

Safety and efficacy evaluation of pertuzumab in patients with solid tumors

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Abstract

Background: The development of targeted therapies benefits patients with certain markers in the treatment of breast cancer. Pertuzumab is a novel humanized monoclonal antibody that blocks human epidermal growth factor receptor 2 (HER2) dimerization. The Food and Drug Administration has approved pertuzumab in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer.

Methods: To assess the safety and efficacy profile of pertuzumab, we searched PubMed and Embase (articles from January 1966 to January 2015) using the keyword “pertuzumab”.

Results: Fourteen eligible studies were included in our final analysis. From the results of our analysis, diarrhea (56.9%, 95% confidence interval [CI] 49.6%–63.9%), nausea (34.0%, 95% CI 27.7%–40.8%), and rash (25.6%, 95% CI 20.8%–31.0%) were the most common adverse effects in pertuzumab alone and pertuzumab-based therapies. Based on randomized controlled clinical trials, diarrhea (odds ratio [OR] 2.310, 95% CI 1.818–2.936), rash (OR 1.848, 95% CI 1.094–3.122), and febrile neutropenia (OR 1.672, 95% CI 1.130–2.474) were of statistical significance, which meant that pertuzumab played a prominent role in the incidence of diarrhea. Meanwhile, pertuzumab showed its effective role in cancer control and lifetime prolongation.

Conclusion: In conclusion, considering that the common adverse effects for pertuzumab are gastrointestinal and skin toxicities, which are easier to handle than other toxicities, pertuzumab is a safe and effective drug for patients with solid tumors.

Abbreviations: CI = confidence interval, HER2 = human epidermal growth factor receptor 2, NSCLC = nonsmall cell lung cancer, OR = odds ratio, PFS = progression-free survival, RCT = randomized controlled trial.

Keywords: adverse effect, diarrhea, nausea, pertuzumab, rash

1. Introduction

Breast cancer is one of the most common cancer among women worldwide.^[1,2] Each year, approximately 1.68 million women were diagnosed with breast cancer worldwide, and over 500,000

women died of the disease (about 1400 deaths per day).^[3] Breast cancer might be controlled but usually not cured when diagnosed in the metastatic setting. However, the revolution in the molecular biology gives rise to an improved understanding of this disease and more options for the treatment. Although the incidence of the disease is continuously high, the mortality rate is reducing.^[4] The 5-year survival rate of breast cancer was around 89% according to the statistics in 2014.^[5] Many new systematic therapies for advanced breast cancer have been available over the decades, especially for human epidermal growth factor receptor 2 (HER2)-positive breast cancer. The intracellular pathways of HER2 proto-oncogene (also known as “neu” or “c-erbB-2”) are important pathways related to cell growth, proliferation, differentiation, and death,^[6] and the overexpression or amplification of HER2 often indicates higher rates of recurrence and mortality in breast cancer.^[7] A total of 15% to 20% of all the breast cancers are estimated to overexpress HER2 receptor, and thus, these patient populations can benefit from HER2-targeted therapy.^[8]

Pertuzumab is a humanized, recombinant, immunoglobulin G monoclonal antibody that targets HER2.^[9] Unlike trastuzumab, pertuzumab shows its novelty which can either homodimerize with another HER2 receptor or heterodimerize with a different receptor of the HER family to activate certain downstream signaling pathways through phosphorylation of the tyrosine kinases.^[10] It acts on the extracellular portion of HER2 receptor like trastuzumab, but the binding region is different,^[7] leading to different effects on cancers. In previous clinical trials, pertuzumab showed its efficacy in HER2-overexpressed breast cancer and other cancers, such as ovarian and prostate cancer. The Food and Drug Administration (FDA) has approved pertuzumab in

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combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapies or chemotherapy for metastatic diseases.^[11] The European Medicines Agency also recommended this combination for the treatment of adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer.^[7]

Previous clinical trials have reported that this monoclonal antibody is effective in the therapies for cancer patients, but the adverse effects caused by pertuzumab or pertuzumab-based therapies should also be considered, such as gastrointestinal, skin, and hematopoietic toxicities. The adverse effects might differ in each clinical trial, and some might not be caused by pertuzumab. Thus, we conducted this meta-analysis to evaluate the safety and efficacy profile of this drug.

