

Original Article

COST-EFFECTIVENESS ANALYSIS OF TRASTUZUMAB EMTANSINE IN THE TREATMENT OF METASTATIC BREAST CANCER

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ABSTRACT

Objective: To investigate the cost-effectiveness of second-line pharmacological treatments for metastatic breast cancer (MBC) by comparing trastuzumab emtansine (T-DM1) versus a combination of lapatinib and capecitabine (LAP+CAP) from the perspective of the Brazilian health system, the Unified Health System (Sistema Único de Saúde-SUS).

Methods: The results of each treatment were simulated based on a three-state Markov decision model applied to a hypothetical cohort of 1,000 women, aged 50 y old or older, with MBC and HER2 (human epidermal growth factor receptor 2) overexpression. The data on the effectiveness of treatments were taken from reports in the literature. The period considered for simulation was three years subdivided into monthly cycles of transition between health states. A discount rate of 5% per year was applied to costs and outcomes. Possible uncertainty was assessed by means of a sensitivity analysis.

Results: Chemotherapy for women with refractory MBC using T-DM1 monotherapy was ruled out by extended dominance. Treatment with LAP+CAP proved to be the most efficient strategy because the cost in relation to the overall survival (BRL 72,035.43/quality-adjusted life year-QALY) was the lowest and fell within the acceptability threshold, BRL 86,628.00.

Conclusion: T-DM1 demonstrated pharmacological superiority over other agents used for the treatment of MBC in clinical studies. However, the price set for T-DM1 in Brazil is the determinant variable that contraindicates its inclusion in the SUS, in agreement with other international assessments.

Keywords: Metastatic breast cancer, Cost-effectiveness, Trastuzumab emtansine

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INTRODUCTION

Cancer, a generic term used to allude to a condition of quick and abnormal cell growth, is one of the main causes of morbidity and mortality worldwide, particularly in developing countries. According to World Health Organization (WHO) estimates, 14 million new cases will occur every year, with a trend of increase of at least 70% until 2030 [1].

In Brazil, neoplasms and cardiovascular diseases have been the main causes of death in recent years, largely due to the local lifestyle and population ageing associated with continuous urbanisation and actions for health promotion and recovery [2, 3]. According to the José Alencar da Silva National Cancer Institute, excluding non-melanoma skin cancer, approximately 430,000 new cases occurred in Brazil in 2016, with breast cancer having the highest prevalence among women, representing 28.1% of cases [4].

Although its incidence rates are still high, the prognosis of breast cancer varies as a function of the stage of the disease at the time of diagnosis and onset of treatment. More frequent early diagnosis resulting from screening and timely systemic treatment increase the average survival of patients [5-7].

In contrast, delay in the identification of disease and the onset of treatment may result in the opposite outcomes. Metastatic breast cancer (MBC), a more advanced stage of the disease, occurs when the original tumour cells maintain their full cell division activity to the point of spreading away from the primary tumour site. MBC is considered an aggressive disease, and increasing evidence confirms its very poor prognosis compared to the early stages [8, 9]. Although the treatments currently available for MBC are not able to eradicate

disease, they may afford a relief of symptoms, maintain the patients' quality of life within acceptable levels, and prolong their survival. The first-choice pharmacological treatment for patients with HER2 protein overexpression is based on the combination of trastuzumab (TRA) (Herceptin®, Roche) with other chemotherapy agents. Although TRA may be used for retreatment of refractory cases, to date, there is no consensus on its indication for this specific scenario [10].

The combination of lapatinib and capecitabine (LAP+CAP) is an efficacious therapeutic option in the event of failure of first-line treatment with TRA, taxanes, and anthracycline. A study conducted by Cameron *et al.* (2008) suggests that LAP+CAP is superior to capecitabine alone, particularly relative to the time to tumour progression and the overall response rate [11].

More recently, trastuzumab emtansine (T-DM1-Kadcyla®, Roche), a drug-antibody conjugate, has become a therapeutic option for cases with initial treatment failure [12, 13]. T-DM1 is indicated as a monotherapy for patients with HER2-positive metastatic or unresectable locally advanced breast cancer previously treated with TRA and a taxane [14]. The commercialisation of T-DM1 in Brazil was approved by the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária-ANVISA) in 2014. However, for the drug to be included on the list of agents delivered by the national health system, it still needs to be subjected to analysis and obtain a favourable recommendation from the National Commission for Technology Incorporation (Comissão Nacional de Incorporação de Tecnologias no SUS-CONITEC) of the Unified Health System (Sistema Único de Saúde-SUS) [12].

The aim of the present study was to assesses the cost-effectiveness of pharmacological treatments indicated as second-line for the

treatment of refractory MBC, comparing (a) TDM-1 monotherapy and b) LAP+CAP, from the perspective of the SUS.

MATERIALS AND METHODS

Model structure

A simulation model was developed based on Markov chains and comprising three states (overall survival, progression, and death) in a hypothetical cohort of 1,000 women aged 50 y old or older diagnosed with MBC and HER2 overexpression previously treated with TRA. The simulation anticipated the shift between or permanence of subgroups of patients in the various Markov states according to the effectiveness of treatment and the corresponding transition probability at the end of each cycle. The progression of MBC was simulated for a three-year period [14].

