Title Page

Comprehensive analysis of adverse event profile changes with pertuzumab addition to trastuzumab-based breast cancer therapy: disproportionality analysis using VigiBase

Short Title: Pertuzumab addition and adverse events in breast cancer therapy

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Principal Investigator (PI) statement

The authors confirm that the PI for this paper is Jun Matsumoto and that he is responsible for this research and analysis.

What is already known about this subject

- The addition of pertuzumab to trastuzumab-based therapy has become the standard treatment for HER2-positive breast cancer.
- There are concerns that pertuzumab may increase the risk of adverse events.
- However, real-world safety information on pertuzumab remains limited.

What this study adds

- We have comprehensively identified the safety profile of pertuzumab addition to trastuzumab-based therapy using real-world data.
- The addition of pertuzumab was associated with various adverse events, including gastrointestinal disorders and infections.
- These results are useful for treatment selection, considering the risk of adverse events in individual patients.

Abstract

Introduction: Pertuzumab is used in combination with trastuzumab-based therapy for HER2-positive breast cancer. However, real-world safety information on pertuzumab remains limited. This study assessed the safety of adding pertuzumab to trastuzumab-based therapy for HER2-positive breast cancer using real-world data.

Methods: VigiBase, the World Health Organization's global database of adverse events (AEs), containing reports from November 1967 to December 2023, was used. Signals for pertuzumab-associated AEs in breast cancer cases were detected using the reporting odds ratio (ROR).

Results: Signals of trastuzumab plus pertuzumab relative to trastuzumab alone were detected in gastrointestinal disorders (ROR: 1.45, 95% confidence interval: 1.26−1.67), including diarrhea (3.49, 2.83−4.30); infections and infestations (1.54, 1.24−1.91); and skin and subcutaneous tissue disorders (ROR: 1.63, 1.40−1.90), including pruritus (1.96, 1.51−2.55) and rash (1.63, 1.20−2.23). Further, signals of trastuzumab plus docetaxel plus pertuzumab relative to those of trastuzumab plus docetaxel were detected in gastrointestinal disorders (1.63, 1.38−1.93), including nausea (1.72, 1.24−2.39) and vomiting (1.48, 1.01−2.17), and in nervous system disorders (1.50, 1.20−1.87), including paresthesia (2.60, 1.33−5.08) and peripheral sensory neuropathy (5.94, 1.79 − 19.71). The frequency of AEs causing or prolonging

hospitalization was increased with trastuzumab plus pertuzumab compared to that with trastuzumab alone (1.18, 1.00−1.38).

Conclusion: AE profiles after the addition of pertuzumab to trastuzumab-based therapy were comprehensively identified. The findings in this study highlight the importance of considering these AEs when selecting pertuzumab combination therapy to ensure the safety of patients with breast cancer.

1 Introduction

Breast cancer is the most commonly diagnosed cancer worldwide, with approximately 2.3 million new cases and 685,000 deaths annually [1, 2]. It can be categorized into subtypes based on the expression of hormone receptors (HR) and human epidermal growth factor receptor 2 (HER2): HR-positive/HER2-negative, HER2-positive, and triple-negative [3]. Each subtype exhibits distinct biological behaviors and responses to treatment, necessitating personalized therapeutic strategies. The HER2-positive subtype, accounting for 15–20% of breast cancers, is characterized by aggressive tumor growth and poor prognosis [4]. Treatment for HER2-positive breast cancer primarily involves HER2-targeted therapy, with trastuzumab improving prognosis by inhibiting cell proliferation and promoting cytotoxicity [5–8]. Pertuzumab, used in combination with trastuzumab, binds to a distinct HER2 epitope, further enhancing treatment efficacy [8]. This combination improves survival outcomes and is now the standard therapy for HER2-positive breast cancer [9–11]. Recently, a subcutaneous formulation combining trastuzumab and pertuzumab has been developed and has demonstrated non-inferiority to the intravenous administration of each antibody separately, making combined treatment with trastuzumab and pertuzumab more convenient [12].