2. Methods

2.1. Data source

PubMed (articles from January 1966 to January 2015) was searched using the keyword “pertuzumab”. The search was limited to clinical trials published in English. In addition, we reviewed Embase (articles from January 2000 to January 2015) for “pertuzumab” to make sure no additional studies were missed. After screening the titles and/or abstracts, duplicates were removed, and for those articles with similar data and study designs, only the most complete and recent clinical trial was included in our analysis. Two authors independently selected studies and discrepancies were resolved by discussion with a third author. As this was a meta-analysis, no ethical approval was required.

2.2. Study selection

In all phase I clinical trials, pertuzumab was used in the range of 0.5 to 20 mg/kg to evaluate the dose-limiting toxicity and maximum tolerated dose. In phase II and III clinical trials, pertuzumab was studied in 2 different dosing schedules: 840 mg as a loading dose followed by 420 mg every 3 weeks and 1050 mg every 3 weeks. Trials that met the following criteria were selected for the final analysis: prospective phase I, II, and III clinical trials in cancer patients; participants were treated with pertuzumab; data were available regarding the survival outcomes and incidences of all-grade or grade ≥ 3 adverse effects. Studies using pertuzumab as a single agent or in combination with other drugs were both included in our analysis.

2.3. Clinical endpoints

Data of clinical endpoints extracted from the trials were low-grade (1–2), high-grade (3–5), and all-grade (1–5) adverse effects according to the National Cancer Institute Common Toxicity Criteria version 2 or Common Terminology Criteria for Adverse Effects version 3. Other extracted data included the first author's name, year of publication, the study design, population information, dosing schedules of pertuzumab, type of cancers, and concurrent antineoplastic medications used with pertuzumab.

2.4. Statistical analysis

We performed the statistical analyses using the Comprehensive Meta-Analysis program (Biostat, Englewood, NJ) version 2. For each study, the proportion of patients with each adverse effect (both all-grade and grade ≥ 3) in the pertuzumab arm was

calculated, and the 95% confidence interval (CI) was derived. For all the randomized controlled studies comparing pertuzumab with placebo, we calculated the odds ratio (OR) of each adverse effect mentioned in at least 2 studies to determine the role pertuzumab plays in each adverse effect. We also extracted median progression-free survival (PFS) from single-agent pertuzumab trials and hazard ratios (HRs) with 95% CI from control-arm studies to evaluate the efficacy of pertuzumab. I^2 and P values were evaluated to test heterogeneity, and when $I^2 > 50\%$ and $P < .1$, a random-effects model was used in the analysis.

2.5. Risk of bias and quality assessment

To evaluate the risk of bias and quality of the studies, QUADAS-2 was used as a systematic review assessment method, which consisted of 4 key domains: patient selection, index test, reference standard, and flow and timing. Risk of bias was rated as high/low/unclear. The assessment was measured using Review Manager (Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen, Sweden). A sensitivity analysis was also performed with a Newcastle–Ottawa Scale. Studies that achieved 6 or more stars on the Newcastle–Ottawa Scale were considered of high quality.

3. Results

3.1. Searching results

The initial search identified 20 potentially relevant articles on pertuzumab. The search of Embase did not yield any additional results. Six studies were excluded because they did not provide enough data for specific adverse effects. Our selection process is shown in Fig. 1.

Characteristics of the 14 eligible studies included in our final analysis are presented in Table 1. These studies included 2 phase I^[12,13] trials, 11 phase II^[14–23] trials, and 1 phase III^[24] trial. Five phase II trials used pertuzumab as a single agent,^[14–18] 3 phase II trials used pertuzumab in combination with at least 1 agent,^[22,23,25] and the remaining 3 phase II trials were randomized controlled trials (RCTs).^[19–21] The phase III trial was a randomized, placebo-controlled study.^[24]

3.2. Patients

A total of 2249 patients from 14 clinical trials were included in our analysis. Seven trials ($n=392$) evaluated pertuzumab as monotherapy. Three trials ($n=353$) used pertuzumab plus other agents. Four trials ($n=1504$; pertuzumab: 853; control: 651) compared the effects of pertuzumab arm with the control arm. The 14 studies included breast cancer (6 articles), prostate cancer (2 articles), ovarian cancer (3 articles), nonsmall cell lung cancer (NSCLC) (1 article), and other kinds of solid tumors (2 articles).

