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Efficacy and safety of PI3K/Akt/mTOR inhibitors combined with trastuzumab therapy for HER2-positive breast cancer: a meta-analysis

D.-S. PENG[1,3], B.-Q. HUANG[2], H.T. NING[1], X.-Z. ZHU[1]

[1]School of Basic Medicine, Gannan Medical University, Ganzhou, China
[2]Department of Pediatrics, Xiamen Children's Hospital, Xiamen, China
[3]The Third Affiliated Hospital, Gannan Medical University, Ganzhou, China

Abstract. – OBJECTIVE: Activation of the PI3K/AKT/mTOR pathway in patients with HER2-positive breast cancer is associated with acquired resistance to trastuzumab. This randomized controlled trial (RCTs) meta-analysis was designed to evaluate the clinical efficacy and safety of PI3K/Akt/mTOR inhibitors in combination with trastuzumab in HER2-positive breast cancer.

MATERIALS AND METHODS: We searched on Web of Knowledge, PubMed, Embase, Cochrane, CNKI, and ClinicalTrials.Gov for RCTs comparing PI3K/Akt/mTOR inhibitors plus trastuzumab *vs.* standard trastuzumab treatments. Pooled estimates of progression-free survival (PFS), pathologic complete response (pCR), and incidence of adverse events were determined.

RESULTS: 5 studies out of 610 were found to be eligible and were included in our analysis (n=1,548 participants). PI3K/Akt/mTOR inhibitors combination with trastuzumab treatments resulted in a statistically significant increase in PFS compared with conventional trastuzumab therapy (HR 0.82; 95% CI: 0.76-0.90; $p<0.00001$). The new combination treatment was more effective on hormone receptor-negative patients (HR 0.73; 95% CI: 0.58-0.93; $p=0.010$). In addition, the combination of PI3K/Akt/mTOR inhibitors with trastuzumab slightly increased the risk of some adverse events, such as neutropenia, leukopenia, fatigue, and anemia.

CONCLUSIONS: The combination treatments of PI3K/Akt/mTOR inhibitors and trastuzumab for PI3K/Akt/mTOR inhibitors combined with trastuzumab treatments for patients with HER2-positive breast cancer can improve median progression-free survival while increasing the incidence of adverse events. It is still controversial based on the current evidence. Due to the limited number and quality of included studies, more high-quality studies are needed for further analysis.

Key Words:
HER2-positive breast cancer, Trastuzumab resistance, PI3K/Akt/mTOR inhibitor, Combination therapy, Meta-analysis.

Introduction

The incidence of breast cancer has been on the rise in recent years, and it has become the most common malignant tumor that greatly harms women's health and life[1]. With the rapid progress of biomedical science and technology, the research of chemical drugs for the treatment of breast cancer has made some progress[2]. In the 1970s, the main chemotherapy drugs for breast cancer were methotrexate, cyclophosphamide, and fluorouracil, and it was considered a major discovery that paclitaxel was marketed for use in cancer chemotherapy as a new anti-microtubule drug after the 1990s[3]. In recent years, therapeutically targeting breast cancer has demonstrated excellent efficacy, and it has turned to be a safe agent.

Human Epidermal Growth Factor Receptor-2 (HER2) is an important gene associated with breast cancer pathogenesis[4], overexpressed in 20-30% of breast cancer patients[5]. The HER2-positive breast cancer patients generally carry high tumor malignancy, poor treatment outcomes, and prognosis[6]. Monoclonal antibodies against HER2 are widely used in the treatment of HER2-positive breast cancer patients. Herceptin is one of the representatives. Its main active ingredient is trastuzumab[7]. However, there are many problems such as the poor effect of a single drug, drug resistance, and ease to recur and metastases[8].

Trastuzumab significantly improved the outcome of HER2-positive breast cancer in adjuvant therapy, and the apparent survival benefit was even more significant when used in combination with chemotherapy[9]. Adjuvant systemic therapy with anti-HER2 mAb reduces the risk of recurrence and death in patients with HER2-positive breast cancer, as demonstrated by a series of large phase III clinical trials[10-12]. Nonetheless, resistances to trastuzumab can occur: 10% of surgical patients

Corresponding Author: X.-Z. Zhu, MD; e-mail: zhuxiuzhi2006@163.com

who receive trastuzumab therapy developed resistance within 4 years, while almost all patients with the metastatic disease eventually progress with trastuzumab[13,14]. Therefore, the search for more effective combined medicines has become the focus of the next stage of development of targeted therapy for advanced breast cancer[15,16]. As the role of related signaling pathways (such as the PI3K/Akt/mTOR pathway) in primary and secondary resistance becomes increasingly apparent, combinations of anti-HER2 agents and agents acting on these pathways are currently being explored extensively in new-generation clinical trials[17,18].

