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# Combination chemotherapy with trastuzumab in early-stage breast cancer: a meta-analysis and Bayesian decision analysis of different treatment regimens

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**Abstract. – OBJECTIVE: HER2-positive breast cancer is a high-risk malignant tumor, and trastuzumab is an effective targeted therapy drug, but its optimal duration remains uncertain. To compare the efficacy and cost-effectiveness of different durations (6 months, 9 months, 12 months, and 18 months) of trastuzumab combined with chemotherapy in patients with early breast cancer by meta-analysis and Bayesian decision analysis.**

**PATIENTS AND METHODS: Randomized controlled trials comparing the effectiveness of different durations of trastuzumab combination chemotherapy in early-stage breast cancer patients were collected by searching multiple databases. Data synthesis was performed using the R software, and a decision tree model was constructed to simulate the expected outcomes and anticipated costs associated with different treatment durations.**

**RESULTS: This study included 9 randomized controlled trials involving 11,328 early-stage breast cancer patients. The meta-analysis results demonstrated that, compared to the control group, trastuzumab combination chemotherapy at different durations significantly improved disease-free survival and overall survival in early-stage breast cancer patients. Among the various treatment durations, it was observed that 12 months of trastuzumab combination chemotherapy, in comparison to other durations, significantly reduced the risk of recurrence and mortality in early-stage breast cancer patients while maintaining a favorable cost-effectiveness ratio. Bayesian decision analysis also confirmed that 12 months of trastuzumab combination chemotherapy is the optimal treatment duration.**

**CONCLUSIONS: It is recommended to use 12 months of trastuzumab combination chemotherapy as the standard treatment for early-stage breast cancer patients.**

*Key Words:*

Trastuzumab, Different courses, Disease-free survival rate, Overall survival rate, Meta-analysis, Bayesian decision analysis.

## Introduction

Breast cancer is the most common malignancy in women and a major cause of female mortality. According to global cancer statistics, in 2023, there were approximately 2.7 million new cases of breast cancer, accounting for 24.2% of all female malignancies, and resulting in about 680,000 female deaths, representing 15.0% of all female cancer-related deaths[1]. Among these, HER2-positive breast cancer, characterized by high invasiveness and recurrence risk, constitutes 15% to 20% of all breast cancer cases. HER2, a member of the human epidermal growth factor receptor family, regulates processes such as cell proliferation, differentiation, migration, and apoptosis. In HER2-positive breast cancer, tumor cells exhibit overexpression or amplification of the HER2 gene, leading to aberrant activation of the HER2 signaling pathway, and promoting malignant biological behaviors of the tumor cells[2].

Trastuzumab is a targeted biological therapy for HER2-positive breast cancer, capable of binding to the HER2 receptor and blocking its signaling pathway, thus inhibiting tumor cell proliferation and survival. Trastuzumab has been demonstrated to improve disease-free survival and overall survival in early-stage breast cancer patients and is recommended as one of the standard treatment options. However, there is still debate regarding the optimal duration of trastuzumab treatment. Currently, most guidelines[3] and clinical practices recommend 12 months of trastuzumab combination chemotherapy as the standard treatment for early-stage breast cancer patients. This recommendation primarily relies on results from large randomized controlled trials such as HERA, BCIRG 006, and NSABP B-31[4-6]. However, these tri-

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als were conducted during the early stages of trastuzumab's development, when its efficacy and safety profile were not well understood, leading to the choice of longer treatment durations[4]. With the widespread use of trastuzumab, concerns have emerged regarding its high cost, extended treatment duration, and associated adverse effects. Therefore, it is imperative to investigate whether shorter trastuzumab treatment durations can be considered to alleviate the burden on patients and healthcare systems while maintaining therapeutic efficacy[6].

In recent years, several new randomized controlled trials[7,8] have compared the efficacy of different durations (6 months, 9 months, 12 months, and 18 months) of trastuzumab in combination with chemotherapy in early-stage breast cancer patients[9]. However, the results of these trials have been inconsistent. Some trials[10] have shown no significant differences in disease-free survival and overall survival between 6 or 9 months of trastuzumab in combination with chemotherapy and 12 or 18 months of the same combination. On the other hand, some trials[23] have indicated that 12 or 18 months of trastuzumab in combination with chemotherapy outperforms 6 or 9 months of the same regimen. These inconsistent results may be attributed to factors such as trial design, patient characteristics, chemotherapy protocols, follow-up duration, and others[11,12]. The purpose of this paper is to conduct a meta-analysis and Bayesian decision analysis to compare the efficacy and cost-effectiveness of different durations (6 months, 9 months, 12 months, and 18 months) of trastuzumab in combination with chemotherapy in early-stage breast cancer patients, providing a reference for clinical decision-making[13,14].