3.3. Rates of adverse effects and subgroup analysis

We recorded and evaluated the adverse effects in all 14 trials. We also compared the adverse effects in different dose levels and different tumor types. RCTs were analyzed to determine the role of pertuzumab in main adverse effects. We found that diarrhea, nausea, and rash were the most common all-grade adverse effects. The rates ranged from 20.9% to 86.5% for diarrhea, 6.1% to 75.4% for nausea, and 5.7% to 37.1% for rash. Then, we calculated the overall rate and 95% CI for each adverse effect. The pooled rates for diarrhea, nausea, and rash were 56.9%

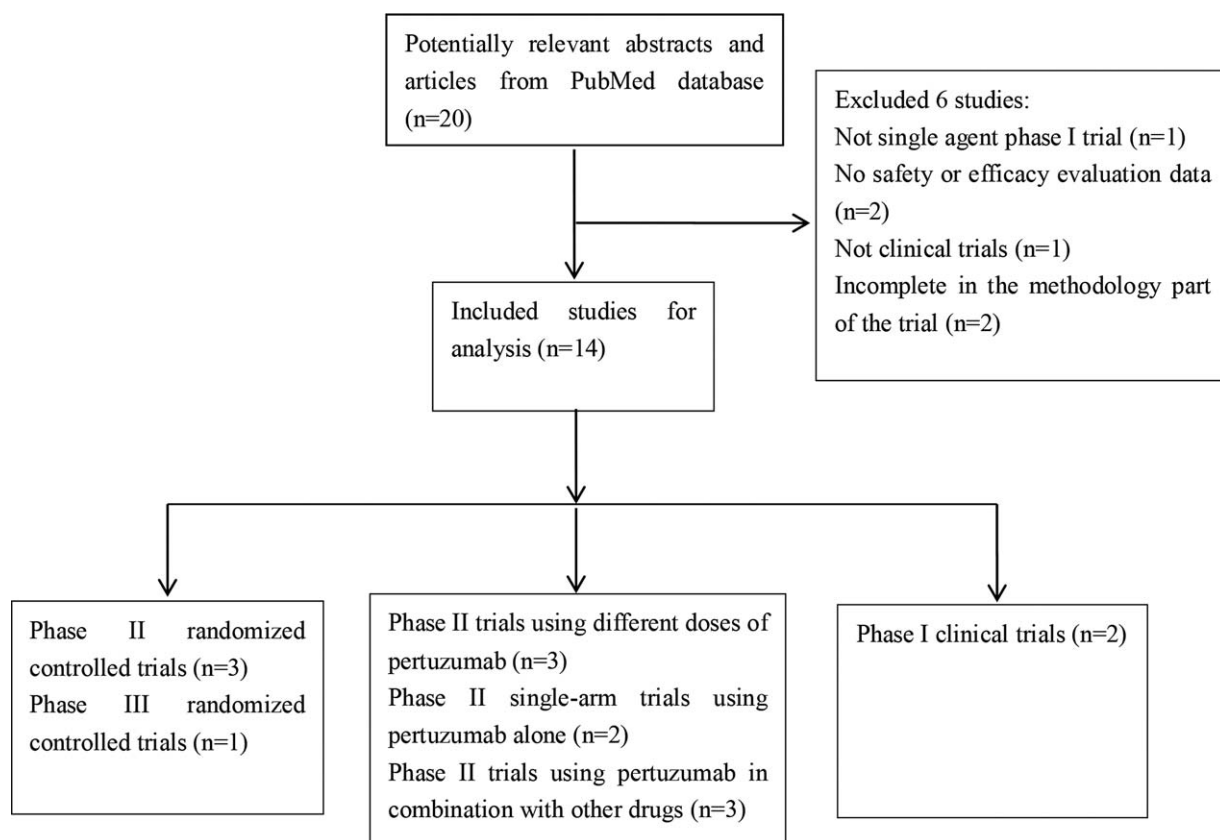


Figure 1. Search results and study selection for all the clinical trials included in our study.

Table 1

Characteristics of all the eligible clinical trials.