Given the rationale, we assessed a series of clinical trials conducted in the neoadjuvant therapy for HER2-positive breast cancer comparing PI3K/Akt/mTOR inhibitors combined with conventional trastuzumab treatment *vs.* commonly routine trastuzumab therapy. Recognizing that individual studies alone may not provide sufficient data to influence practice, nevertheless we sought to objectively evaluate the potential role of this treatment in the treatment of HER2-positive breast cancer. Therefore, we did a meta-analysis of RCTs to establish a scientific basis for clinical application.

Materials and Methods

Search Strategy and Selection Criteria

This meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and was registered at the International Prospective Register of Systematic Reviews (No.: CRD42022301003).

We included studies if they were randomized clinical trials conducted in adults with HER2-positive breast cancer, compared PI3K/Akt/mTOR inhibitors and basal trastuzumab combination treatment to another treatment strategy, had at least 4 weeks' duration of intervention, and reported changes in overall survival (OS), progression-free survival (PFS), pathological complete response (pCR), clinical benefit rate (CBR) or objective response rate(ORR) at the end of the intervention period.

For this meta-analysis, we selected relevant studies published up to November 24, 2021, by searching Web of Knowledge, PubMed, Embase, CNKI, Cochrane and ClinicalTrials.gov. PRISMA quality standards were followed in conducting this meta-analysis. We performed this meta-analysis according to PRISMA's stated quality criteria. The following combined text and MeSH terms were used: "trastuzumab" and "PI3K/Akt/mTOR inhibitors" and "breast neoplasm". For PubMed, the complete search was performed: "(trastuzumab[Text Word]) OR (Herceptin[Text Word])" AND "(PI3K inhibitor[Text Word]) OR (Akt inhibitor"[Text Word]) OR (mTOR inhibitor[Text Word]) OR (everolimus[Text Word]) OR (copanlisib[Text Word]) OR (GDC-0077[Text Word]) OR (alpelisib [Text Word]) OR (BYL719[Text Word]) OR (Piqray[Text Word]) OR (duvelisib[Text Word]) OR (idelalisib[Text Word]) OR (MK2206[Text Word]) OR (BKM120[Text Word]) OR (MEN1611[Text Word]) OR (REMD-477[Text Word]) OR (CUDC-907[Text Word]) OR (CYH33[Text Word]) OR (Ipatasertib[Text Word]) OR (GSK2141795[Text Word]) OR (AZD5363[Text Word]) OR (GDC-0941[Text Word])" AND "(breast neoplasm[Text Word]) OR (breast cancer[Text Word]) OR (breast tumor[-Text Word])".

As a supplement, we analyzed conference reports, reviews, and other article types on trastuzumab retreatment in HER2-positive patients. Additionally, the bibliographies of eligible articles were manually screened for additional studies.

Eligibility Criteria

To be included in this meta-analysis, the RCTs had to fulfill the following criteria: (i) HER2-positive breast cancer is treated by neoadjuvant therapy; (ii) type of intervention: PI3K/Akt/mTOR inhibitors combined with conventional trastuzumab therapy *vs.* commonly routine trastuzumab therapy; (iii) primary endpoint: median progression-free survival rate (PFS), pathological complete response (pCR), overall survival (OS), objective remission rate (ORR), clinical benefit rate (CBR).

Exclusion criteria were as follows: (i) the trial size or study population was unclear; (ii) studies with duplicate publications or overlapping data. Only those with the most recent and complete data were included.

Data Extraction

From each study, the following data were extracted: the total number of participants, differential interventions in study groups, trial duration, the number of patients in study groups, mean age, median follow-up, and primary outcome. Outcome indicators: (i) PFS or OS or pCR or ORR or CBR;

