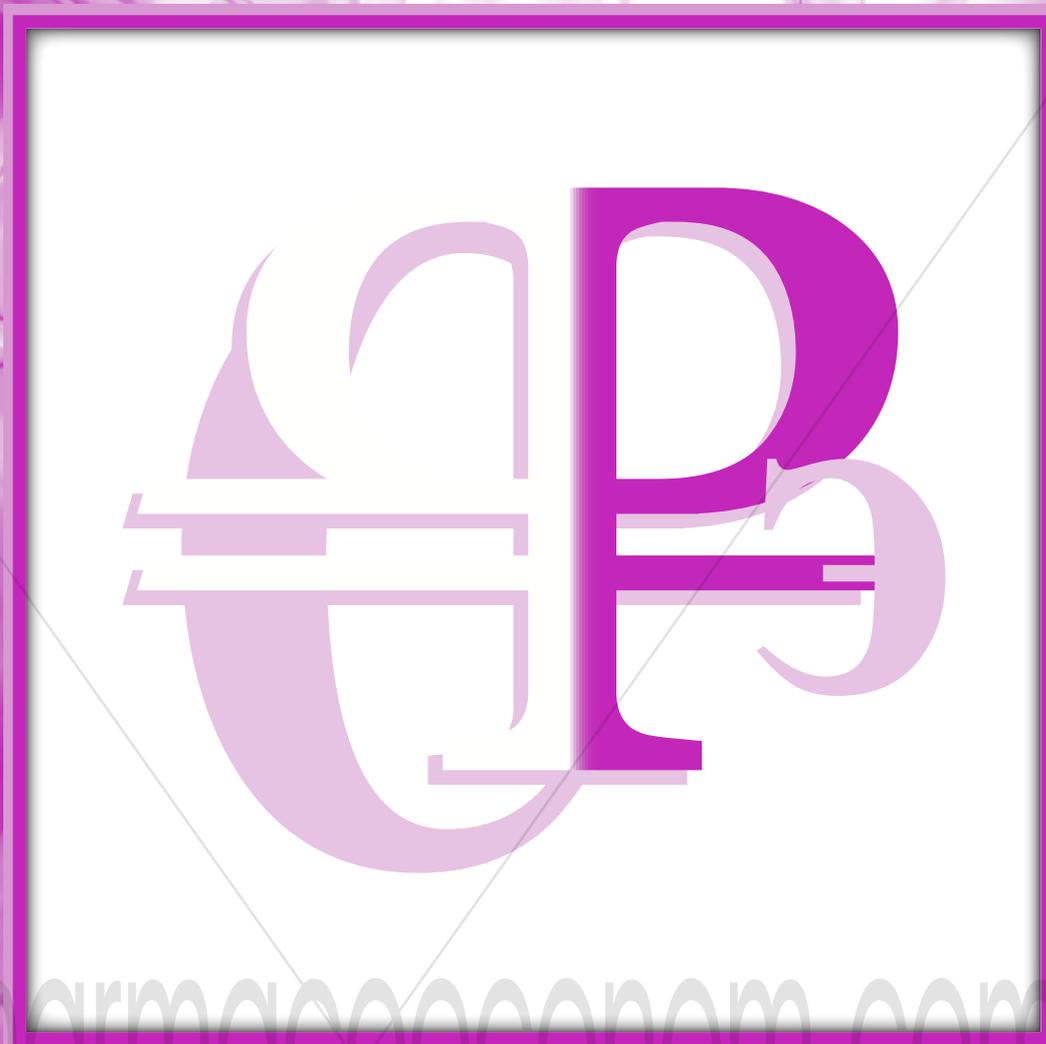


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- **IX НАЦИОНАЛЬНЫЙ КОНГРЕСС С МЕЖДУНАРОДНЫМ УЧАСТИЕМ «РАЗВИТИЕ ФАРМАКОЭКОНОМИКИ И ФАРМАКОЭПИДЕМИОЛОГИИ В РОССИЙСКОЙ ФЕДЕРАЦИИ»**  
г.УФА, 16-17 МАРТА 2015 года
- **ОРИГИНАЛЬНЫЕ РОССИЙСКИЕ ФАРМАКОЭКОНОМИЧЕСКИЕ ИССЛЕДОВАНИЯ**