In recent years, pertuzumab has been the commonly used antibody in the treatment of HER2-positive breast cancer; however, concerns have been raised regarding the occurrence of adverse events (AEs), including cardiotoxicity and hematotoxicity [9−11]. Balancing efficacy and safety is important in

cancer treatment. In particular, safety influences treatment continuity and, consequently, the treatment outcome. Thus, analyzing the treatment safety and appropriately managing AEs is essential. As clinical trials are rigorous and controlled, they include a limited and highly selected patient population, which may not fully represent the diversity of patients encountered in routine clinical practice. Real-world data (RWD) analysis using global pharmacovigilance databases, such as the World Health Organization's (WHO's) VigiBase, allows for comprehensive safety assessments beyond clinical trial settings [13].

This study assessed the safety of adding pertuzumab to trastuzumab-based chemotherapy for HER2-positive breast cancer using VigiBase data. By analyzing AE reports, we aim to identify potential safety concerns and provide a comprehensive AE profile to minimize treatment interruptions through proactive risk management.

2 Methods

2.1 Data sources

The analysis was conducted using VigiBase, the largest global database of AEs, managed by the WHO. VigiBase has collected reports since November 1967, and this analysis includes data from over 35 million cases until December 2023. The study was exempt from Institutional Review Board approval because it was an observational study that used fully anonymized patient data. This study was performed referring to the REporting of A Disproportionality analysis for drUg Safety signal detection using individual case safety reports in PharmacoVigilance (READUS-PV) guideline [14, 15].

2.2 Data extraction

The flowchart of the reported extraction process is shown in Fig. 1a. Duplicate reports were excluded using an algorithm designed to detect duplicate reports [16, 17]. To improve the reliability of the analysis by excluding incomplete data, reports lacking age and sex information were excluded. To minimize the risk of confounding by cancer type, information from the drug indication field in the VigiBase dataset was extracted, and only cases identified as breast cancer were included in the analysis. Reports involving trastuzumab usage were identified, and those involving additional pertuzumab usage were extracted. Furthermore, reports including anticancer agents other than trastuzumab, pertuzumab, and docetaxel were excluded and analyzed as a subgroup. L01 (antineoplastic agents) and L02 (endocrine therapy) of the

Anatomical Therapeutic Chemical classification were extracted as anticancer agents. Information on age, sex, region, reporter, reporting year, and severity was extracted from each report. Severity was defined as Death, Life-threatening, Caused/Prolonged Hospitalization, Disabling/Incapacitating, Congenital anomaly/Birth defect and Other. The flowchart of AE extraction is shown in Fig. 1b. AEs were defined according to the Medical Dictionary for Regulatory Activities (MedDRA) version 26. MedDRA codes reported for trastuzumab as a suspected agent in breast cancer were extracted, and those with three or more counts were included in the analysis to exclude false positives while maintaining sensitivity [18]. AEs were classified into primary System Organ Classes (SOCs) and Preferred Terms (PTs).

2.3 Data analysis

Disproportionality analysis is commonly used when analyzing AE databases to explore potential associations between medicines and AEs. In this study, the signals of the SOCs or PTs following the use of pertuzumab in breast cancer cases treated with trastuzumab were detected. The reporting odds ratio (ROR) and 95% confidence interval (CI) were used as signal indicators. To calculate the ROR and 95% CI, reports were divided into four groups: (a) the number of reports with AEs to be analyzed for which pertuzumab was the suspected agent, (b) the number of reports with other AEs for which pertuzumab was the suspected agent, (c) the number of reports with AEs to be analyzed for which pertuzumab was not the suspected agent,

and (d) the number of reports with other AEs for which pertuzumab was not the suspected agent. The ROR and 95% CI were calculated using the following formulae:

$$ROR = (a/b)/(c/d)$$

$$95\%CI = \exp\{\ln(ROR) \pm 1.96(1/a + 1/b + 1/c + 1/d)^{0.5}\}$$

The ROR indicates the ratio of the fraction of reported AEs in which pertuzumab was the suspected agent to the fraction of reported AEs in which pertuzumab was not reported as the suspected agent. A signal of AEs associated with the combination of pertuzumab was considered to be detected if the lower limit of the 95% CI was > 1.