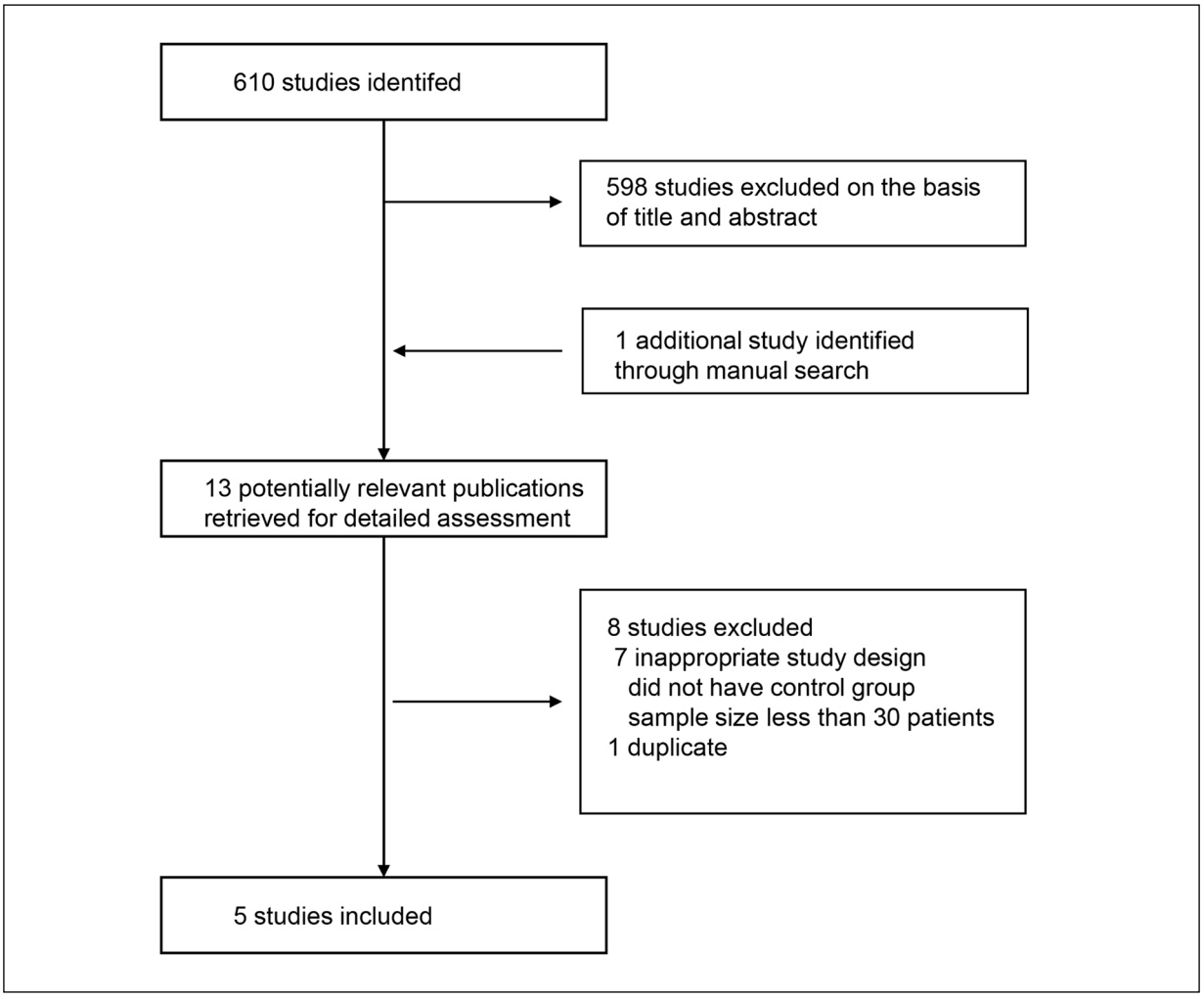

Figure 1. Flow-chart diagram of selected studies included in the meta-analysis.

(ii) the incidence of grade 3 to 4 treatment-related adverse reactions. All data were checked for internal consistency. Two independent investigators (D.-S. Peng, B.-Q. Huang) reviewed study titles and abstracts, and retrieved studies that met inclusion criteria for full-text evaluation. Trials selected for detailed analysis and data extraction were analyzed by two investigators (D.-S. Peng, B.-Q Huang) and the risk of bias was assessed according to the PRISMA recommendations. Disagreements were resolved by a third investigator (H.-T. Ning).

Statistical Analysis

Meta-analysis was carried out by pooled effect sizes of PFS, pCR in the including studies. χ^2 and I^2 were used for statistical heterogeneity tests, and $I^2 > 50\%$ was considered to have substantial heterogeneity. When the heterogeneity test showed I^2 value < 50%, the fixed effect model was selected; otherwise, the random effect model was used. Review Manager software (version 5.4, Review Manager Web, The Cochrane collaboration, Copenhagen) was used for the analysis.

Results

Characteristics of Included Studies

Our analysis included data from five (with 1,548 participants) of 610 studies[10,18-21] (Figure 1). The five trials were all released between 2013 and 2021 (only one was published in 2021) (Table I).

Quality Assessment

In this section, two investigators independently assessed the risk of bias in RCTs using the Cochrane Collaboration's tool. The overall quality

Table I. General characteristics of the identified studies.

Study	Year	Differential interventions in study groups T	C	Duration of interventions	n T	C	Mean age	Median follow-up	Primary outcome
Chien et al[18]	2021	MK-2206 Paclitaxel trastuzumab	Paclitaxel trastuzumab	12 weeks	34	10	50.3	NA	pCR; Safety evaluation
Andre et al[19]	2014	everolimus trastuzumab	Vinorelbine trastuzumab	continued treatment	284	285	54.2	20·2 months	PFS; Safety evaluation
Toi et al[20]	2013	Everolimus vinorelbine tastuzumab	tastuzumab vinorelbine	continued treatment	88	78	52	24 months	PFS; Safety evaluation
Hurvitz et al[21]	2015	everolimus paclitaxel tastuzumab	Paclitaxel tastuzumab	4 weeks	480	239	54	41·3 months	PFS; Safety evaluation
Loibl et al[10]	2017	Buparlisib trastuzumab	trastuzumab	6 weeks	25	25	50	NA	pCR; OS; Safety evaluation

pCR = pathological complete response; PFS = progression-free survival; OS = overall survival.

assessment results showed high standards, including prospective design, multicenter enrollment, selection bias, performance bias, attrition bias, detection bias, and multivariate adjustment for potential confounders (Figure 2).