## Materials and Methods

### Search Strategy

We conducted a systematic search of databases, including PubMed, Cochrane Library, Medline, and EMBASE, from inception up to July 2023, to collect all randomized controlled trials comparing the efficacy of different durations (6 months, 9 months, 12 months, and 18 months) of trastuzumab in combination with chemotherapy in early-stage breast cancer patients. The following search terms were employed: ("trastuzumab" OR "Herceptin") AND ("breast cancer" OR "breast neoplasm" OR "breast carcinoma") AND ("duration" OR "course" OR "regimen"). Additionally, we manually examined the reference lists of relevant articles to identify potentially missed trials. This study followed the guidance of the PRISMA statement to ensure the quality and transparency of the systematic review and meta-analysis. After the initial search, a total of 1,523 relevant articles were retrieved and screened for their titles and abstracts. Among these, 1,420 articles did not meet our inclusion criteria. As a result, 103 articles remained eligible for full-text review. After reviewing the full texts, we excluded 94 articles, of which 41 were non-randomized controlled trials, 23 were duplicates or updates, 15 had incomplete or unextractable data, and 15 received quality assessment scores below 3 points. Finally, we included 9 randomized[14-22] controlled trials involving 11,328 early-stage breast cancer patients. The literature selection process is illustrated in Figure 1.

### Inclusion and Exclusion Criteria

We included randomized controlled trials that met the following criteria: (1) Study participants were early-stage breast cancer patients with HER2-positive status; (2) The intervention involved trastuzumab in combination with chemotherapy, and compared different durations (6 months, 9 months, 12 months, and 18 months); (3) Reported at least one clinical outcome such as disease-free survival, overall survival, recurrence risk, or mortality risk. We excluded trials of the following types: (1) Non-randomized controlled trials, such as observational studies, cohort studies, or case-control studies; (2) Duplicate or updated publications of trials; (3) Trials for which complete full texts or data could not be obtained.

### Clinical Outcome

This study selected the following four clinical outcomes as endpoints for the meta-analysis: 1) Disease-free survival rate, defined as the time ratio from randomization to the first occurrence of recurrence or death. 2) Overall survival rate, defined as the time ratio from randomization to death or the last follow-up. 3) Cardiac toxicity, defined as the relative hazard of experiencing heart failure or other cardiac events during the follow-up period.

### Data Extraction

Two reviewers independently extracted the following data from the included trials: basic information, such as authorship, publication year, country, and sample size. Patient characteristics,

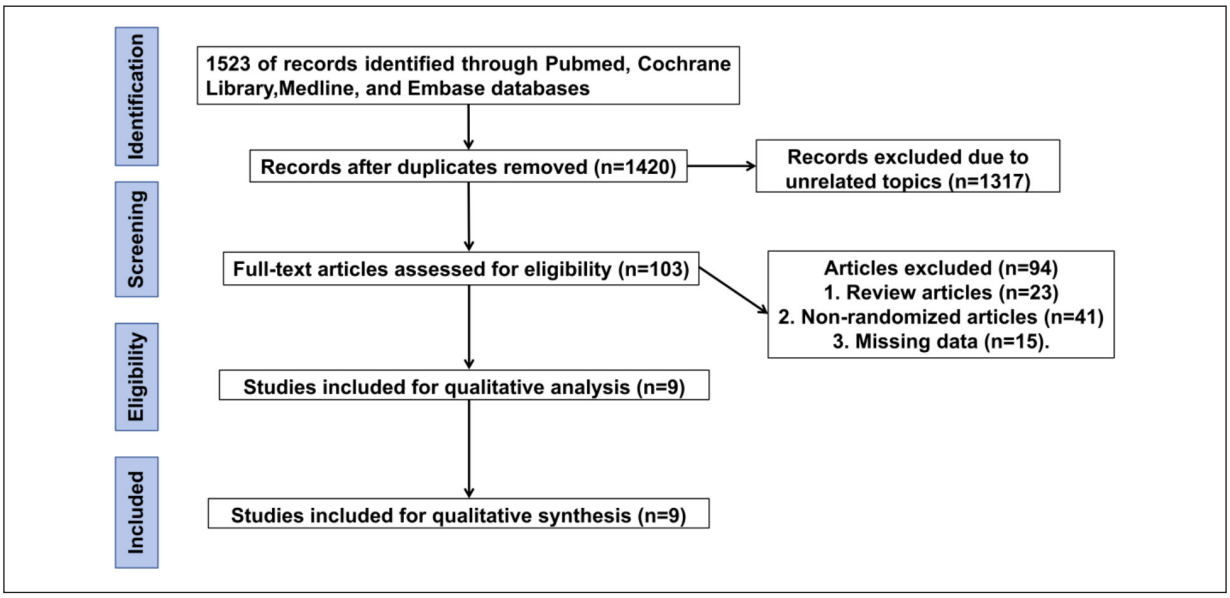


**Figure 1.** Flow diagram of study inclusion procedure.

including age, gender, staging, receptor status, and more. Intervention details, such as the dosage, frequency, and duration of trastuzumab. Clinical outcomes, such as disease-free survival, overall survival, recurrence risk, or mortality risk. In cases of any inconsistencies or missing data, reviewers resolved these issues through discussion or by contacting the original authors.