## PHARMACOECONOMIC ANALYSIS OF BEYODYME (PERTUZUMAB+ TRASTUZUMAB [SET]) IN THE TREATMENT OF PATIENTS WITH HER2- POSITIVE METASTATIC BREAST CANCER

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### Abstract:

Breast cancer (BC) is the most common type of cancer in women and one of the leading causes of death among women worldwide, including our country. According to the World Health Organization, over 11,000,000 women with diagnosed BC receive care and treatment worldwide. Each year approximately 1,200,000 new cases of breast cancer are registered and more than 500,000 women die, and it is estimated that the incidents will increase up to 1,450,000. The objective of this study was to determine a treatment regimen (pertuzumab+trastuzumab+docetaxel or placebo+trastuzumab+docetaxel) more advantageous from the pharmacoeconomic point of view, used in the treatment of HER2+ metastatic breast cancer (mBC), on the basis of comparison of cost-effectiveness ratio, safety and life quality. The results of the cost-effectiveness analysis showed that cost-effectiveness ratios (effectiveness criterion – Life Years Gained, LYG) were as follows (over a period of 25 years): 1,823,530 rubles in the pertuzumab+trastuzumab+docetaxel group and 587,120 rubles in the placebo+trastuzumab+docetaxel group. The incremental cost-effectiveness ratio for the health technologies compared was 8,150,535 rubles/LYG. The results of the cost-utility analysis showed that the cost-utility ratios (utility criterion – Quality Adjusted Life Years, QALY) were as follows (over a period of 25 years): 2,716,738 rubles in the pertuzumab+trastuzumab+docetaxel group and 908,787 rubles in the placebo+trastuzumab+docetaxel group. The incremental cost-effectiveness ratio for the health technologies compared was 10,187,748 rubles/QALY. The results of the budget impact analysis demonstrated that for the Perjeta-trastuzumab-docetaxel treatment regimen, the difference in the required budgetary funds was 5,711,668 rubles in comparison with the placebo-trastuzumab-docetaxel treatment regimen per treatment of one patient with BC (over a period of 25 years).

**Key words:** effectiveness analysis, utility analysis, cost analysis, cost-effectiveness analysis, cost-utility analysis, breast cancer, health technology assessment, Beyodyme, Perjeta, pertuzumab, trastuzumab, docetaxel, pharmacoeconomics, clinical and economic analysis.

### Introduction

Breast cancer (BC) is the most common type of cancer in women and one of the leading causes of death among women worldwide, including our country. According to the World Health Organization, over 11,000,000 women with diagnosed BC receive care and treatment worldwide. Each year approximately 1,200,000 new cases of breast cancer are registered and more than 500,000

women die [1], and it is estimated that the incidence rate will increase up to 1,450,000 [5]. In the Russian Federation, over 48,000 new cases of breast cancer are detected and approximately 22,600 deaths are registered every year, or approximately 34.06 deaths per 100,000 women aged 15 years and older [3]. Besides, irrespective of innovations in treatment and diagnosis technologies, breast cancer incidence rates have risen by 50% over 20 years and continue to grow dramatically.

Breast cancer is the third leading cause of death in both females and males accounting for 23,095 cases in absolute figures. Breast cancer mortality is 15.68 deaths per 100,000 women and the disease is the leading cause of cancer deaths among women (17%) [2].

Of the total number of patients with BC, HER2 overexpression occurs in approximately 20-30% of cases, - about 15,000 new cases per year [14]. In case of HER2 overexpression, excess HER2 protein found on the surface of tumor cells promotes cancer cell growth and replication. This form of BC is characterized by rapid growth and metastasis of the tumor and is associated with a poor BC prognosis and, in particular, with lower disease-free and overall survival rates. Therefore, HER2+ BC is the most aggressive form among all breast cancers that requires more effective methods of treatment.