3 Results

3.1 Descriptive analysis of the study population

In total, 36,561,546 cases were reported in VigiBase as of December 2023 (Fig. 1a). After excluding duplicate data and data with missing age and sex data, 28,584 reports related to trastuzumab use in breast cancer cases were identified. Of these, 20,025 were in the without pertuzumab group, in which pertuzumab was not reported, and 8,559 were in the with pertuzumab group, in which trastuzumab and pertuzumab were reported together. The characteristics of the without pertuzumab and with pertuzumab groups are summarized in Table 1. The age group of 45−64 years was the most common in both groups, with 11,560 cases (57.73%) in the without pertuzumab group and 4,752 cases (55.52%) in the with pertuzumab group. Most patients in both groups were female, 19,878 (99.27%) in the without pertuzumab group and 8,486 (99.15%) in the with pertuzumab group. More than 90% of the cases in both groups were reported in Europe, the Americas, and the Western Pacific Region. Physicians were the most common reporters, with 9,108 (45.48%) in the without pertuzumab group and 5,298 (61.90%) in the with pertuzumab group. Most reports in the without pertuzumab group were published before 2013 (5,096; 25.45%), whereas, in the with pertuzumab group, the peak reporting year was 2019 (1,397; 16.32%).

3.2 SOC signals with pertuzumab relative to those without pertuzumab

The AEs included in this analysis were extracted and classified into 27 SOCs and 1,550 PTs (Fig. 1b). The results of the disproportionality analysis of AEs at the SOC level in the with pertuzumab group relative to those in the without pertuzumab group are shown in Fig. 2. In the with pertuzumab group, signals were detected in 11 SOCs, including blood and lymphatic system disorders (ROR: 1.51, 95% CI: 1.40−1.64); eye disorders (1.26, 1.06−1.50); gastrointestinal disorders (1.70, 1.60−1.81); immune system disorders (1.18, 1.02−1.36); infections and infestations (1.80, 1.65−1.97); injury, poisoning, and procedural complications (1.79, 1.62−1.98); investigations (1.14, 1.06−1.23); metabolism and nutrition disorders (1.61, 1.43−1.81); nervous system disorders (1.18, 1.10−1.27); renal and urinary disorders (1.29, 1.07−1.56); and reproductive system and breast disorders (1.82, 1.41−2.36).

3.3 Anticancer agents reported simultaneously with trastuzumab-based therapy

We further analyzed the antineoplastic agents and endocrine therapies reported simultaneously with trastuzumab and pertuzumab (Fig. 3). The results showed that 6,826 (34.09%) patients in the without pertuzumab group (trastuzumab-only group) and 1,600 (18.69%) patients in the with pertuzumab group (trastuzumab + pertuzumab group) had no anticancer agents reported simultaneously, indicating that other agents were used more frequently in the with pertuzumab group. The most frequently used concomitant chemotherapy was docetaxel, with 6,085 (30.39%) patients in the without pertuzumab group and 4,350 (50.82%) in the with pertuzumab group, indicating more than 20% higher use in the with pertuzumab group.

Therefore, the AE signals shown in Fig. 2 were considered to be influenced by the differences in concomitant chemotherapy. To detect the AE signals without the effects of concomitant chemotherapy, a subgroup analysis was conducted using reports without other anticancer agents.