### *Quality Assessment*

We assessed the quality of the chosen randomized controlled trials (RCTs) according to Cochrane criteria, and a summary graph depicting the risk of bias was produced using RevMan 5.4 software (Cochrane, London, UK). Each of the following criteria was used to categorize risk levels: (1) Random sequence generation; (2) Allocation concealment; (3) Blinding of participants or personnel; (4) Blinding in outcome assessment; (5) Handling of incomplete outcome data; (6) Evaluation of selective reporting and other potential biases.

### *Statistical Analysis*

We performed data synthesis using the R software (open source software) and combined the results from individual trials based on the degree of heterogeneity, employing either a fixed-effects model or a random-effects model. Risk ratios (RR) with 95% confidence intervals (CI) were used as effect size measures, and a significance level of $p<0.05$ was applied. We assessed heterogeneity among the trials using the $I^2$ statistic and the Q-test and selected an appropriate model based on the magnitude of $I^2$. If $I^2<50\%$, a fixed-effects model was employed; if $I^2\geq50\%$, a random-effects model was used. We conducted a meta-regression analysis using R software to examine the association between population characteristics and clinical outcomes. A statistically significant distinction was determined when $p<0.05$.

## Results

### *Included Studies and Quality Assessment*

We identified a total of 9 randomized controlled trials that met the inclusion criteria, involving 11,328 early-stage breast cancer patients. Among them, 5,698 patients received trastuzumab in combination with chemotherapy, while 5,630 patients underwent standard treatment in the control group[12-20]. The flowchart for the present study is shown in Figure 1. Specifically, 5 trials compared 6 months and 12 months of trastuzumab in combination with chemotherapy[18,20-24], 2 trials compared 9 months and 12 months of the same combination[14,15], and 2 trials compared 12 months and 18 months of trastuzumab in combination with chemotherapy[16,17]. All trials had a follow-up duration exceeding 3 years, with the longest follow-up period extending to 10 years. Figure 2 is a risk summary plot,

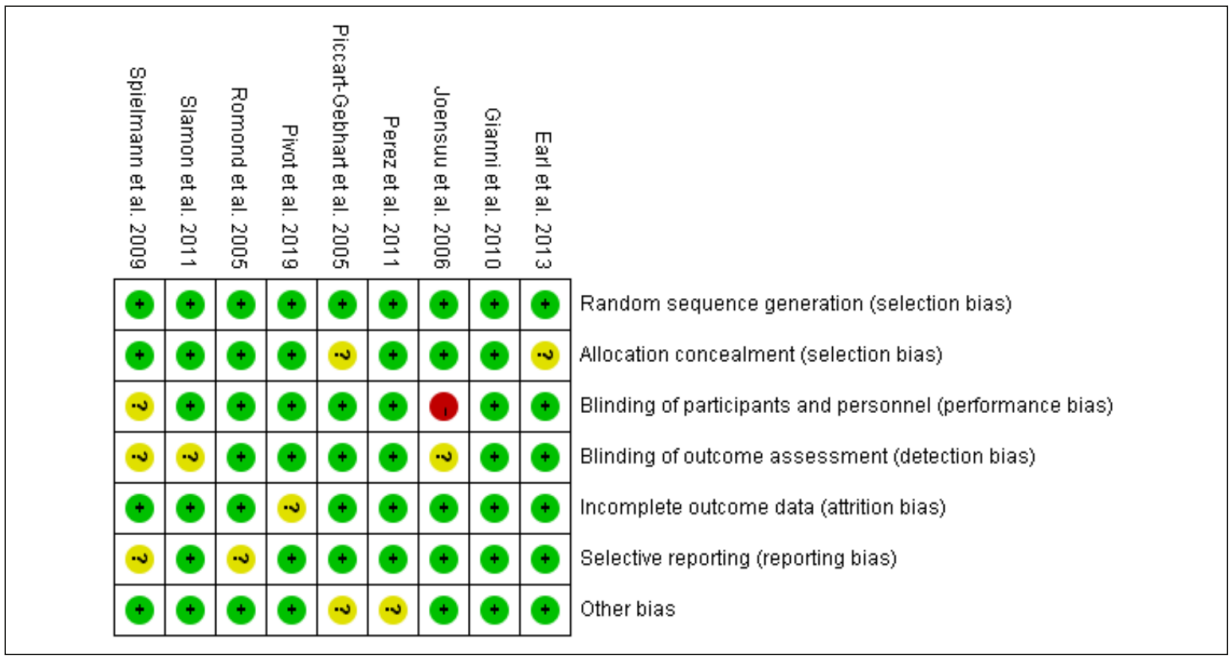


**Figure 2.** Risk summary of included studies.

showing the bias risk of the 9 randomized controlled trials included in this article. Each row in the figure represents a trial, and each column represents a criterion for assessing bias risk. The results of each criterion are indicated by circles of different colors: green for low risk, red for high risk, and yellow for uncertain risk. Figure 2 shows the quality and credibility of the trials selected in this article, as well as the factors that may affect the outcomes. From Figure 2, it can be seen that most of the trials have a moderate to high level of risk, with no obvious bias risk.