In the end of 2014, a new medicine (Beyodyme)® was approved in the Russian Federation for use in combination with docetaxel in the treatment of metastatic or locally recurrent unresectable HER2-positive breast cancer in patients with previously untreated or progressive disease after adjuvant therapy. This product comprises of a pack kit consisting of Perjeta® (pertuzumab) concentrate for solution for infusion, Herceptin® (trastuzumab) lyophilisate for concentrate for solution for infusion, and diluent (bacteriostatic water for injection).

Significant improvement in overall survival was reported in foreign clinical studies of pertuzumab, trastuzumab, and docetaxel in patients with HER2-positive metastatic breast cancer compared to the placebo, trastuzumab and docetaxel group [12,13].

**The objective of this study** is to determine a treatment regimen (pertuzumab+trastuzumab+docetaxel or placebo+trastuzumab+docetaxel) more advantageous from the pharmacoeconomic point of view, used in the treatment of HER2+ metastatic breast cancer (mBC), on the basis of comparison of cost-effectiveness ratio, safety and life quality.

To achieve this objective, the following tasks were solved:

1. Collection and analysis of mBC therapy data in pertuzumab+trastuz



umab+docetaxel and placebo+trastuzumab+docetaxel groups in clinical practice.

2. Selection of criteria for evaluating the effectiveness of pertuzumab+trastuzumab+docetaxel and placebo+trastuzumab+docetaxel used for mBC treatment.
3. Cost analysis of the compared treatment regimens used in mBC therapy.
4. Use of the following methods in this pharmacoeconomic study: cost-effectiveness analysis, cost-utility analysis, budget impact analysis.

**Effectiveness analysis**

After completion of the information retrieval for the studies of mBC therapy relevance using various treatment regimens, the effectiveness analysis was performed. The analysis was aimed at selecting the effectiveness criteria for the alternatives being compared for the purpose of using the obtained results further in the pharmacoeconomic analysis [4].

The information search performed in the course of this study yielded the results of pertuzumab+trastuzumab+docetaxel and placebo+trastuzumab+docetaxel regimens evaluation in the treatment of patients with HER2-positive mBC that employed such criteria as life years gained (LYG) and quality adjusted life years (QALY).

It should be noted that, for the purposes of pharmacoeconomic research, these effectiveness (utility) criteria have the highest significance and consequently are of the greatest interest. The selected criteria of effectiveness and utility for the regimens being compared in the treatment of patients with HER2-positive mBC are presented in Tables 1 and 2. Effectiveness and utility of the alternatives being studied were evaluated over a period of 25 years in accordance with life expectancy of patients with the form of BC being studied.

**Table 1** – Results of the effectiveness analysis for pertuzumab+trastuzumab+docetaxel and placebo+trastuzumab+docetaxel regimens in the treatment of patients with HER2-positive mBC (over a period of 25 years) [12,13].

Effectiveness parameter (LYG)	Pertuzumab+trastuzumab+docetaxel	Placebo+trastuzumab+docetaxel
Value during progression-free period, years	2,119	1,490
Value after disease progression, years	2,168	2,096
Total LYGs	4,287	3,586

As seen from the table above, the use of pertuzumab+trastuzumab+docetaxel in the treatment of patients with HER2-positive mBC resulted in more life years gained compared to the use of the placebo+trastuzumab+docetaxel treatment regimen. The use of the pertuzumab+trastuzumab+docetaxel regimen also significantly increased life years gained both in the progression-free period and after disease progression.

**Table 2** – Results of the utility analysis for pertuzumab+trastuzumab+docetaxel and placebo+trastuzumab+docetaxel regimens in the treatment of patients with HER2-positive mBC (over a period of 25 years) [12,13].