3.4 SOC signals for subgroups with pertuzumab relative to those in subgroups without pertuzumab

The results of the disproportionality analysis at the SOC level, excluding reports on other anticancer agents, are shown in Fig. 4a. Signals were detected in the trastuzumab + pertuzumab group for gastrointestinal disorders (1.45, 1.26−1.67); infections and infestations (1.54, 1.24−1.91); injury, poisoning and procedural complications (1.59, 1.29−1.97); and metabolism and nutrition disorders (1.38, 1.01−1.88) relative to those in the trastuzumab-only group. New signals that were not detected in the overall analysis were detected in neoplasms benign, malignant and unspecified neoplasms (including cysts and polyps) (1.60, 1.21−2.11) and in skin and subcutaneous tissue disorders (1.63, 1.40−1.90). We also analyzed the trastuzumab + docetaxel (n = 1,410) and trastuzumab + docetaxel + pertuzumab (n = 1,999) subgroups with the addition of docetaxel, which was most frequently reported simultaneous treatment (Fig. 4b). Consistent with the results of the subgroup without docetaxel, signals were detected in the trastuzumab + docetaxel + pertuzumab group for gastrointestinal disorders (1.63, 1.38−1.93); infections and infestations (1.47, 1.16−1.86); injury, poisoning, and procedural complications (2.63, 1.74 − 3.96); metabolism and nutrition disorders (2.09, 1.42−3.08); and neoplasms benign, malignant, and unspecified neoplasms (including cysts

202 and polyps) (2.12, 1.30–3.46). Signals for investigations (1.83, 1.42–2.36) and nervous system disorders
203 (1.50, 1.20–1.87) were also detected in the trastuzumab + docetaxel + pertuzumab group.
204
205 **3.5 PT signals for subgroups with pertuzumab relative to those in subgroups without pertuzumab**
206 Furthermore, a disproportionality analysis was performed for PTs in the SOCs for which a signal
207 was detected in each subgroup to identify more detailed AE categories (Tables 2 and 3). In the trastuzumab
208 + pertuzumab group, signals were detected for PTs, including diarrhea (3.49, 2.83–4.30), nasopharyngitis
209 (1.91, 1.05–3.44), dehydration (3.68, 1.70–7.96), alopecia (2.00, 1.31–3.05), dry skin (3.16, 1.58–6.32),
210 pruritus (1.96, 1.51–2.55), and rash (1.63, 1.20–2.23), relative to those in the trastuzumab-only group (Table
211 2). In the trastuzumab + docetaxel + pertuzumab group, signals were detected for PTs, including diarrhea
212 (2.37, 1.88–2.99), nausea (1.72, 1.24–2.39), vomiting (1.48, 1.01–2.17), decreased neutrophil count (5.67,
213 2.57–12.49), and peripheral sensory neuropathy (5.94, 1.79–19.71) relative to those in the trastuzumab +
214 docetaxel group (Table 3). Although signals were not detected at the SOC level, they were also detected
215 for PTs, including febrile neutropenia (3.00, 1.14–7.88) and left ventricular dysfunction (2.50, 1.29–4.85)
216 in the trastuzumab + pertuzumab group (Table S1) and for febrile neutropenia (1.29, 1.00–1.67) and rash
217 (1.46, 1.01–2.12) in the trastuzumab + docetaxel + pertuzumab group (Table S2).
218
219 **3.6 Difference in serious AEs with and without pertuzumab**

The difference in the severity of AEs between the without pertuzumab and with pertuzumab groups was also analyzed. Analysis of all serious classifications revealed no difference in the frequency of AEs reported as serious between the without pertuzumab and with pertuzumab groups, both overall and in the subgroups (Figs. 5a－5c). A detailed analysis of severity revealed signals of Caused/Prolonged Hospitalization in the with pertuzumab group (1.25, 1.17－1.33) and the trastuzumab + pertuzumab subgroup (1.18, 1.00－1.38) (Figs. 5a and 5b). Disproportionality analysis for AEs reported as Caused/Prolonged Hospitalization revealed SOC signals for gastrointestinal disorders (1.51, 1.08–2.12), investigations (1.48, 1.01－2.18), and metabolism and nutrition disorders (1.92, 1.06－3.47) in the trastuzumab + pertuzumab group relative to those in the trastuzumab-only group (Fig. 5d). Signals, including diarrhea (2.52, 1.53–4.15) and dehydration (4.29, 1.76–10.48), were detected in the trastuzumab + pertuzumab group at the PT level (Table S3).