First author	Year of publication	Phase	Number of patients	Treatment regimen	Indications
Agus	2005	Phase I	21	Pertuzumab	Incurable, locally advanced, recurrent, or metastatic solid tumors
Yamamoto	2009	Phase I	18	Pertuzumab	Solid tumors (rectal, stomach, ovarian, etc.)
Gordon	2006	Phase II	123 (61, 62)	Pertuzumab once every 3wk with a loading dose of 840 mg followed thereafter by either 420 mg (arm A) or 1050 mg (arm B)	Advanced ovarian cancer
de Bono	2007	Phase II	68 (35, 33)	Pertuzumab once every 3wk with a loading dose of 840 mg followed thereafter by either 420 mg (arm A) or 1050 mg (arm B)	Hormone-refractory prostate cancer
Agus	2007	Phase II	41	Pertuzumab	Castration-resistant prostate cancer
Herbst	2007	Phase II	43	Pertuzumab	Nonsmall cell lung cancer
Gianni	2010	Phase II	78 (41, 37)	Pertuzumab once every 3wk with a loading dose of 840 mg followed thereafter by either 420 mg (arm A) or 1050 mg (arm B)	HER2-negative metastatic breast cancer
Makhija*	2010	Phase II	130 (65, 65)	Gemcitabine + placebo/pertuzumab	Platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer
Kaye*	2013	Phase II	149 (74, 75)	Chemotherapy + pertuzumab/-	Relapsed, platinum-sensitive ovarian cancer
Gianni*	2012	Phase II	417 (310, 107)	Pertuzumab + trastuzumab + docetaxel/pertuzumab + trastuzumab/pertuzumab + docetaxel, trastuzumab + docetaxel	Locally advanced, inflammatory, or early HER2-positive breast cancer
Schneeweiss	2013	Phase II	223	Pertuzumab + trastuzumab + neoadjuvant chemotherapy	HER2-positive early breast cancer
Baselga	2010	Phase II	66	Pertuzumab + trastuzumab	HER2-positive metastatic breast cancer (disease progression from prior trastuzumab treatment)
Baselga*	2012	Phase III	808 (404, 404)	Trastuzumab + docetaxel + pertuzumab/placebo	HER2-positive breast cancer
Miller	2014	Phase IIa	64	T-DM1 + pertuzumab	HER2 positive, locally advanced, or metastatic breast cancer

HER2 = human epidermal growth factor receptor 2.

* Randomized controlled trials.

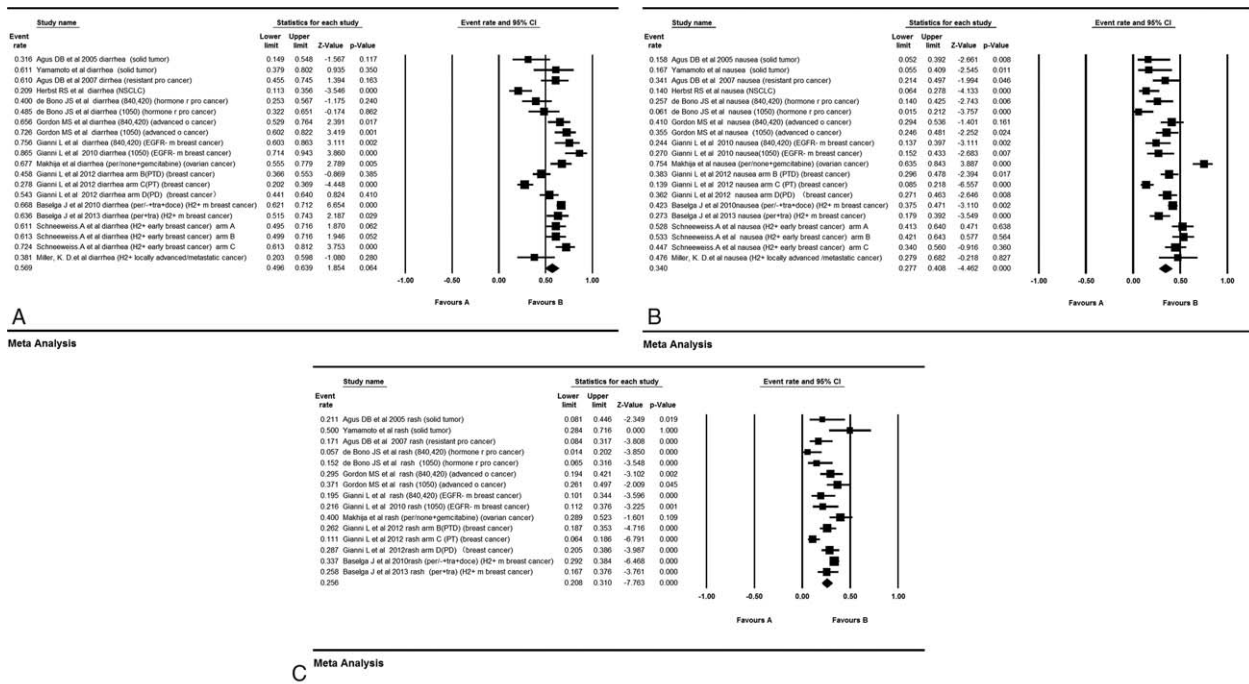


Figure 2. Forest plot of the incidence of all-grade (A) diarrhea, (B) nausea, and (C) rash in pertuzumab-based therapies.