This manuscript includes a total of 9 randomized controlled trials comparing the effects of different durations (6 months, 9 months, 12 months, and 18 months) of trastuzumab in combination with chemotherapy in early-stage breast cancer patients (Table I). These trials encompassed 11,328 HER2-positive early-stage breast cancer patients from various regions worldwide, with 5,698 patients receiving trastuzumab in combination with chemotherapy and 5,630 patients receiving standard treatment in the control group. The publication years of these trials ranged from 2005 to 2019, with publications in authoritative journals such as the New England Journal of Medicine, the Journal of Clinical Oncology, Lancet Oncology, and others. The follow-up duration in these trials exceeded 3 years, with the longest follow-up period extending to 10 years. The quality of these trials was rated as moderate to high, indicating no significant risk of bias. Different chemotherapy regimens were utilized across these trials, including anthracycline-based chemotherapy, platinum-based combination therapy, and paclitaxel-based combination therapy, among others. Patient characteristics, such as age, gender, staging, and receptor status, were similar or balanced in these trials.

### *Meta-Analysis Between Groups*

The study findings revealed that compared to the control group, trastuzumab in combination with chemotherapy for durations of 6 months, 9 months, 12 months, and 18 months significantly improved both disease-free survival and overall survival in early-stage breast cancer patients, with no significant heterogeneity observed (Figure 3). When assessing the impact of different treatment durations on disease-free survival in comparison to the control group, all durations of trastuzumab in combination with chemotherapy demonstrated an increased disease-free survival rate [OR: 0.60, 95% CI (0.56, 0.65), $p<0.01$] (Figure 4). In evaluating the influence of different treatment durations on overall survival compared to the control group, the results indicated a significant improvement in the overall survival of early-stage breast cancer patients with all durations of trastuzumab

**Table I.** Basic information on trials of combined chemotherapy with trastuzumab for different courses of early breast cancer.

| Study | Inclusion criteria | Randomized groups | Treatment regimen |
|---|---|---|---|
| Piccart-Gebhart et al[1] | Early breast cancer patients with HER2 positivity, who had received surgery and chemotherapy | Observation group, trastuzumab for one year group, trastuzumab for two years group | Observation or trastuzumab for one or two years |
| Romond et al[2] | Operable breast cancer patients with HER2 positivity, who had received surgery and chemotherapy | Chemotherapy group, trastuzumab combined with chemotherapy group | AC followed by T or AC followed by TH for one year |
| Slamon et al[3] | Early breast cancer patients with HER2 positivity, who had received surgery and chemotherapy | Trastuzumab combined with chemotherapy and pertuzumab group, trastuzumab combined with chemotherapy and placebo group | Trastuzumab and pertuzumab or placebo for one year |
| Joensuu et al[4] | Breast cancer patients with axillary lymph node metastasis or high-risk without metastasis, who had received surgery and chemotherapy | Docetaxel group, vinorelbine group; in the HER2/neu positive subgroup, there were also trastuzumab group and control group | Docetaxel or vinorelbine for three cycles, then FEC for three cycles; in the HER2/neu positive subgroup, also simultaneously received or not received trastuzumab for nine weeks |
| Spielmann et al[5] | Operable lymph node-positive breast cancer patients, who had received surgery and chemotherapy | Docetaxel combined with anthracycline-based chemotherapy group, anthracycline-based chemotherapy group; in the HER2 positive subgroup, there were also trastuzumab group and observation group | Docetaxel combined with anthracycline-based chemotherapy or anthracycline-based chemotherapy for four cycles; in the HER2 positive subgroup, also received trastuzumab or observation for one year |
| Perez et al[6] | Operable breast cancer patients with HER2 positivity, who had received surgery and chemotherapy | AC followed by T group; AC followed by TH group | AC for four cycles, followed by T or TH for 12 weeks |
| Gianni et al[7] | Locally advanced or inflammatory breast cancer patients with HER2 positivity, who had not received surgery and chemotherapy | Neoadjuvant chemotherapy plus trastuzumab group, neoadjuvant chemotherapy group | Neoadjuvant chemotherapy regimen was FEC for three cycles, followed by docetaxel for three cycles; simultaneously received or not received trastuzumab for one year |
| Earl et al[8] | Early breast cancer patients with HER2 positivity, who had received chemotherapy, breast axillary surgery and up to 6 months of trastuzumab treatment | Trastuzumab for 6 months group, trastuzumab for 12 months group | During or after chemotherapy, received trastuzumab for 6 months or 12 months |
| Pivot et al[9] | Early breast cancer patients with HER2 positivity, who had received surgery and chemotherapy | Trastuzumab combined with chemotherapy group, chemotherapy group | Added or not added trastuzumab for one year on the basis of adjuvant chemotherapy |

in combination with chemotherapy [OR: 2.37, 95% CI (2.05, 2.74), $p$=0.54] (Figure 5). When comparing the impact of different treatment durations on the occurrence of cardiac toxicity, the results showed that, compared to the control group, all durations of trastuzumab in

