles was very low. The presented data provide additional evidence to support the administration of PH FDC SC by HCPs outside a hospital setting.

Disclosure of prior presentation

The current analysis was presented at the ESMO virtual congress 2021 (Swain SM *et al.*, abstract number 138P).

- The individual studies have been presented either fully or in part:
  - **CLEOPATRA:**
    - Primary analysis (NEJM 2012; PMID 22149875)
    - Interim overall survival analysis (Lancet Oncol 2013; PMID 23602601)
    - Final overall survival analysis (NEJM 2015; PMID 25693012)
    - End-of-study analysis (Lancet Oncol 2020; PMID 32171426)
  - **MetaPHER:**
    - First interim analysis (SABCS 2016; P4-21-42)
    - Second interim analysis (ESMO 2018; 323P)
    - Final analysis (Breast Cancer Res Treat 2021; PMID: 33748921)
  - **APHINITY**
    - Primary analysis (NEJM 2017; PMID 28581356)
    - Six-year follow-up analysis (J Clin Oncol 2021; PMID 33539215)
  - **NeoSphere**
    - Primary analysis (Lancet Oncol 2012; PMID 22153890)
    - Five-year analysis (Lancet Oncol 2016; PMID 27179402)
  - **TRYPHAENA**
    - Primary analysis (Ann Oncol 2013; PMID 23704196)
    - Five-year analysis (Eur J Cancer 2018; PMID: 29223479)

- **BERENICE**
  - Primary analysis (Ann Oncol 2018; PMID 29253081)
  - Interim analysis of safety (SABCS 2017; P5-20-04)
  - Final analysis (Cancers 2022; PMID 35681574)
- **FeDeriCa**
  - Primary analysis (Lancet Oncol 2021; PMID: 33357420)
  - Adjuvant safety analysis (ESMO Breast Cancer 2021; 46P)
- **PHranceSCa**
  - Primary analysis (Eur J Cancer 2021; PMID: 34147014)

Data sharing

Qualified researchers may request access to individual patient-level data through the clinical study data request platform: https://vivli.org/. Further details of Roche's criteria for eligible studies are available here: https://vivli.org/members/ourmembers/. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

Author contributions

Conceptualisation: CA, SH, ER, LG, SK, AS, HL, HM, SMS, JOS, CTD.

Investigation: CA, SH, ER, LG, SK, SL, AS, HL, HM, SMS, ART, KY, JOS, CTD.

Methodology: HL, HM.

Software: HM.

Supervision: CA.

Roles/Writing - original draft: SMS.

Writing - review & editing: All authors.

Role of the funding source

F. Hoffmann-La Roche Ltd funded the studies and the analysis, provided study drugs and was involved in the study design, protocol development, regulatory and ethics approvals, safety monitoring and reporting, data management and data analysis and interpretation of the studies included. The sponsor funded third-party writing assistance, provided by Alison McGonagle, PhD.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

SMS reports honoraria (self) and advisory/consultancy roles for AstraZeneca, Daiichi Sankyo, F. Hoffmann-La Roche Ltd/Genentech, Inc., Exact Sciences (Genomic Health), Molecular Templates, Silverback Therapeutics, Lilly, Natera, Athenex, Beijing Medical Foundation, Merck and Inivata; institutional research funding from F. Hoffmann-La Roche Ltd/Genentech, Inc. and Kailos Genetics; and travel/accommodation/expenses from F. Hoffmann-La Roche Ltd/Genentech, Inc. and Daiichi Sankyo. **ART** reports institutional research funding from F. Hoffmann-La Roche Ltd/Genentech, Inc., Merck, Pfizer and Tesaro; advisory role for AbbVie, Athenex, Celgene, Eisai, G1 Therapeutics, Genentech, Inc., Immunomedics, Merck and Novartis. **LG** reports advisory/consultancy roles for ADC Therapeutics, Amgen, AstraZeneca, Celgene, Eli Lilly, F. Hoffmann-La Roche Ltd, Forty Seven, G1 Therapeutics, Genentech, Inc., Genomic Health, Menarini Ricerche, Metis Precision Medicine, MSD, Novartis, Odonate Therapeutics, Oncolytics Biotech, Onkaido Therapeutics, Pfizer, Revolution Medicines, Sandoz, Seattle Genetics, Synthon, Synaffix and Taiho Pharmaceutical; institutional research funding from Pfizer, Revolution Medicines and Zymeworks; pending patent (self) with F. Hoffmann-La Roche Ltd. **SK** reports advisory role for Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Exact Science, F. Hoffmann-La Roche Ltd, Genomic Health, Lilly, MSD, Novartis, Pfizer, pfm medical, Seattle Genetics and Somatex; non-financial relationship with Daiichi Sankyo, F. Hoffmann-La Roche Ltd, Lilly and Sonoscape. **CTD** reports honoraria (self) from Daiichi Sankyo, F. Hoffmann-La Roche Ltd, Genentech, Inc., Lilly and Puma Biotechnology. **AS** reports institutional research funding from AbbVie, Celgene and F. Hoffmann-La Roche Ltd; expert testimony for AstraZeneca and F. Hoffmann-La Roche Ltd; travel expenses from Celgene, F. Hoffmann-La Roche Ltd and Pfizer; honoraria (self) from AstraZeneca, Celgene, F. Hoffmann-La Roche Ltd, Lilly, MSD, Novartis, Pfizer, Seattle Genetics and Tesaro. **JOS** reports advisory role for AbbVie, Agendia, Amgen, AstraZeneca, BMS, Celgene, Daiichi Sankyo, Eisai, F. Hoffmann-La Roche Ltd, Genentech, Inc., Immunomedics, Ipsen, Lilly, Merck, Novartis, Odonate Therapeutics, Pfizer, Prime Oncology, Puma Biotechnology and Seattle Genetics. **HL** reports full-time/part-time employment and stocks/shares (self) with Genentech, Inc. **CA** reports full-time employment at F. Hoffmann-La Roche Ltd and stocks/shares (self) with F. Hoffmann-La Roche Ltd. **SH** reports full-time/part-time employment and stocks/shares (self) with F. Hoffmann-La Roche Ltd; patent (self) with F. Hoffmann-La Roche Ltd. **HM** reports full-time/part-time employment with F. Hoffmann-La Roche Ltd. **KY** reports full-time/part-time employment with F. Hoffmann-La Roche Ltd. **ER** reports full-time/part-time employment with F. Hoffmann-La Roche Ltd; and stocks/shares (self) with F. Hoffmann-La Roche