(95% CI 49.6%–63.9%), 34.0% (95% CI 27.7%–40.8%), and 25.6% (95% CI 20.8%–31.0%), respectively (Fig. 2A–C, Table 2).

Subgroup analysis based on types of tumors including breast cancer, ovarian cancer, prostate cancer, and NSCLC was performed. For the 3 main adverse effects discussed above, we found that adverse rates were higher in breast cancer and ovarian cancer than in prostate cancer and NSCLC. The adverse rates in ovarian cancer tended to be the highest. In patients with breast cancer, regardless of the stages and surface markers, the rates of adverse effect were similar, and this was also the case in ovarian and prostate cancer. Among all types of cancers, hormone refractory prostate cancer was prone to have the lowest rate of the 3 adverse effects (Table 3).

3.4. Adverse events of pertuzumab in RCTs

We selected RCTs to determine the OR of each adverse effect mentioned in more than 2 studies. Among all the adverse effects, diarrhea (OR 2.310, 95% CI 1.818–2.936), rash (OR 1.848, 95% CI 1.094–3.122), and febrile neutropenia (OR 1.672, 95% CI 1.130–2.474) were of statistical significance, which meant pertuzumab played a prominent role in the incidence of diarrhea^[26] (Fig. 3A and B, Table 4). In grade ≥ 3 adverse effects, the rate of febrile neutropenia in the experimental group was significantly higher than that in the control group (OR 1.585, 95% CI 1.045–2.403) (Fig. 4).

3.5. Survival outcomes of pertuzumab

The data of median PFS which is the time from the date of first dose of study medication to documented progressive disease or death at any time^[23] for pertuzumab in different kinds of tumors are shown in Table 5. In single-arm trials with pertuzumab alone, median PFS for ovarian cancer was 1.65 (95% CI 1.5–2.725) and for small-cell lung cancer was 1.525 (95% CI 1.325–2.825). Median PFS did not differ between different doses administered in patients with

prostate cancer (420mg: 1.433, 95% CI 0.767–2.7 vs 1050mg: 1.433, 95% CI 0.833–2.1). Similar results were also seen in breast cancer (420mg: 1.467, 95% CI 1.267–2.733 vs 1050mg: 1.433, 95% CI 1.3–2.833). In control-arm trials using combination therapies, gemcitaine + pertuzumab and trastuzumab + docetaxel + pertuzumab showed a prolonged PFS, whereas chemotherapy + pertuzumab indicated that the addition of pertuzumab to carboplatin-based chemotherapy did not substantially prolong PFS in unselected patients with platinum-sensitive ovarian cancer.^[20] Pertuzumab might stabilize diseases and prolong the survival of cancer patients; however, large-scale studies are needed to confirm the results we have obtained so far.

3.6. Risk of bias and quality assessment

The risk of bias and quality assessments of the included studies are outlined in Fig. 5A and B. Overall, the quality of the studies was satisfactory. Thirteen of the 14 included studies got 6 scores or more in methodological assessment. One study^[13] got a score of 5.

4. Discussion

The safety profile of pertuzumab showed that the most significant adverse effect was diarrhea, indicating the high rate of gastrointestinal toxicities due to the use of pertuzumab in clinical

Table 2

All-grade adverse effects.

Adverse effect	Event rate with 95% CI
Diarrhea	0.569 (0.496, 0.639)
Nausea	0.340 (0.277, 0.408)
Rash	0.256 (0.208, 0.310)

CI = confidence interval.

Table 3

The highest and lowest rates of 3 meaningful adverse effects and the pooled event rates in different kinds of tumor.