Efficacy

PFS was measured by HR as a survival outcome. Three papers present corresponding data. We extracted HRs and their 95% CI directly. RR was used to measure dichotomy results including pCR. Heterogeneity among the included studies was analyzed using the χ^2 test (test level α=0.1), and the I^2 quantification was used to determine the magnitude of heterogeneity. We classified an I^2 value < 50% as homogeneity, and the fixed-effects model was accepted. An I^2 value > 50% predicted potential heterogeneity; if statistical heterogeneity existed between studies, the source of heterogeneity was further analyzed, and a random-effects model was used for meta-analysis after the effect of significant clinical heterogeneity was excluded. The meta-analysis level was set at α=0.05. In addition, if no clear heterogeneity was detected, we combined the results with a random-effects model.

The HRs about PFS in randomized controlled trials were extracted and pooled. In these trials, PI3K/Akt/mTOR inhibitors combined with conventional trastuzumab therapy regimens (*vs.* routine trastuzumab therapy arm) demonstrated a statistical improvement in PFS. As shown in Figure 3, the result revealed that the pooled HR for PFS was 0.82 (95% CI: 0.76-0.90) without heterogeneity (I^2 = 0, p<0.00001).

Hormone receptor status has been regarded as an important factor affecting therapeutic effect. The HRs about PFS in hormone receptor–negative tumors RCTs were extracted and pooled. The new combination treatment demonstrated a greater statistical improvement in PFS. The pooled HR for PFS was 0.73 (95% CI: 0.58-0.93) without heterogeneity (I^2 = 0, p<0.00001). The results are shown in Figure 3.

The primary endpoint of treatment in two of these studies[10,18] was pathological complete response (pCR). We extracted these data and calculated Risk Ratio (RR) based on them. The RRs about pCR were pooled. It showed the new combination treatment did not demonstrate better improvement than routine trastuzumab therapy in pCR, two treatment strategies were not significant difference by statistics analysis (Figure 4).

Safety

All included studies mentioned serious drug adverse events. The Risk Ratio (RR) of about 12 kinds of Grade 3/4 adverse events in the therapeutic process was counted and pooled. The analysis results showed that the test group had significantly more serious adverse events than the control group. While the PI3K/Akt/mTOR inhibitors combined with trastuzumab therapy arm in the new combination treatment arm demonstrated