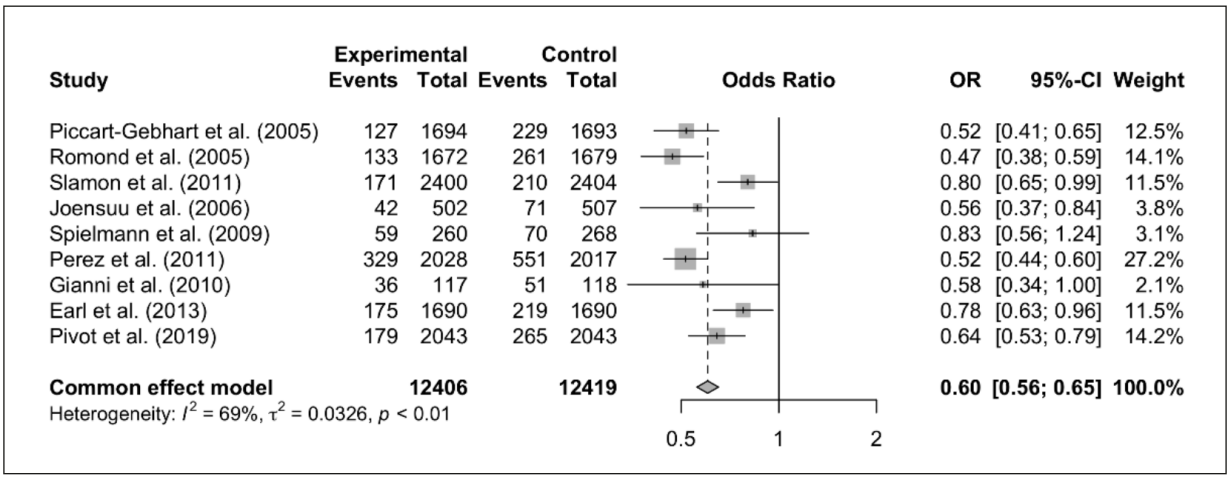


**Figure 3.** Meta-analysis of risk ratios for disease-free survival.

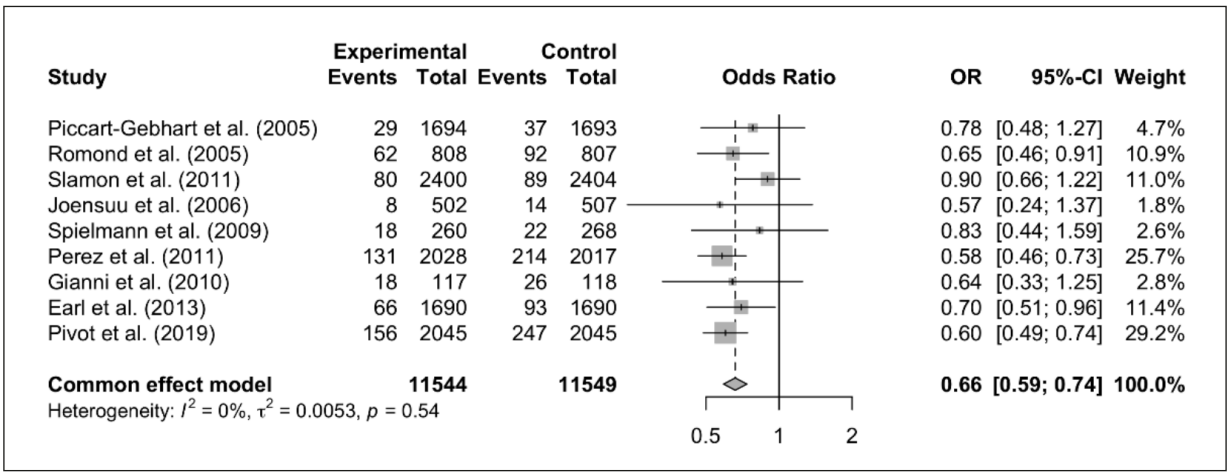


**Figure 4.** Meta-analysis of total survival risk ratio.

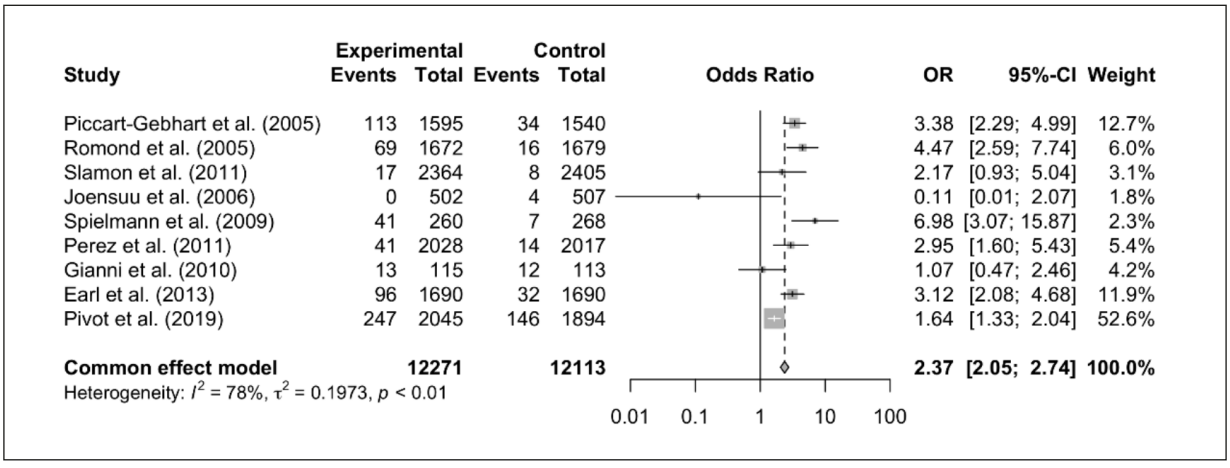


**Figure 5.** Meta-analysis of cardiotoxicity incidence risk ratio.

combination with chemotherapy significantly increased the incidence of cardiac toxicity in early-stage breast cancer patients [OR: 2.37, 95% CI (2.05, 2.74), $p<0.01$] (Figure 6).

### *Bayesian Decision Analysis*

We utilized Bayesian decision analysis to assess the cost-effectiveness of different durations (6 months, 9 months, 12 months, and 18 months) of trastuzumab in combination with chemotherapy in early-stage breast cancer patients. This involved comparing the expected outcomes and costs of different durations to determine the optimal treatment regimen. We constructed a decision tree model that simulated the clinical outcomes and economic burden of early-stage breast cancer patients receiving various durations of trastuzumab in combination with chemotherapy. The structure of the decision tree model is illustrated in Figure 6. We obtained the impact of different durations on disease-free survival and overall survival from the results of the meta-analysis and acquired relevant data from literature and official websites as input parameters for the model.

We employed Bayesian methods, integrating meta-analysis and prior knowledge, to generate posterior distributions for each input parameter. We used the Incremental Cost-Effectiveness Ratio (ICER) as the metric for cost-effectiveness analysis, the cost per quality-adjusted life year (QALY) gained, with ICER<100,000 RMB/QALY considered cost-effective, ICER>100,000 RMB/QALY as not cost-effective, and ICER=100,000 RMB/QALY as equivalent to the comparator. The results of the uncertainty analysis were displayed using a cost-effectiveness plane and a cost-effectiveness acceptability curve. We determined the optimal treatment regimen using the Consistency Cost-Effectiveness Ratio (CER) and Consistency Net Benefit (CNE). The outcomes of Bayesian decision analysis are presented in Table II. Both the 12-month and 18-month durations of trastuzumab in combination with chemotherapy increased the expected QALY for early-stage breast cancer patients but also raised the expected costs. The ICER, representing the incremental cost per unit of incremental health outcome, was negative, indicating that the new intervention had higher costs and less favorable outcomes compared to the control intervention. In such cases, the new intervention is not superior and does not require comparison with a threshold; it can be rejected outright. When comparing different durations, we found that the 12-month duration of trastuzumab in combi-