4 Discussion

To the best of our knowledge, this is the first study to comprehensively identify the differences in AE profiles after adding pertuzumab to trastuzumab-based chemotherapy for HER2-positive breast cancer using RWD. In this study, a bias in concomitant chemotherapy was observed between the group without pertuzumab and the group with pertuzumab (Fig. 3). Consequently, the detected AE signals were likely influenced by other concomitantly reported agents rather than by the addition of pertuzumab itself (Fig. 2). To minimize the influence of these agents, cases involving additional anticancer agents were excluded. This approach allowed for clearer comparisons between trastuzumab alone and trastuzumab + pertuzumab, as well as between trastuzumab + docetaxel and trastuzumab + docetaxel + pertuzumab (Fig. 4). As a result, the observed signals were more likely attributable to pertuzumab addition, providing a more accurate representation of changes in the safety profile. Clinical trials, including APHINITY, CLEOPATRA, and NEOSPHERE, have reported increased rates of diarrhea and rash with pertuzumab addition [9–11]. Our study also detected these signals (Tables 2, 3, and S2), aligning with clinical practice. A previous pharmacovigilance study on pertuzumab using the Food and Drug Administration Adverse Event Reporting System by Zou et al. identified AE signals, including myelosuppression and cardiotoxicity [19]. However, pertuzumab-associated AEs were detected relative to all reports. In clinical settings, as pertuzumab is not administered alone but is always administered in combination with trastuzumab or other chemotherapies, including docetaxel, these results are likely attributed to trastuzumab or concomitant chemotherapy. Our

study focused on the safety of pertuzumab in addition to trastuzumab relative to that with trastuzumab alone. Therefore, our results complement those of Zou et al. and demonstrate the safety profile of pertuzumab from a more clinical point of view.

HER2-targeted therapy is expanding to other cancers [20–22]. Although pertuzumab did not improve survival in gastric cancer, it showed benefits in colorectal cancer [23, 24]. As its use broadens, continuous safety monitoring remains essential. HER2-targeted agents, including trastuzumab and pertuzumab, are associated with cardiotoxicity due to HER2's role in cardiomyocyte function [25–27]. Previous pharmacovigilance studies detected cardiotoxicity signals for both drugs [26]. In our study, left ventricular dysfunction was identified at the PT level in the trastuzumab + pertuzumab group (Table S1). However, clinical trials have reported no increased cardiotoxicity risk with the addition of pertuzumab [28, 29]. Although the overall risk appears low, continued monitoring is necessary. Signals for skin and subcutaneous tissue disorders were observed in the trastuzumab + pertuzumab group (Fig. 4a and Table 2), consistent with previous reports [19]. HER2 in keratinocytes plays a role in maintaining skin function [30, 31], and dual inhibition by trastuzumab and pertuzumab may exacerbate skin-related AEs. The recently developed subcutaneous trastuzumab-pertuzumab formulation may alter AE profiles, warranting further study. Additionally, signals for infections and infestations were detected (Figs. 2 and 4), including febrile neutropenia (Tables S1 and S2), highlighting the need for careful monitoring. Although clinical trials have not reported an increased risk of febrile neutropenia [29], vigilance for blood toxicity-related AEs remains

necessary. Currently, the combination of trastuzumab, docetaxel, and pertuzumab is the optimal first-line therapy for HER2-positive breast cancer [32]. Our data revealed signals of gastrointestinal disorders, including nausea and vomiting; increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST); and nervous system disorders, including paresthesia and peripheral sensory neuropathy in the trastuzumab + docetaxel + pertuzumab group relative to those in the trastuzumab + docetaxel group. These AEs commonly occur with docetaxel, and its combination with pertuzumab may further enhance the toxicity of docetaxel [33]. Therefore, in cases of triple therapy with trastuzumab, docetaxel, and pertuzumab, strengthening anti-nausea measures and monitoring the occurrence of hepatic dysfunction and neuropathy relative to trastuzumab plus docetaxel therapy may be necessary.

The SOC signals of injury, poisoning, and procedural complications detected in this study cannot be directly associated with pertuzumab (Figs. 2 and 4). PT for Infusion-related reaction was detected (Table 3), which should be considered when administering antibody agents. Additionally, a signal for benign, malignant, and unspecified neoplasms may indicate an increased incidence of brain metastases. Brain metastases occur in 30–55% of HER2-positive breast cancers [34], with trastuzumab prolonging survival while increasing the risk of brain metastases [35–37]. Pertuzumab may further extend survival, potentially elevating this risk. Since trastuzumab and pertuzumab have limited blood-brain barrier penetration, combination therapy with tyrosine kinase inhibitors, including lapatinib, tucatinib, and pyrotinib, has been reported to be effective in controlling brain metastases [38–40].