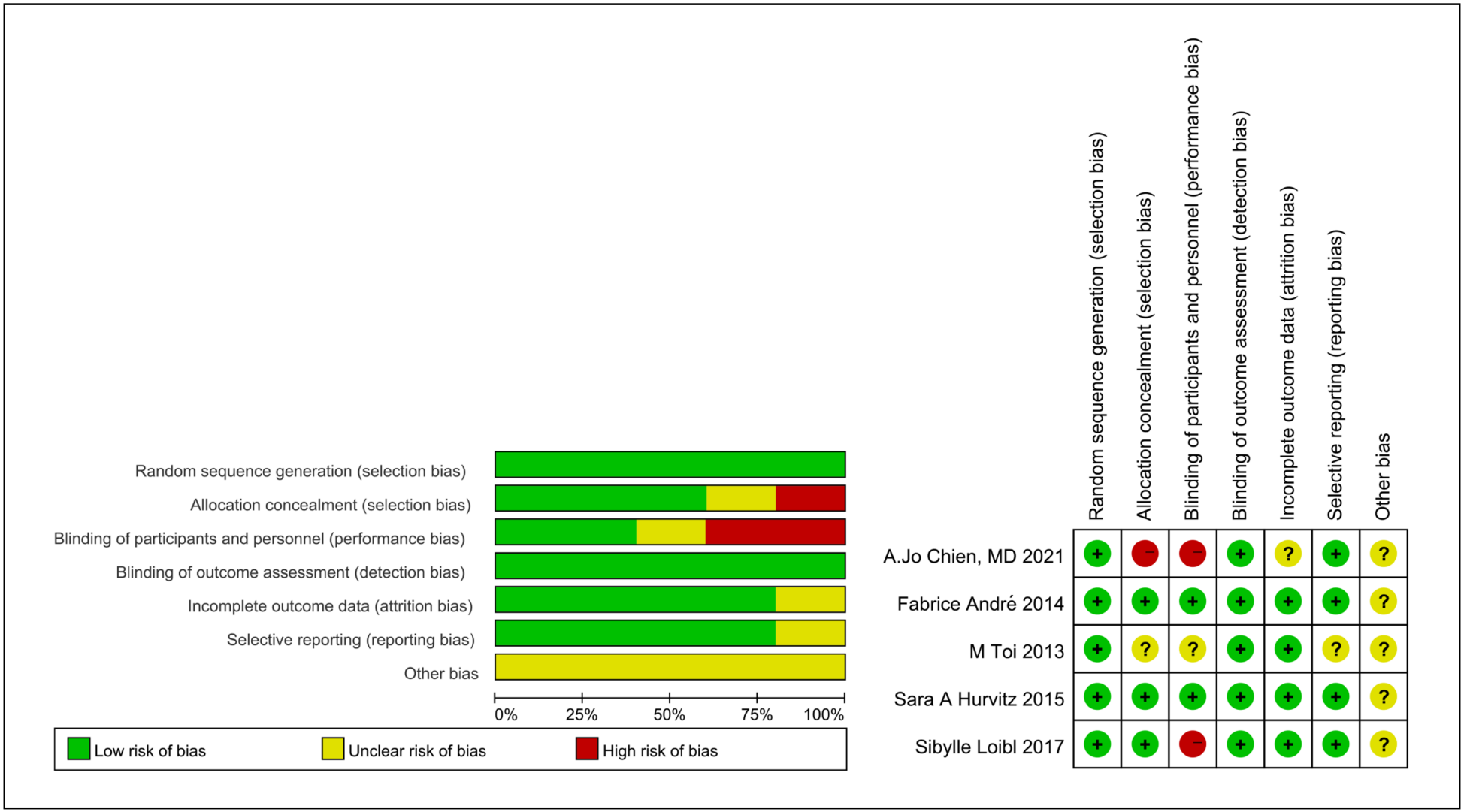

Figure 2. Review authors' judgments about each risk of bias item for RCTs.

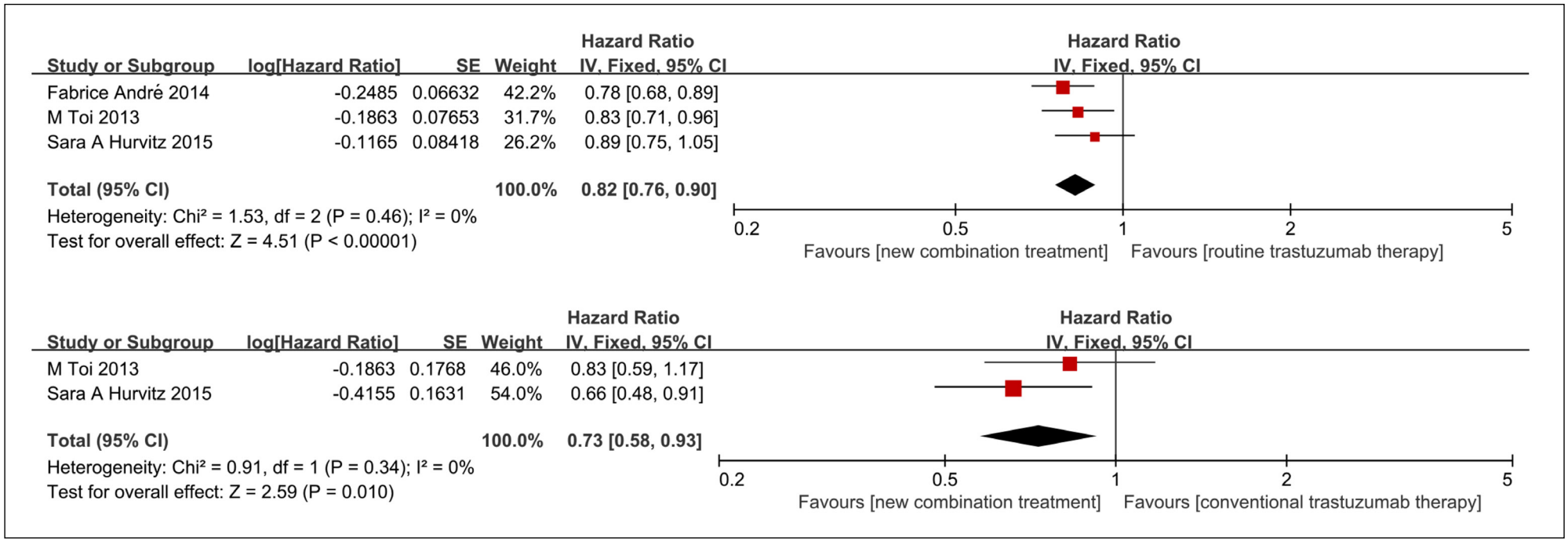

Figure 3. Forest plot of effect sizes of PI3K/Akt/mTOR inhibitors combined with trastuzumab therapy for composite end points: progression free survival (PFS) in patients with HER2-positive breast cancer.