Utility parameter (QALY)	Pertuzumab+trastuzumab+docetaxel	Placebo+trastuzumab+docetaxel
Value during progression-free period, years	1,718	1,196
Value after disease progression, years	1,160	1,121
Total QALYs	2,877	2,317

As seen from the table above, the use of pertuzumab+trastuzumab+docetaxel in the treatment of patients with HER2-positive mBC resulted in more quality adjusted life years compared to the use of the placebo+trastuzumab+docetaxel treatment regimen. The use of the pertuzumab+trastuzumab+docetaxel regimen also increased quality adjusted life years both in the progression-free period and after disease progression. The difference between the treatment regimens being compared is more clearly seen in the QALY analysis of progression-free period where higher values are achieved with the use of pertuzumab+trastuzumab+docetaxel.

Therefore, as a result of the effectiveness analysis performed it was

found that the use of pertuzumab+trastuzumab+docetaxel in the treatment of patients with HER2-positive mBC is more effective and useful as compared to the placebo+trastuzumab+docetaxel regimen.

**Cost analysis**

The total cost included basic pharmacotherapy costs, costs related to the introduction of the treatment regimens compared, costs related to the correction of adverse effects due to the use of health technologies being analyzed, and supporting therapy costs.

The study was performed over a period of 25 years. The discount rate of 3.5% was also used. The obtained results of the cost analysis are presented in Table 3.

**Table 3** – Results of the cost analysis for the use of pertuzumab+trastuzumab+docetaxel in the treatment of patients with HER2-positive mBC in comparison with the placebo+trastuzumab+docetaxel regimen, rubles

Cost analysis parameter	Pertuzumab+trastuzumab+docetaxel	Placebo+trastuzumab+docetaxel
Basic pharmacotherapy costs		1 864 776
Treatment regimen introduction costs	7 346	2 942
Costs related to the correction of adverse effects due to the use of basic pharmacotherapy	8 705	4 306
Supporting therapy costs	1 994	1 430
Costs in the period of disease progression	222 194	227 170
Total cost	7 817 093	2 105 425

On the basis of the values obtained in the cost analysis it was concluded that the total cost of using pertuzumab+trastuzumab+docetaxel in the treatment of patients with HER2-positive mBC was higher in comparison with the placebo+trastuzumab+docetaxel regimen. The use of the pertuzumab+trastuzumab+docetaxel treatment regimen also resulted in higher costs of each component analyzed: basic pharmacotherapy costs, costs related to the introduction of the treatment regimens compared, costs related to the correction of adverse effects due to the use of health technologies being analyzed, and supporting therapy costs.

**Cost-effectiveness analysis**

In the course of this pharmacoeconomic study, the cost-effectiveness analysis was performed on the basis of treatment of one patient with mBC. The cost-effectiveness ratio was calculated according to the formula [6-8]:

$$CER = \frac{Cost}{Ef}$$

where: CER is the cost-effectiveness ratio;  
Cost is the cost of the technology used, rubles;  
Ef is the effectiveness of the technology used.  
Therefore, in the course of this study, values of cost-effectiveness ratios were obtained for the use of the pertuzumab+trastuzumab+docetaxel regimen in the treatment of patients with HER2-positive mBC compared to the placebo+trastuzumab+docetaxel treatment regimen. As noted above, life years gained were used as the effectiveness criterion. The analysis was performed over a period of 25 years. The obtained values of cost-effectiveness ratios are presented in Table 4 and in Figure 1.

**Table 4** – Results of the cost-effectiveness analysis (effectiveness criterion – Life Years Gained)

Parameter	Pertuzumab+trastuzumab+docetaxel	Placebo+trastuzumab+docetaxel
Costs, rubles	7 817 093	2 105 425
LYG	4,29	3,59
Cost-effectiveness ratio	1 823 530	587 120

As seen from the results above, the placebo+trastuzumab+docetaxel regimen requires lower cost per one life year gained. In contrast, along with the highest costs, the use of the pertuzumab+trastuzumab+docetaxel regimen also has the highest effectiveness expressed as maximum values of life years gained for the alternatives being compared.