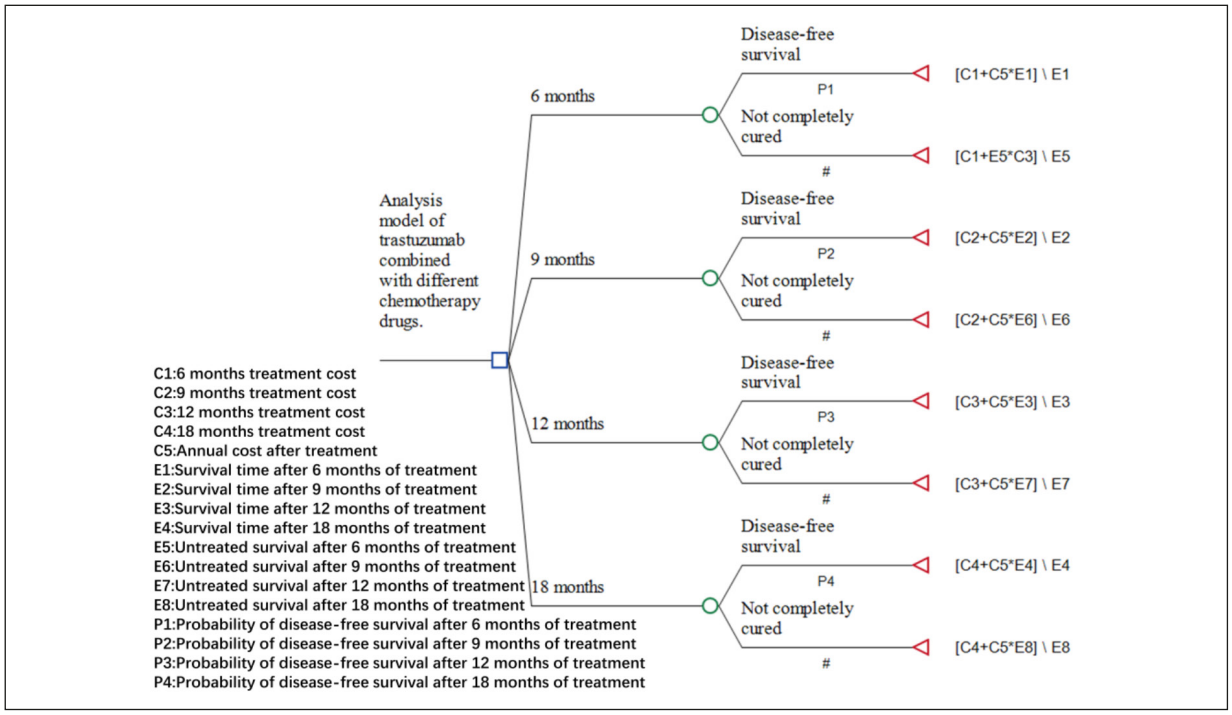


**Figure 6.** Analysis model of trastuzumab combined with different chemotherapy drugs.

**Table II.** Cost-effectiveness rankings report.

| Strategy | Cost (RMB) | Incr Cost (RMB) | Eff (QALY) | Incr Eff (QALY) | ICER (RMB/QALY) |
|---|---|---|---|---|---|
| **Trastuzumab combined with chemotherapy with anthracyclines (Treatment Plan A)** | | | | | |
| 6 months | 221,976.16 | —— | 15.50 | —— | —— |
| 9 months | 226,270.00 | 4,293.84 | 13.91 | -1.59 | -2,693.75 (non-dominant) |
| 12 months | 290,940.00 | 68,963.84 | 16.40 | 0.89 | 77,313.72 |
| 18 months | 386,880.00 | 95,940.00 | 14.69 | 1.06 | 90,509.43 |
| **Platinum-based trastuzumab combined with chemotherapy (Treatment Plan B)** | | | | | |
| 6 months | 195,225.00 | —— | 13.04 | —— | —— |
| 9 months | 228,345.60 | 33,120.60 | 12.03 | -1.01 | -32,890.37 (non-dominant) |
| 12 months | 243,325.00 | 48,100.00 | 13.99 | 0.95 | 50,631.58 |
| 18 months | 330,520.00 | 871,95.00 | 14.08 | 0.10 | 880,757.58 |
| **Trastuzumab with paclitaxel in combination with chemotherapy (Treatment Plan C)** | | | | | |
| 6 months | 257,617.60 | —— | 10.95 | —— | —— |
| 9 months | 177,050.00 | 38,370.00 | 11.80 | -1.66 | -25,420.24 (non-dominant) |
| 12 months | 215,420.00 | 42,197.60 | 10.14 | 0.85 | 44,929.74 |
| 18 months | 287,000.00 | 71,580.00 | 12.48 | 0.68 | 105,887.57 |

RMB: Renminbi, QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio, CER: consistency cost-effectiveness ratio, CNE: consistency net benefit.

nation with chemotherapy, in comparison to the 6-month, 9-month, and 18-month durations, offered higher expected QALY and lower expected costs, making it significantly more favorable than the other regimens.

## Discussion

The key findings of this study indicate that, in comparison to the control group, various durations of trastuzumab in combination with chemo-