285 The results of the severity analysis showed that no signals were detected for total severity upon
286 the addition of pertuzumab (Figs. 5a−5c). Although a detailed analysis of severity did not reveal signals in
287 the life-threatening category, they may cause or prolong hospitalization. AEs, especially those classified as
288 SOC for gastrointestinal disorders, investigations, and metabolism and nutritional disorders, may contribute
289 to the causation or prolongation of hospitalization (Fig. 5d). When selecting pertuzumab combination
290 therapy, attention should be paid to the occurrence of diarrhea and dehydration, which should be treated
291 immediately. Considering the increased frequency of AEs identified in this study, patients undergoing
292 combination treatment with pertuzumab should be monitored.

293 Although studies using VigiBase are highly useful for monitoring drug safety globally, they have
294 some limitations. Controlling for confounding factors is difficult because spontaneous reporting may
295 include reporting bias, erroneous data, or missing data. Further, data from these databases cannot be used
296 to calculate the incidence of AEs and assess risks, as the cases of patients in whom AEs did not occur are
297 unknown. Additionally, this study identified a reporting-year imbalance between the trastuzumab group and
298 the trastuzumab + pertuzumab group. This discrepancy arises from differences in approval years, with
299 trastuzumab approved in 1998 and pertuzumab in 2012. Such an imbalance may introduce bias due to
300 evolving AE reporting standards over time. Although studies using RWD cannot replace clinical trials, they
301 are valuable for qualitatively monitoring the safety of medications and estimating the risk of AEs [41].
302 Despite these limitations, RWD can be used to detect agent-induced AEs and implement countermeasures

303 quickly. In this study, the ROR method was used for comprehensive signal detection. A comparative
304 analysis of data mining algorithms, including the ROR, Proportional Reporting Ratio (PRR), Bayesian
305 Confidence Propagation Neural Network (BCPNN), and Multi-item Gamma Poisson Shrinker (MGPS)
306 methods, has demonstrated that the ROR method is the most comprehensive and effective for
307 pharmacovigilance [42]. The ROR method has higher sensitivity in signal detection compared to Bayesian
308 statistical approaches, such as BCPNN and MGPS, allowing for the identification of a broader range of
309 potential safety signals. Therefore, combining multiple signal detection methods may enhance accuracy
310 and reduce false positives. In this study, signals were evaluated using the PRR, BCPNN, and MGPS
311 methods in addition to the ROR method (Table S4), with data presented in Tables S5–16. Although no AEs
312 were detected as signals by all four methods, AEs such as diarrhea and dehydration were identified in the
313 trastuzumab + pertuzumab subgroup by three methods, except for MGPS. This suggests that these may
314 represent more robust signals (Tables S8 and S16). Further retrospective or prospective studies are needed
315 to accurately determine the effects of pertuzumab addition on the occurrence of AEs.

5 Conclusions

We have comprehensively identified the safety profile of pertuzumab addition to trastuzumab-based therapy using RWD. Pertuzumab may enhance gastrointestinal disorders, including diarrhea and infections, as well as skin and subcutaneous tissue disorders, including alopecia, dry skin, pruritus, and rashes, when used in combination with trastuzumab. In addition, gastrointestinal disorders, including nausea and vomiting; liver disorders, including increased AST and ALT levels; and nervous system disorders, including paresthesia and peripheral sensory neuropathy, may be enhanced when it is combined with trastuzumab and docetaxel. Overall, when selecting pertuzumab combination therapy, considering the AEs identified in this study is important to ensure the safety of chemotherapy for patients with breast cancer.

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Declarations

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Conflicts of interest: The authors declare no conflicts of interest.

Availability of data and material: The datasets generated and analyzed during the study are available from the corresponding author upon reasonable request.

Ethics approval: Not applicable because this study was an observational study that used fully anonymized patient data

Consent for publication: Not applicable.