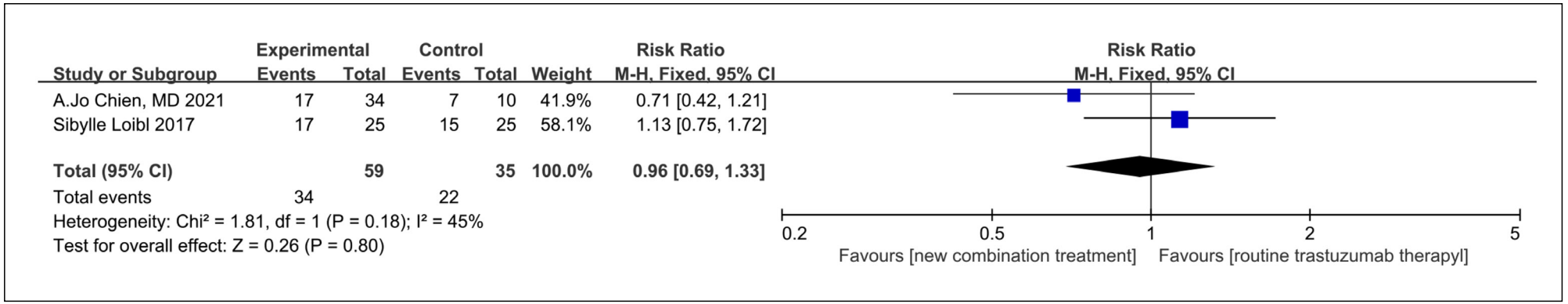

Figure 4. Forest plot of effect sizes of PI3K/Akt/mTOR inhibitors combined with trastuzumab therapy for composite end points: pathological complete response (pCR) in patients with HER2-positive breast cancer.

better improvement than the routine trastuzumab therapy arm, the patients in the new combination treatment arm experienced a higher incidence of anemia, febrile neutropenia, rash maculopapular, diarrhea, stomatitis, fatigue, hyperglycemia, leucopenia, pneumonitis, hepatotoxicity. The differences were statistically significant by fixed effects model analysis in the ten kinds of Grade 3/4 adverse events (as shown in Figure 5, Figure 6 and Table II). No statistically significant differences were found in RR of Neutrophil count decreased and Hypertension.

Discussion

HER2-positive breast cancer entails a poor prognosis[22]. Trastuzumab has improved the treatment outcome in HER2-positive breast cancer. Some studies[15] have shown an advantage in response rate, disease-free survival, and overall survival when trastuzumab is added to chemotherapy, probably because HER2-positive breast cancer patients develop resistance to trastuzumab. Resistance to trastuzumab can derive from dysregulation of multiple factors[23]. It provides a rationale for the combination of PI3K/Akt/mTOR inhibitors for the treatment of HER2-positive breast cancer[24]. We performed this meta-analysis to comprehensively summarize and compare the relative survival benefits of different PI3K/Akt/mTOR inhibitors combined with trastuzumab treatment strategies, tested in RCTs, to assist in clinical decision-making.

This meta-analysis shows that, in HER2-positive breast cancer, PI3K/Akt/mTOR inhibitors combined with trastuzumab therapy significantly increase the PFS as compared with the routine trastuzumab therapy, especially in hormone receptor-negative tumors. Nevertheless, it is worth questioning whether the new combination treatment did not demonstrate better improvement than routine trastuzumab therapy in pCR in two studies[10,18]. The findings of the two studies appear to be in conflict: Loibl et al[10] affirmed that the addition of the pan-PI3K inhibitor buparlisib to taxane-trastuzumab-based therapy in HER2-positive early breast cancer was not feasible, although the overall response rates significantly improved. On the other hand, Chien et al[18] believed that the Akt inhibitor MK-2206 combined with standard neoadjuvant therapy was of clinical value for HR-negative and HER2-positive breast cancer. We analyzed that this difference could be due to different drugs.

Disturbingly, our results show that, compared to routine trastuzumab therapy, PI3K/Akt/mTOR inhibitors combined with trastuzumab therapy can yield more grade 3/4 adverse events. The most common serious adverse events are neutropenia and leucopenia. PI3K/Akt/mTOR inhibitors are likely to be active agents for breast cancer receptor subtypes, but strategies to prevent the adverse effects of PI3K/Akt/mTOR pathway blockade and to predict susceptible individuals with a specific risk of toxicity are critical to the success of such agents[25]. Hurvitz et al[21] thought proactive monitoring and early management of adverse events in patients given chemotherapy is crucial. Chien et al[18] believed that MK-2206-related adverse events could be manageable through increased provider, patient education and clear guidelines for toxicity management. The author of the included studies generally confirmed that drug safety was acceptable. Future studies should focus on the relationship between the dose and frequency of drug use and efficacy. More research should be done to establish drug combinations in terms of improving efficacy and reducing adverse effects for better clinical guidance.

Limitations

Our meta-analysis had the following limitations: (1) PI3K/Akt/mTOR inhibitors are relatively new drugs, the research on them is rather little the number of relevant studies is small, which may affect the accuracy of the results; (2) the intervention drugs used in the researches were not identical, and subgroup analysis could not be performed due to the small number of included studies, and there was clinical heterogeneity among the studies; (3) due to the short duration of the study, many outcome indicators were still unreported and could not be analyzed; therefore, their long-term efficacy needs to be further evaluated.