Then the incremental cost-effectiveness ratio was calculated for the health technologies compared which was 8,150,535 rubles/LYG.

**Cost-utility analysis**

In the course of this pharmacoeconomic study, the cost-utility analysis was performed on the basis of treatment of one patient with mBC.

The results of cost-utility analysis (CUA) and incremental cost-utility ratio analysis are expressed as the respective ratios which are calculated according to the following formulas [6-8]:

$$CUR = DC/Ut,$$

$$ICUR = (DC1 - DC2)/(Ut1 - Ut2),$$

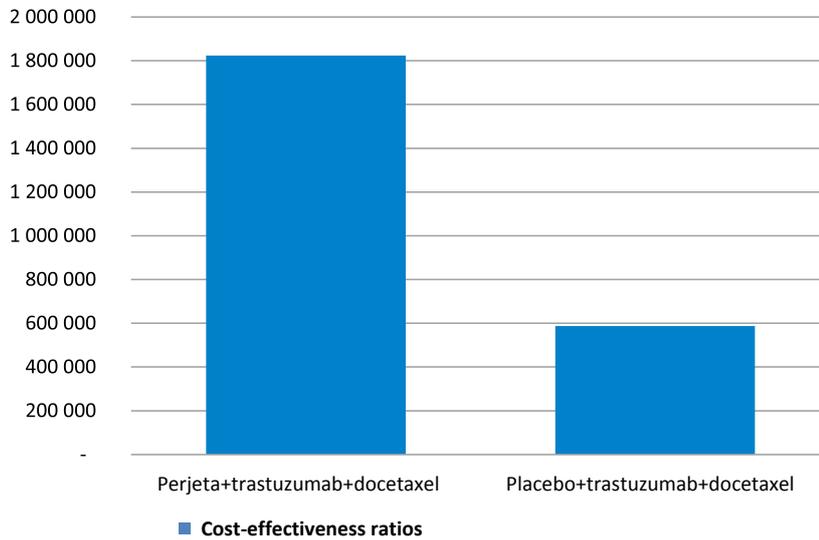
where CUR is the cost-utility ratio (cost per one utility unit - QALY);  
ICUR is the incremental cost-utility ratio (incremental cost per one additional utility unit);  
DC1 are direct costs of the first treatment option;  
DC2 are direct costs of the second treatment option;  
Ut1 and Ut2 are utility values of the first and second treatment options (QALY value).

Therefore, in the course of this study, values of cost-utility ratios were obtained for the use of the pertuzumab+trastuzumab+docetaxel regimen in the treatment of patients with HER2-positive mBC compared to the placebo+trastuzumab+docetaxel treatment regimen. As noted above, quality adjusted life years were used as the effectiveness criterion. The analysis was performed over a period of 25 years. The obtained values of cost-utility ratios are presented in Table 5 and in Figure 2.

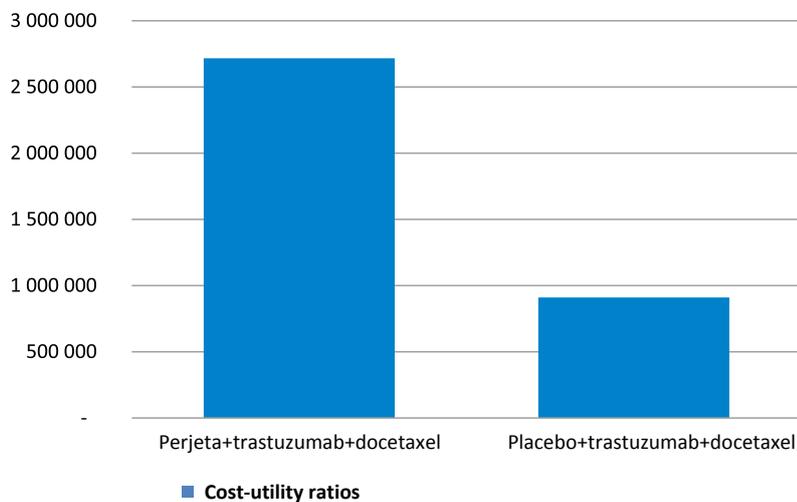
**Table 5** - Results of the cost-utility analysis (utility criterion – Quality Adjusted Life Years)