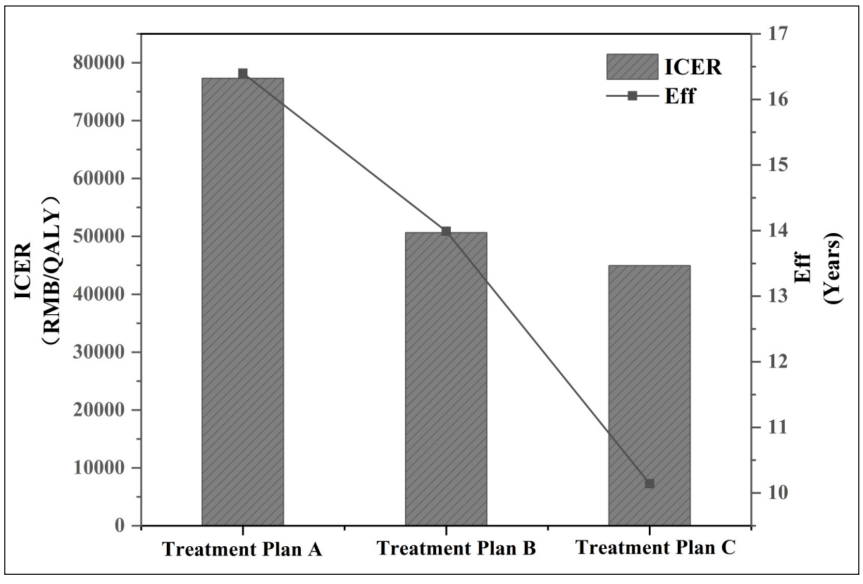


**Figure 7.** Cost-effectiveness analysis of trastuzumab combined with different drugs over a 12-month course of treatment.

therapy significantly enhance disease-free survival and overall survival in early-stage breast cancer patients, with no significant heterogeneity observed. In the comparisons between different durations, we found that the 12-month duration of trastuzumab in combination with chemotherapy, when compared to 6-month, 9-month, and 18-month durations, significantly reduces the risk of recurrence and mortality in early-stage breast cancer patients while maintaining a higher cost-effectiveness ratio. Therefore, we recommend the 12-month duration of trastuzumab in combination with chemotherapy as the standard treatment for early-stage breast cancer patients. The findings of this study are consistent with the results of some previous large randomized controlled trials[24,25], such as HERA, BCIRG 006, and NSABP B-31, which have also demonstrated the significant improvement of prognosis in early-stage breast cancer patients with 12 months of trastuzumab in combination with chemotherapy. This study's strength lies in its utilization of meta-analysis and Bayesian decision analysis, integrating a more extensive dataset and prior knowledge, thus enhancing statistical power and clinical applicability. Additionally, it considers the cost-effectiveness of different durations, providing a more comprehensive and objective basis for clinical decision-making.

This study has certain limitations that require improvement in future research. Firstly, the number of trials included in our analysis was limited, and variations in the design, patient characteristics, chemotherapy regimens, and follow-up durations among these trials could potentially impact the robustness and consistency of the results[26,27]. Secondly, we used the results of the meta-analysis as input parameters for the decision analysis; however, meta-analysis results may carry some degree of bias and uncertainty, necessitating further validation of the decision analysis outcomes. Third, we used early breast cancer patients in mainland China as the decision object, used RMB as the currency unit, and used 100,000 RMB/QALY as the threshold for cost-effectiveness analysis. These parameters may differ from those of other regions and countries, so the decision analysis results of this article may have some limitations and cannot be universally applicable. Generally speaking, developed countries have higher medical resources and economic levels and can afford the cost and risk of longer durations of trastuzumab combined with chemotherapy, while developing countries may face medical resource and economic pressure and need to consider the feasibility and effectiveness of shorter durations of trastuzumab combined with chemotherapy. Future research should consider the medical environment and economic conditions of different regions and countries, and explore the cost-effectiveness differences of different durations of trastuzumab combined with chemotherapy in different scenarios, and provide more robust evidence for clinical decision-making. For example, sensitivity analysis or multi-criteria decision analysis can be performed using different currency units, different cost-effectiveness analysis thresholds, different utility preferences, different medical resource consumption, etc., to evaluate the advantages and disadvantages of different durations of trastuzumab combined with chemotherapy.

## Conclusions

This study conducted a meta-analysis and Bayesian decision analysis to compare the efficacy and cost-effectiveness of different durations (6 months, 9 months, 12 months, and 18 months) of trastuzumab in combination with chemotherapy in early-stage breast cancer patients. We found that, compared to the control group, various durations of trastuzumab in combination with chemotherapy significantly improved the disease-free survival and overall survival of early-stage breast cancer patients, with no significant heterogeneity observed. In the comparisons between different durations, we observed that the 12-month duration of trastuzumab in combination with chemotherapy significantly reduced the risk of recurrence and mortality in early-stage breast cancer patients when compared to 6-month, 9-month, and 18-month durations while maintaining a higher cost-effectiveness ratio. Therefore, we recommend the 12-month duration of trastuzumab in combination with chemotherapy as the standard treatment for early-stage breast cancer patients. We also suggest that future research should focus on increasing the number and quality of trials and exploring cost-effectiveness differences in different regions and countries to provide stronger evidence.

### Conflict of Interest

The author declares no conflict of interest.

### Informed Consent
Not applicable.

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### Data Availability
Data will be made available on request.

### Ethics Approval
As this is a meta-analysis, ethical approval was not required.

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