Conclusions

In summary, our findings indicated PI3K/Akt/mTOR inhibitors in combination with trastuzumab could well increase the PFS of patients with HER2-positive breast cancer in the clinical management, especially in hormone receptor-negative tumors, while there was an increase in serious adverse events. Limited by the number of studies, further research is needed to determine the best way to apply this treatment in practice. Highly

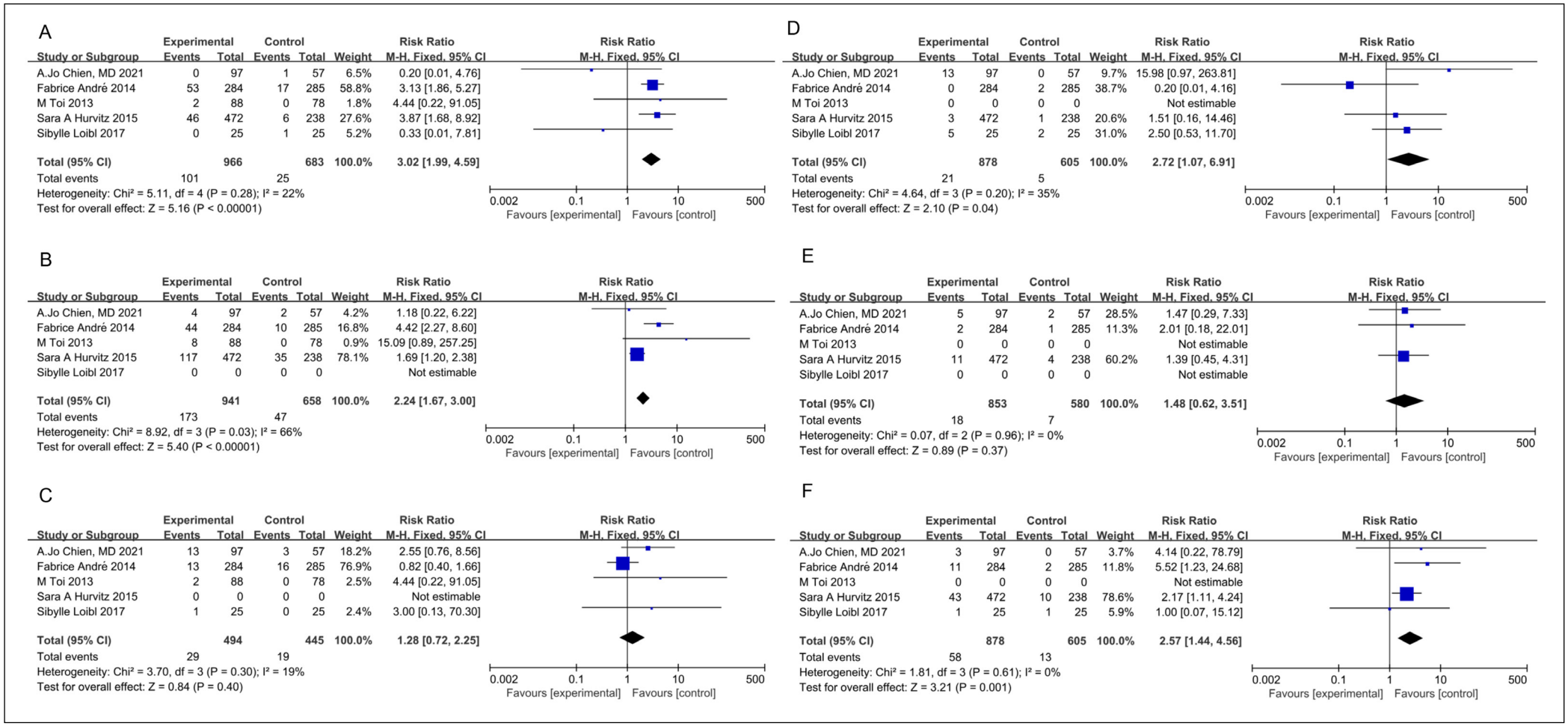

Figure 5. Forest plot: anemia (**A**), febrile neutropenia (**B**), neutrophil count decreased (**C**), rash maculopapular (**D**), diarrhea (**E**), hypertension **(F)**.