Adverse effect	Highest rate and 95% CI	Lowest rate and 95% CI	Pooled event rate in ovarian cancer	Pooled event rate in breast cancer	Pooled event rate in prostate cancer and NSCLC
Diarrhea	HER2-negative metastatic breast cancer (0.865, 0.714–0.943)	NSCLC (0.209, 0.113–0.356)	0.685 (0.615–0.748)	0.596 (0.566–0.626)	0.420 (0.261–0.598)
Nausea	Ovarian cancer (0.754, 0.635–0.843)	Hormone refractory prostate cancer (0.061, 0.015–0.212)	0.512 (0.274–0.744)	0.382 (0.352–0.413)	0.196 (0.102–0.344)
Rash	Advanced ovarian cancer (0.371, 0.261–0.497)	Hormone refractory prostate cancer (0.057, 0.014–0.202)	0.358 (0.292–0.429)	0.240 (0.182–0.310)	0.137 (0.080–0.225)

CI = confidence interval, HER2 = human epidermal growth factor receptor 2, NSCLC = none small cell lung cancer.

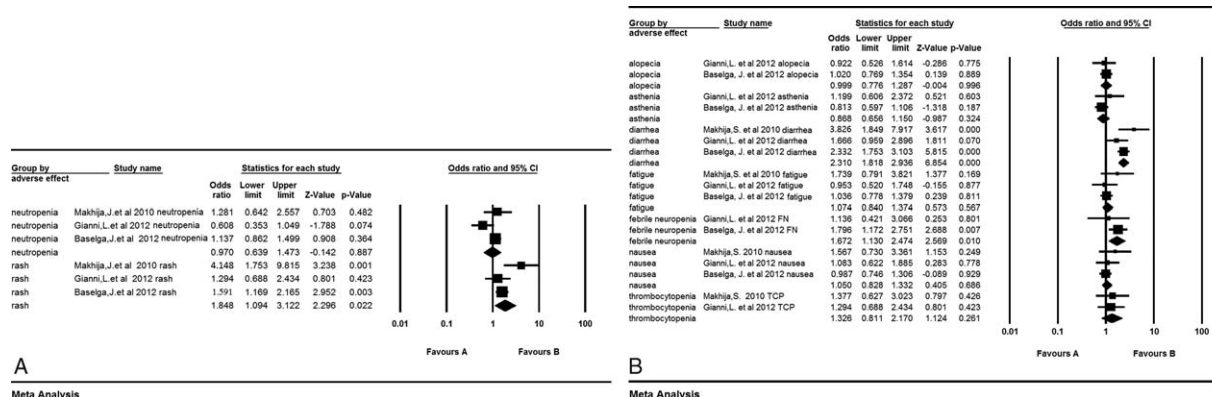


Figure 3. Forest plot of the odds ratio of main adverse effects in pertuzumab-based therapies from all the randomized controlled trials using (A) random model and (B) fixed model.

settings. Other adverse effects did not have such a strong relationship with pertuzumab compared with diarrhea. Single-arm and control-arm trials showed a prolonged PFS of pertuzumab, which meant that this drug might possess the capability to stabilize diseases and prolong the survival of cancer patients.

Gastrointestinal toxicities might be related to the blockage of HER2 function on normal cells.^[27] Previous studies have shown that the proper functions of gastrointestinal tracts relied on the expression of HER2 receptors in many vital structures,^[28] such as epithelial cells and enteric nervous system neurons.^[29] Pertuzumab might act on receptors of these normal cells and interfere with their functions, leading to gastrointestinal toxicities. No specific guidelines were available for dealing with gastrointestinal toxicities caused by HER2 antibody, but similar situations caused by other chemotherapies could give us some hints. Intravenous amifostine was recommended for the management of gastrointestinal toxicities caused by chemotherapies inhibiting epidermal growth factor receptor (EGFR) in NSCLC.^[30] As EGFR pathway is related to anti-HER2 therapy^[31] and diarrhea is actually a manifestation of mucositis,^[32] this mucosa protector amifostine might be effective in treating the diarrhea caused by pertuzumab as well. Furthermore, probiotics containing lactobacillus species were advised when the malignancy existed in the pelvic cavity, either in chemotherapy or radiation therapy.^[30] Therefore, we could use lactobacillus probiotics to treat patients with diarrhea caused by ovarian cancer if pertuzumab is approved for future ovarian cancer therapy.

Nausea, rash and severe neutropenia also occurred in patients with pertuzumab-based therapies. Nausea was mainly of grades.