Ltd and Genentech, Inc. **SL** reports consulting/advisory board roles (self) for AbbVie, Amgen, AstraZeneca, Beyer, BMS, Celgene, Daiichi Sankyo, Eirgenix, GSK, Gilead, F. Hoffmann-La Roche Ltd, Lilly, Merck, Novartis, Pfizer, Pierre Fabre, Puma, PriME/Medscape, Sanofi and Seagen; honoraria (self) from AstraZeneca, Daiichi Sankyo, F. Hoffmann-La Roche Ltd, Novartis, Pfizer, Pierre Fabre, PriME/Medscape and Samsung; funded research (self) from Abbvie, AstraZeneca, Celgene, Daiichi Sankyo, F. Hoffmann-La Roche Ltd, Gilead, Novartis and Pfizer; royalties/patents (self), numbers EP14153692.0, EP21152186.9, EP15702464.7, EP19808852.8, and with VM Scope GmbH; employment (self) from GBG Forschungs GmbH; and non-financial medical writing support from Daiichi Sankyo, F. Hoffmann-La Roche Ltd, Gilead, Novartis, Pfizer, Puma and Seagen. **All authors** received research support via third-party writing assistance, furnished by Alison McGonagle, PhD, of Health Interactions, provided by F. Hoffmann-La Roche Ltd.

Acknowledgements

We would like to acknowledge all patients and investigators participating in these trials. Support for third-party writing assistance for this manuscript, furnished by Alison McGonagle, PhD, of Health Interactions, was provided by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Appendix 1

Preferred terms included in the analysis
Administration site hypersensitivity
Allergic reaction to excipient
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Application site hypersensitivity
Catheter site hypersensitivity
Challenge site reaction
Circulatory collapse
Dialysis membrane reaction
Documented hypersensitivity to administered product
Drug hypersensitivity
Human seminal plasma hypersensitivity
Hypersensitivity
Hypersensitivity myocarditis
Hypersensitivity vasculitis
Hypotensive crisis
Implant site hypersensitivity
Infusion related hypersensitivity reaction
Infusion site hypersensitivity
Infusion site recall reaction
Injection related reaction
Injection site hypersensitivity
Instillation site hypersensitivity
Kounis syndrome
Medical device site hypersensitivity
Nutritional supplement allergy
Reaction to excipient
Shock
Shock symptom
Stoma site hypersensitivity
Type I hypersensitivity
Type II hypersensitivity
Type IV hypersensitivity reaction
Vaccination site hypersensitivity

Appendix 2

Summary of related study treatments and treatments administered for anaphylaxis/hypersensitivity events leading to discontinuation in pivotal clinical trials of PH IV and PH FDC SC.