Parameter	Pertuzumab+trastuzumab+docetaxel	Placebo+trastuzumab+docetaxel
Costs, rubles	7 817 093	2 105 425
QALY	2,88	2,32
Cost-utility ratio	2 716 738	908 787

**Figure 1.** Cost-effectiveness ratios per one patient



**Figure 2.** Cost-utility ratios per one patient





As seen from the results above, the placebo+trastuzumab+docetaxel regimen requires lower cost per one quality adjusted life year. In contrast, along with the highest costs, the use of the pertuzumab+trastuzumab+docetaxel regimen also has the highest utility expressed as maximum values of quality adjusted life years for the alternatives being compared.

Then the incremental cost-utility ratio was calculated for the health technologies compared which was 10,187,748 rubles/ QALY.

#### Budget impact analysis

Budget impact analysis involves assessment of all types of expenditure associated with the introduction of a new treatment regimen in relation to all types of expenditure associated with the already existing treatment regimen [6]. Costs are calculated according to the following formula:

$$BIA = Cost1 - Cost2, , \text{ where}$$

*Cost1 is the total cost of the first treatment option (rubles);*

*Cost2 is the total cost of the second treatment option (rubles);*

*BIA is the budget impact analysis (rubles)*

The results of the budget impact analysis demonstrated that for the Perjeta-trastuzumab-docetaxel treatment regimen, the difference in the required budgetary funds was 5,711,668 rubles as compared to the placebo-trastuzumab-docetaxel treatment regimen per treatment of one patient with mBC (over a period of 25 years).

#### Results

1. As a result of the cost analysis performed, the following costs of mBC therapy were obtained (over a period of 25 years): costs in the pertuzumab+trastuzumab+docetaxel group amounted to 7,817,093 rubles, while costs for the placebo+trastuzumab+docetaxel treatment regimen were 2,105,425 rubles.

2. The results of the cost-effectiveness analysis showed that the cost-effectiveness ratios (effectiveness criterion – Life Years Gained, LYG) were as follows (over a period of 25 years): 1,823,530 rubles in the pertuzumab+trastuzumab+docetaxel group and 587,120 rubles in the placebo+trastuzumab+docetaxel group. The incremental cost-effectiveness ratio for the health technologies compared was 8,150,535 rubles/LYG.

3. The results of the cost-utility analysis demonstrated that the cost-utility ratios (utility criterion – Quality Adjusted Life Years, QALY) were as follows (over a period of 25 years): 2,716,738 rubles in the pertuzumab+trastuzumab+docetaxel group and 908,787 rubles in the placebo+trastuzumab+docetaxel group. The incremental cost-effectiveness ratio for the healthcare technologies compared was 10,187,748 rubles/QALY.

4. The results of the budget impact analysis showed that for the Perjeta-trastuzumab-docetaxel treatment regimen, the difference in the required budgetary funds was 5,711,668 rubles in comparison to the placebo-trastuzumab-docetaxel treatment regimen per treatment of one patient with BC (over a period of 25 years).

#### Discussion

As noted above, the incremental cost-effectiveness ratio for the health technologies being compared was 8,150,535 rubles/LYG, and the incremental cost-utility ratio was 10,187,748 rubles/QALY. These parameters are above the willingness to pay threshold applied to the national healthcare system. Nevertheless, using the precedent approach, we compared the obtained

values with the respective parameters for the medicines already included in the Vital and Essential Drugs List.

Thus, it was found that the incremental cost-effectiveness ratio for eculizumab, a medicine indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) was over 40 million rubles per additional utility unit, which is significantly higher than the results obtained for the treatment regimens being studied. Such comparison may become an argument for healthcare decision makers when selecting a BC treatment regimen.

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