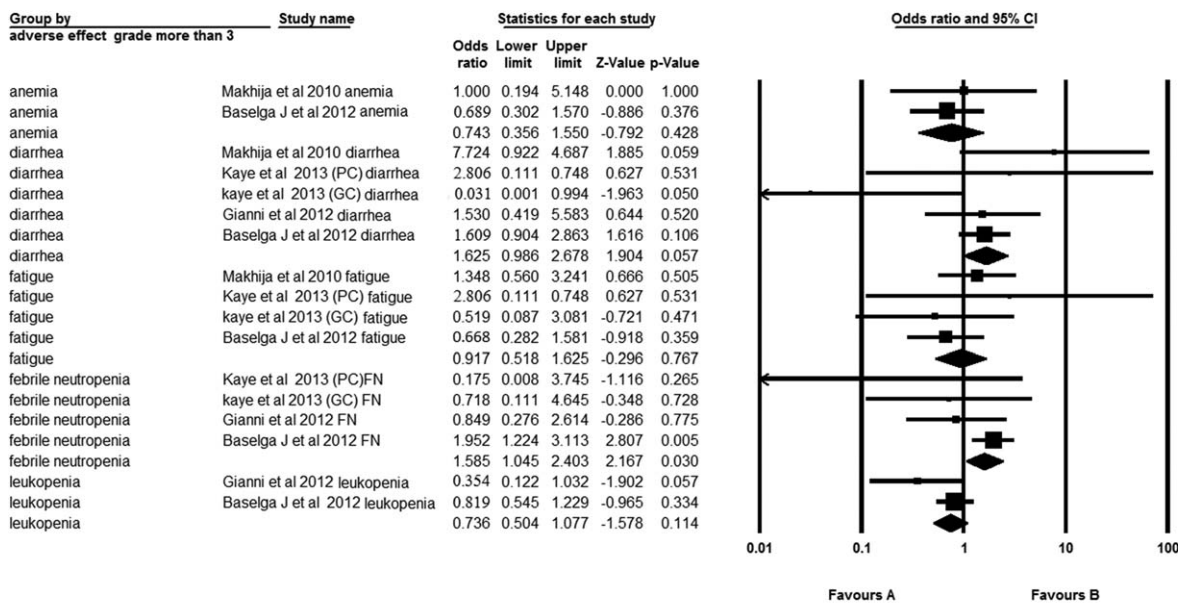
Papulopustule was the most common in pertuzumab-related rash.^[33] Drucker et al^[33] advised that regular moisturization and the twice-daily application of sun-block SPF 15 or higher would be helpful. We also reviewed some studies to find out the mechanism of the rash. The finding showed that pertuzumab could affect EGFR pathway as in the mechanism of diarrhea. Some studies showed that novel anticancer drugs could inhibit the EGFR-RAS-RAF-MEK and PI3 kinase-AKT-m-TOR pathways to cause skin rash.^[34–36] Since EGFRs are highly expressed on keratinocytes, the inhibition of these pathways might be associated with keratinocyte stress and therefore rash occurs.^[37] However, future studies are needed to explore a clearer mechanism of HER2 inhibitors.

Table 4

Odds ratio and 95% CI of adverse effects using random or fix model.

Adverse effect	Odds ratio with 95% CI	Model
Neutropenia	0.970 (0.639–1.473)	Random model
Rash	1.848 (1.094–3.122)	Random model
Alopecia	0.999 (0.776, 1.287)	Fix model
Asthenia	0.868 (0.656, 1.150)	Fix model
Diarrhea	2.310 (1.818, 2.936)	Fix model
Fatigue	1.074 (0.840, 1.374)	Fix model
Febrile neutropenia	1.672 (1.130, 2.474)	Fix model
Nausea	1.050 (0.828, 1.332)	Fix model
Thrombocytopenia	1.326 (0.811, 2.170)	Fix model

CI = confidence interval.



Meta Analysis

Figure 4. Forest plot of the odds ratio of the grade ≥3 adverse effects in pertuzumab-based therapies.

Moreover, we tried to find out what were the related factors of these adverse effects. We took tumor types, dosages of pertuzumab and concurrent drugs into consideration. As is shown in Table 3, tumors in females like breast cancer and ovarian cancer have noticeable higher rates in all 3 adverse effects when compared with prostate cancer and NSCLC, but no significant difference was found in different subtypes of tumors. In addition, prostate cancer seemed to have less adverse effects, which might indicate that the adverse effects were related to the sex hormone or genders, but the reason was unclear. No difference between the rates in 2 different dosages of pertuzumab was found.