Trial	Anaphylaxis/hypersensitivity event leading to discontinuation (grade)	Study treatment that event was related to	Treatment for anaphylaxis/hypersensitivity event
CLEOPATRA	Hypersensitivity (2)	Study medication[a]	Chlorphenamine
	Hypersensitivity (3)	P and D	• Hydrocortisone (for both P and D) • Nimodipine, ipratropium bromide, fenoterol, furosemide and diphenhydramine (for reaction to D)
	Hypersensitivity (3)	Study medication[b]	No treatment was given
	Anaphylactic reaction (4)	P and H	Epinephrine, diphenhydramine, oxygen therapy and dexamethasone
MetaPHER	Anaphylactic reaction (3)	P	Clemastine, hydrocortisone and epinephrine
APHINITY	Hypersensitivity (3)	D	Hydrocortisone, chlorphenamine and IV fluids
	Hypersensitivity (1)	P and H	Paracetamol (same day as event); betamethasone (11 days after event)
	Hypersensitivity (1)	D	Methylprednisolone and dexchlorpheniramine
	Hypersensitivity (3)	P and H	Prednisolone, clemastine, pethidine, metoclopramide and ranitidine
	Hypersensitivity (2)	P and H	No treatment was given
	Hypersensitivity[c]	P	• Cycle 2 event: dexchlorpheniramine, methylprednisolone and sodium chloride infusion • Cycle 3 event: saline solution, loxoprofen and teprenone • Cycle 4 event: no treatment was given
NeoSphere	Hypersensitivity (3)	D	Ranitidine, chlorphenamine and hydrocortisone
	Hypersensitivity (3)	P and/or H[d]	Dose of P was discarded. Nitroglycerine, hydrocortisone, diphenhydramine and pethidine
TRYPHAENA	Hypersensitivity (4)	Study medication[a]	Salbutamol, hydrocortisone and chlorphenamine
	Hypersensitivity (4)	P	Prednisolone hemisuccinate, oxygen, nifedipine and clemastine
	Hypersensitivity[e]	D	Docetaxel infusion stopped. Chlorphenamine, hydrocortisone and oxygen
BERENICE	Anaphylactic reaction (4)	D	Docetaxel permanently discontinued. Hydrocortisone
FeDeriCa	IRR (2)	T	Prednisolone

D, docetaxel; H, trastuzumab; IRR, infusion-related reaction; IV, intravenous; P, pertuzumab; T, paclitaxel.

[a] Exact study treatment not specified.

[b] The event occurred days after study drug administration, so it is not clear which of the three drugs was most likely to be the cause.

[c] Grade 2 allergic reaction during cycle 2, after completion of P infusion. Grade 2 allergic reaction during P infusion on cycle 3. At cycle 4, patient received pre-medication with dexamethasone and dexchlorpheniramine before P infusion. After P and H infusions, patient presented with a grade 2 allergic reaction.

[d] Investigator assessed the event as also being related to pre-existing disease (hypertension) and related to new illness stress related to infusion reaction.

[e] Grade not specified.

References

[1] National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in Oncology (NCCN Guidelines®): breast cancer. Version 2.2022, https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. [Accessed 1 June 2022].

[2] Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019;30:1194–220. https://doi.org/10.1093/annonc/mdz173.

[3] Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021;32:1475–95. https://doi.org/10.1016/j.annonc.2021.09.019.

[4] Burstein HJ, Curigliano G, Thürlimann B, Weber WP, Poortmans P, Regan MM, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. Ann Oncol 2021;32:1216–35. https://doi.org/10.1016/j.annonc.2021.06.023.

[5] US Food and Drug Administration (FDA). FDA approves breast cancer treatment that can be administered at home by health care professional [press release]. 29 June 2020, https://www.fda.gov/news-events/press-announcements/fda-approves-breast-cancer-treatment-can-be-administered-home-health-care-professional. [Accessed 1 June 2022].

[6] Hoffmann-La Roche Ltd F. European Commission approves Roche's Phesgo (fixed-dose combination of Perjeta and Herceptin for subcutaneous injection) for people with HER2-positive breast cancer. 2020 [press release]. 23 December 2020, https://www.roche.com/media/releases/med-cor-2020-12-23.htm. [Accessed 1 June 2022].

[7] Roche Registration Ltd. PERJETA® (pertuzumab). Summary of product characteristics. 2021. https://www.ema.europa.eu/en/documents/product-information/perjeta-epar-product-information_en.pdf. [Accessed 1 June 2022].

[8] Genentech Inc. PERJETA® (pertuzumab). Prescribing Information; 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125409s124lbl.pdf. [Accessed 1 June 2022].