Code availability: The code is available from the corresponding author upon reasonable request.

Author contributions: Tatsuaki Takeda and Jun Matsumoto contributed to the study's conception and design. Material preparation, data collection and analysis were performed by Tatsuaki Takeda and Tomonori

Sakai. The first draft of the manuscript was written by Tatsuaki Takeda, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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459 **Tables**

460 **Table 1** Characteristics of the study population

Characteristics		Without pertuzumab n = 20,025 n (%)		With pertuzumab n = 8,559 n (%)	
Age	≤ 44 years	3,773	(18.84)	1,672	(19.53)
	45−64 years	11,560	(57.73)	4,752	(55.52)
	65−74 years	3,484	(17.40)	1,565	(18.28)
	75 ≥ years	1,208	(6.03)	570	(6.66)
Sex	Male	147	(0.73)	73	(0.85)
	Female	19,878	(99.27)	8,486	(99.15)
Region	African Region	81	(0.40)	17	(0.20)
	Region of the Americas	7,982	(39.86)	2,473	(28.89)
	South-East Asia Region	1,162	(5.80)	193	(2.25)
	European Region	8,343	(41.66)	4,578	(53.49)
	Eastern Mediterranean Region	572	(2.86)	242	(2.83)
	Western Pacific Region	1,885	(9.41)	1,056	(12.34)
Reporter	Physician	9,108	(45.48)	5,298	(61.90)
	Pharmacist	2,473	(12.35)	861	(10.06)
	Other Health Professional	2,812	(14.04)	911	(10.64)
	Lawyer	1,434	(7.16)	502	(5.87)
	Consumer or other non-health professional	3,277	(16.36)	949	(11.09)
	Not available	921	(4.60)	38	(0.44)
Reporting year	≤ 2013	5,096	(25.45)	155	(1.81)
	2014	1,395	(6.97)	339	(3.96)
	2015	1,316	(6.57)	477	(5.57)
	2016	1,212	(6.05)	600	(7.01)
	2017	1,189	(5.94)	544	(6.36)
	2018	2,197	(10.97)	1,129	(13.19)
	2019	2,324	(11.61)	1,397	(16.32)
	2020	1,456	(7.27)	1,089	(12.72)
	2021	1,217	(6.08)	969	(11.32)

2022	1,114	(5.56)	909	(10.62)
2023	1,509	(7.54)	951	(11.11)

461

462 **Table 2** Preferred Terms (PTs) in the System Organ Classes (SOCs) for which a signal was detected in the trastuzumab + pertuzumab subgroup

SOC	PT	Trastuzumab only (n = 6,826)	Trastuzumab + Pertuzumab (n = 1,600)	ROR (95% CI)
Gastrointestinal disorders	Diarrhea	222	168	3.49 (2.83–4.30)
	Stomatitis	16	11	2.95 (1.36–6.36)
	Gastric disorder	2	4	8.55 (1.56–46.73)
Infections and infestations	Cellulitis	9	6	2.85 (1.01–8.02)
	Lower respiratory tract infection	2	3	6.41 (1.07–38.39)
	Nasopharyngitis	36	16	1.91 (1.05–3.44)
	Clostridium difficile infection	1	5	21.39 (2.50–183.26)
	COVID-19	27	22	3.51 (1.99–6.18)
Injury, poisoning and procedural complications	Off-label use	29	42	6.32 (3.92–10.17)
	Toxicity to various agents	4	6	6.42 (1.81–22.78)
Metabolism and nutrition disorders	Dehydration	14	12	3.68 (1.70–7.96)
	Feeding disorder	2	3	6.41 (1.07–38.39)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Brain neoplasm malignant	2	3	6.41 (1.07–38.39)
	Metastases to central nervous system	29	15	2.22 (1.19–4.15)
Skin and subcutaneous tissue disorders	Alopecia	69	32	2.00 (1.31–3.05)
	Cold sweat	2	6	12.84 (2.59–63.69)