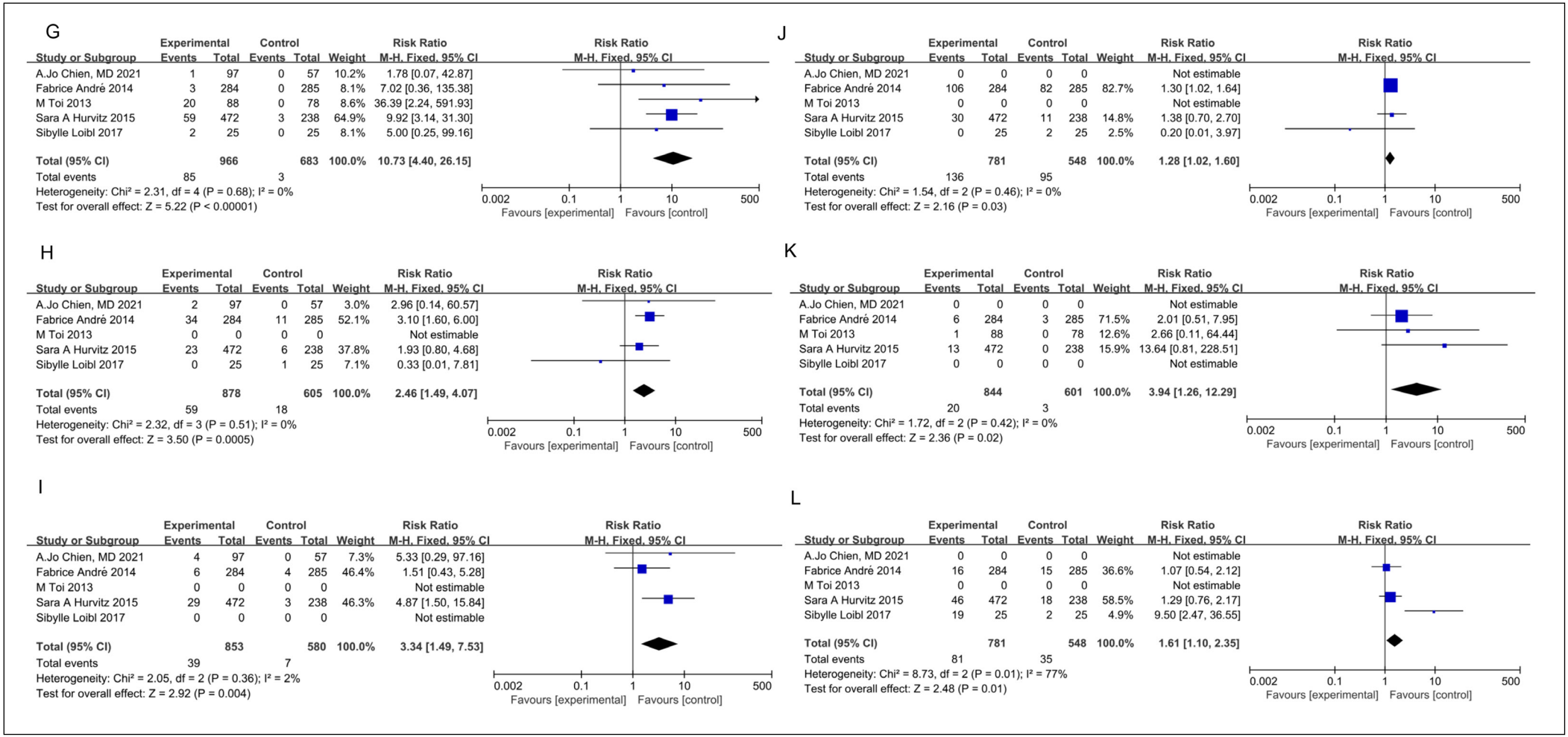

Figure 6. Forest plot: stomatitis (**G**), fatigue (**H**), hyperglycemia (**I**), leucopenia (**J**), pneumonitis (**K**), hepatotoxicity (**L**).

Table II. Pooled adverse events in patients with HER2-positive breast cancer.

Grade 3/4 Adverse event	Effect size (95% CI)	Number of studies	I^2	*p*-value
Anemia	3.02 (1.99, 4.59)	5	22%	0
Febrile neutropenia	2.24 (1.67, 3.00)	4	66%	0
Neutrophil count decreased	1.28 (0.72, 2.25)	4	19%	0.4
Rash maculopapular	2.72 (1.07, 6.91)	4	35%	0.04
Hypertension	1.48 (0.62, 3.51)	3	0%	0.37
Diarrhea	2.57 (1.44, 4.56)	4	0%	0.001
Stomatitis	10.73 (4.40, 26.15)	5	0%	0
Fatigue	2.46 (1.49, 4.07)	4	0%	0
Hyperglycemia	3.34 (1.49, 7.53)	3	2%	0.004
Leucopenia	1.28 (1.02, 1.60)	3	0%	0.03
Pneumonitis	3.94 (1.26, 12.29)	3	0%	0.02
Hepatotoxicity	1.61 (1.10, 2.35)	3	77%	0.01

effective and less toxic drugs for HER2-positive breast cancer should be further developed.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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None.

Authors' Contribution

X.-Z. Zhu designed the meta-analysis; D.-S. Peng and B.-Q. Huang searched the literature; H.-T. Ning analyzed the literature; X.-Z. Zhu wrote and edited the manuscript.

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