In June 2012, the FDA initially approved pertuzumab for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy.^[11] The approval was based on a randomized, double-blind, placebo-controlled phase III CLEOPATRA (clinical evaluation of pertuzumab and trastuzumab). The trial set 2 arms, 1 for trastuzumab, docetaxel plus pertuzumab, and the other for trastuzumab, docetaxel plus placebo. A total of 808 patients were randomly allocated (1:1) to receive either of the 2 arms. Results showed statistically significant improvement in PFS in the pertuzumab arm (HR 0.62, 95% CI 0.51–0.75, $P < .001$).^[24]

Table 5

Survival outcomes of pertuzumab.

Single-arm studies					
Study	Sample size	Tumor types	Median PFS (95% CI), mo		
Gordon (2006)	117	Ovarian cancer	Overall population: 1.65 (1.5–2.725)		
	55		Cohort 1 (420 mg): 1.9 (1.5–2.85)		
	62		Cohort 2 (1050 mg): 1.525 (1.475–2.85)		
de Bono (2007)	46	Prostate cancer	Cohort 1 (420 mg): 1.433 (0.767–2.7)		
			Cohort 2 (1050 mg): 1.433 (0.833–2.1)		
Herbst (2007)	43	Small cell lung cancer	1.525 (1.325–2.825)		
Gianni (2010)	41	Breast cancer	Cohort 1 (420 mg): 1.467 (1.267–2.733)		
	37		Cohort 2 (1050 mg): 1.433 (1.3–2.833)		
Control-arm studies					
Study	Median PFS (95% CI), mo		HR (95% CI)	P	Tumor types
	Pertuzumab arm	Control arm			
Makhija (2010)	Gemcitabine + pertuzumab, 2.9	Gemcitabine + placebo, 2.6	0.66 (0.43–1.03)	0.0708	Ovarian
Kaye (2013)	Chemotherapy + pertuzumab, 8.525	Chemotherapy, 9.325	1.16 (0.79–1.71)	0.4487	Ovarian
Baselga (2012)	Trastuzumab + docetaxel + pertuzumab, 18.5	Trastuzumab + docetaxel + placebo, 12.4	0.62 (0.51–0.75)	<0.001	Breast

CI = confidence interval, HR = hazard ratio, PFS = progression-free survival.



Figure 5. (A) Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies and (B) risk of bias summary: review authors' judgments about each risk of bias item for each included study.

In April 2013, the FDA received a supplemental Biologics License Application for the use of pertuzumab in the neoadjuvant setting which was the first application for the neoadjuvant treatment of breast cancer.^[38] The approval was based in part on a RCT conducted in 417 locally advanced, inflammatory, or early HER2-positive breast cancer patients that were allocated to receive neoadjuvant treatment with trastuzumab+docetaxel, pertuzumab + trastuzumab + docetaxel, pertuzumab + trastuzumab, or pertuzumab + docetaxel.^[21] The pathologic complete response rates were 39.3% and 21.5% in the pertuzumab+trastuzumab+docetaxel and the trastuzumab + docetaxel arms, respectively ($P = .0063$).^[21]

Moreover, a large phase III clinical trial showed that pertuzumab gave an increased PFS of 6.1 months and a significant reduction in the risk of progression or death after adding pertuzumab to 1 current standard of care like trastuzumab.^[24] This combination is also well tolerated and effective.^[21,24] The combination therapy might benefit patients better and FDA's approval^[39] has also embodied this point. However, we should pay more attention to the possible increase of toxicities in the combined therapies.

The heterogeneity of included studies is an important factor influencing the validity of the evaluation. These studies were done on different tumor types, different therapies, and even different races. Because of these differences, we found that it was not easy to obtain an objective value of rates. Under this circumstance, we think our results of subgroup analyses are more meaningful than the overall evaluation.

There are several limitations of our study. The incomplete data of survival outcomes in each article made it hard to draw a specific conclusion of the efficacy of pertuzumab. In addition, the limited number of large phase III trials on pertuzumab might lead to some deviations with the actual situation. Further, large scale phase III RCTs are still needed to confirm our results.

5. Conclusion

In conclusion, pertuzumab is a safe and relatively effective agent in the therapies for solid tumors, even though it may possess some gastrointestinal toxicities such as diarrhea and nausea. Consid-

ering that these toxicities are relatively easy to handle with some mucosa protection agents, its safety can be guaranteed in clinical settings. Pertuzumab-based therapies are promising, and the potency can be further evaluated with more data in the future.

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