[9] Roche Registration Ltd. Herceptin® (trastuzumab). Summary of product characteristics. 2021. https://www.ema.europa.eu/en/documents/product-information/herceptin-epar-product-information_en.pdf. [Accessed 1 June 2022].
[10] Genentech Inc. HERCEPTIN® (trastuzumab). Prescribing Information; 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103792s5345lbl.pdf. [Accessed 1 June 2022].
[11] Registration GmbH Roche. PHESGO® (pertuzumab and trastuzumab). Summary of Product Characteristics. 2022. https://www.ema.europa.eu/documents/product-information/phesgo-epar-product-information_en.pdf. [Accessed 1 June 2022].
[12] Genentech Inc. PHESGO (pertuzumab, trastuzumab, and hyaluronidase-zzxf). Prescribing Information; 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761170s000lbl.pdf. [Accessed 1 June 2022].
[13] Fischer D, Vander Leek TK, Ellis AK, Kim H. Anaphylaxis. Allergy Asthma Clin Immunol 2018;14:8. https://doi.org/10.1186/s13223-018-0283-4.
[14] MSD. Anaphylactic reactions. 2020. https://www.msdmanuals.com/en-gb/home/immune-disorders/allergic-reactions-and-other-hypersensitivity-disorders/anaphylactic-reactions. [Accessed 1 June 2022].
[15] Brown AF. Anaphylactic shock: mechanisms and treatment. J Accid Emerg Med 1995;12:89–100. https://doi.org/10.1136/emj.12.2.89.
[16] Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy 2001;56:813–24. https://doi.org/10.1034/j.1398-9995.2001.t01-1-00001.x.
[17] Warrington R, Silviu-Dan F, Wong T. Drug allergy. Allergy Asthma Clin Immunol 2018;14:11. https://doi.org/10.1186/s13223-018-0289-y.
[18] Mirakian R, Ewan P, Durham S, Youlten L, Dugué P, Friedmann P, et al. BSACI guidelines for the management of drug allergy. Clin Exp Allergy 2009;39:43–61. https://doi.org/10.1111/j.1365-2222.2008.03155.x.
[19] Baselga J, Cortés J, Kim SB, Im SA, Hegg R, Im YH, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109–19. https://doi.org/10.1056/NEJMoa1113216.
[20] Kümmel S, Tondini CA, Abraham J, Nowecki Z, Itrych B, Hitre E, et al. Subcutaneous trastuzumab with pertuzumab and docetaxel in HER2-positive metastatic breast cancer: Final analysis of MetaPHER, a phase IIIb single-arm safety study. Breast Can Res Treat 2021;187:467–76. https://doi.org/10.1007/s10549-021-06145-3.
[21] von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med 2017;377:122–31. https://doi.org/10.1056/NEJMoa1703643.
[22] Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:25–32. https://doi.org/10.1016/s1470-2045(11)70336-9.
[23] Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol 2013;24:2278–84. https://doi.org/10.1093/annonc/mdt182.
[24] Swain SM, Ewer MS, Viale G, Delaloge S, Ferrero JM, Verrill M, et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. Ann Oncol 2018;29:646–53. https://doi.org/10.1093/annonc/mdx773.
[25] Tan AR, Im S-A, Mattar A, Colomer R, Stroyakovskii D, Nowecki Z, 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. Lancet Oncol 2021;22:85–97. https://doi.org/10.1016/S1470-2045(20)30536-2.
[26] O'Shaughnessy J, Sousa S, Cruz J, Fallowfield L, Auvinen P, Pulido C, et al. Preference for the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with HER2-positive early breast cancer (PHranceSCa): a randomised, open-label phase II study. Eur J Cancer 2021;152:223–32. https://doi.org/10.1016/j.ejca.2021.03.047.
[27] US Food and Drug Administration (FDA). FDA adverse events reporting System (FAERS) public Dashboard. https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis. [Accessed 1 June 2022].
[28] European Medicines Agency (EMA). EudraVigilance - European database of suspected adverse drug reaction reports. 2021. https://www.adrreports.eu/en/index.html. [Accessed 1 June 2022]. accessed.
[29] Electronic Medicines Compendium (EMA). Herceptin 600 mg solution for injection in vial SmPC. 2021. https://www.medicines.org.uk/emc/product/1227/smpc#gref. [Accessed 1 June 2022].
[30] ClinicalTrials.gov. An expanded access study to provide at home subcutaneous administration of pertuzumab and trastuzumab fixed-dose combination (PH FDC SC) for patients with HER2-positive breast cancer during the COVID-19 pandemic. ClinicalTrials.gov Identifier: NCT04395508, https://clinicaltrials.gov/ct2/show/NCT04395508?term=AL42478&draw=2&rank=1;. [Accessed 1 June 2022].
[31] Dang CT, Tolaney SM, Riaz F, Tan AR, Tkaczuk KHR, Yu AF, et al. Preliminary analysis of an expanded access study of the fixed-dose combination of pertuzumab (P) and trastuzumab (H) for subcutaneous injection (PH FDC SC) for at-home administration (admin) in patients (pts) with HER2-positive (HER2+) breast cancer (BC) during the COVID-19 pandemic. J Clin Oncol 2022:40. Abstract 1515 and associated poster presentation. https://doi.org/10.1200/JCO.2022.40.16_suppl.1515.