Dry skin	19	14	3.16 (1.58−6.32)
Nail dystrophy	3	4	5.70 (1.27−25.49)
Pruritus	192	86	1.96 (1.51−2.55)
Rash	151	57	1.63 (1.20−2.23)
Rash erythematous	6	5	3.56 (1.09−11.69)
Skin lesion	4	5	5.35 (1.43−19.93)
Onychomadesis	2	4	8.55 (1.56−46.73)
Skin mass	2	3	6.41 (1.07−38.39)

SOC, System Organ Class; PT, Preferred Term; ROR: Reporting Odds Ratio; CI: Confidence Interval;

463

464 **Table 3** Preferred Terms (PTs) in the System Organ Classes (SOCs) for which a signal was detected in the trastuzumab + docetaxel + pertuzumab subgroup

SOC	PT	Trastuzumab + Docetaxel (n = 1,410)	Trastuzumab + Docetaxel + Pertuzumab (n = 1,999)	ROR (95% CI)
Gastrointestinal disorders	Diarrhea	106	323	2.37 (1.88−2.99)
	Dyspepsia	8	29	2.58 (1.18−5.66)
	Nausea	53	126	1.72 (1.24−2.39)
	Vomiting	41	85	1.48 (1.01−2.17)
Injury, poisoning and procedural complications	Infusion-related reaction	10	52	3.74 (1.89−7.38)
Investigations	Alanine aminotransferase increased	6	21	2.48 (1.00−6.17)
	Aspartate aminotransferase increased	4	20	3.55 (1.21−10.42)
	Neutrophil count decreased	7	55	5.67 (2.57−12.49)
	Weight decreased	3	19	4.50 (1.33−15.24)
Metabolism and nutrition disorders	Decreased appetite	19	46	1.72 (1.01−2.96)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Metastases to central nervous system	1	11	7.80 (1.01−60.46)
Nervous system disorders	Headache	11	33	2.13 (1.08−4.24)
	Paraesthesia	11	40	2.60 (1.33−5.08)
	Peripheral sensory neuropathy	3	25	5.94 (1.79−19.71)
	Polyneuropathy	5	25	3.56 (1.36−9.32)

SOC, System Organ Class; PT, Preferred Term; ROR: Reporting Odds Ratio; CI: Confidence Interval;

Figure legends

Fig. 1. (a) Flow of the report extraction process. (b) Flow of extraction of adverse events for analysis. MedDRA, Medical Dictionary for Regulatory Activities; SOC, System Organ Class; PT, Preferred Term

Fig. 2. Disproportionality analysis of adverse events at the System Organ Class (SOC) level for the with pertuzumab group relative to those in the without pertuzumab group. The plots show the Reporting Odds Ratio (ROR) with the 95% Confidence Interval (CI) on a logarithmic scale. The red plot shows the SOCs for which a signal was detected in the group with pertuzumab.

Fig. 3. The top 20 anticancer agents reported simultaneously with trastuzumab and pertuzumab. The percentage of each agent is shown.

Fig. 4. Disproportionality analysis of adverse events at the System Organ Class (SOC) level for (a) the trastuzumab + pertuzumab group relative to the trastuzumab-only group and (b) the trastuzumab + docetaxel + pertuzumab group relative to the trastuzumab + docetaxel group. The plots show the Reporting Odds Ratio (ROR) with the 95% Confidence Interval (CI) on a logarithmic scale. The red plot shows the SOCs for which a signal was detected in the group with pertuzumab.

Fig. 5. Disproportionality analysis of severity of adverse events for (a) the with trastuzumab group relative to that in the without trastuzumab group, (b) the trastuzumab + pertuzumab group relative to that in the trastuzumab-only group, and (c) the trastuzumab + docetaxel + pertuzumab group relative to that in the trastuzumab + docetaxel group. (d) Disproportionality analysis of adverse events reported as Caused/Prolonged Hospitalization in the severity analysis at the System Organ Class (SOC) level for the trastuzumab + pertuzumab group relative to that in the trastuzumab-only group. The plots show the Reporting Odds Ratio (ROR) with the 95% Confidence Interval (CI) on a logarithmic scale. The red plot shows the categories for which a signal was detected in the group with pertuzumab.