The probabilities of progression were derived from the data on overall survival in the clinical trial of Verma *et al.* [14], complying with the difference between outcomes as a function of the compared pharmacological interventions. The survival probabilities were estimated through the derivation of the data in the overall survival curves, attributing monthly survival probabilities to the cohort [15]. Next, the survival parameters were adjusted following the method suggested by Hoyle and Henley [16], according to whom the following variables are considered in the calculation of the individual survival probabilities: (1) the total number of patients at risk and (2) the survival probabilities. Considering that the information provided by the studies used as data sources corresponded to periods of up to 36 mo, the annual probabilities of transition to metastasis and death starting from the third year onwards were assumed to remain constant and homogeneous in all intervention arms.

At the end of each cycle, the patients shifted between the considered health states according to the corresponding treatment and transition probabilities. The transition between health states was assumed to occur on a monthly basis, and the period of transition between health states coincided with the duration of the chemotherapy cycles.

Death by MBC was only possible for patients with the progressive disease, whereas death by other causes could occur in all other health states.

An incremental cost-effectiveness analysis was performed by ranking the assessed strategies in increasing order of effectiveness. The perspective selected was that of the SUS. The comparative efficiencies of the various treatment strategies were measured by means of the incremental cost-effectiveness ratio (ICER). The discount rate for both costs and outcomes was 5% per year; a sensitivity analysis was performed [17].

Efficacy and effectiveness

A literature review was performed to locate data from randomised, controlled, and double-blind clinical trials. Patients aged 50 y old or older, with locally advanced MBC and HER2⁺ confirmed by immunohistochemistry or FISH (fluorescence in situ hybridization), were considered eligible. The patient had to have normal haematological, liver, and kidney function, in addition to having the

left ventricular ejection fraction (LVEF) assessed by echocardiogram. Next, the study by Verma *et al.* (2012) was located; it was used as the source for the effectiveness data. Tumour assessment was planned to be performed at the onset of the study and then every six weeks until disease progression and six weeks afterwards. Laboratory assessment was planned to be performed at the onset of the study, on day 1 of each treatment cycle, on days 8 and 15 of cycles 1 to 4, and 30 d after the last dose of the analysed drug. LVEF was assessed at the onset of the study, at weeks 6 and 12, and then every 12 w until discontinuation of treatment; one additional assessment was performed 30 d after the last dose of the analysed drug.

The patients could have received a first-line chemotherapy regimen for metastatic disease. Patients with a Karnofsky index below 60% and a life expectancy of less than three months or blood, liver, kidney, or heart (LVEF<50%) abnormalities were excluded [15, 18]. Additionally, patients with the advanced metastatic disease, significant sensory or motor neuropathy, or the past or active heart disease were excluded [15].

Based on the phase III studies EMILIA and TH3RESA [19], T-DM1 monotherapy is currently recommended for patients with HER2-positive metastatic disease and progression after treatment with TRA and taxanes or with relapse within six months of adjuvant treatment. Giordano *et al.* (2014) recommend T-DM1 as a second-line treatment for patients with advanced breast cancer and disease progression during or after first-line HER2⁺-targeted therapy [13].

According to the studies EMILIA [14] and TH3RESA [20], premedication is not needed for treatment with T-DM1. In the case of the control, LAP+CAP, premedication is used as needed because these chemotherapy agents exhibit minimum or low emetogenic potential.

The compared interventions were (a) LAP+CAP with lapatinib in a dose of 1,250 mg/day by oral administration and capecitabine in a dose of 1,000 mg/m² every 12 h by oral administration from days 1 to 14 (maximum planned dose: 2,000 mg/m² per day); this cycle was repeated every 21 d [21]; and b) T-DM1 3.6 mg/kg by intravenous administration; this cycle was repeated every 21 d [21].

Geyer *et al.* [22] consider that the following assessments should be performed before treatment with LAP+CAP: physical examination, complete blood count, serum biochemical testing, electrocardiogram, LVEF by echocardiogram, radiological assessment of the tumour, and computed tomography [22]. These same assessments were performed during treatment with changes in their frequency. The same assessments with the corresponding frequency were also performed for T-DM1 [14, 22, 23].

Outcomes

The outcome of interest was overall survival [14]. The values of the overall response rate, complete and partial response, duration of response, and stable disease were based on the number of patients with measurable disease in the base case. The study used as the basis assessed 786 patients divided into the control group (LAP+CAP, 389 participants) and the intervention group (T-DM1, 397 participants) [14].

Table 1: Outcomes of interest included in the Markov model

Parameters	Interventions		Confidence interval (CI)	Source
	LA+CA	T-DM1		
Overall response rate (ORR) (n) (%)	120 (30.8%)	173 (43.6%)	95% 26.3-35.7 and 38.6-48.6; p<0.001	[14]
Complete response (CR) (%)	0.5	1.0		[14]
Partial response (PR) (%)	30.3	42.6		[14]
Average overall survival (OS) (months)				
1 st analysis	6.4	9.6	95% 0.55-0.77; p<0.001	[14]
2 nd analysis	25.1	30.9	95% 0.55-0.85; p<0.001)	[14]
Survival estimate (%)				
1 st year	78.4	85.2	95% 74.6-82.3 and 82.0-88.5	[14]
2 nd year	51.8	64.7	95% 45.9-57.7 and 59.3-70.2	[14]
Time to progression (TTP) (months)	4.6	7.1	95% 0.667 to 0.951; p = 0.012	[14]
Duration of response (DoR) (average, in months)	6.5	12.6	95% 5.5-7.2 and 8.4-20.8	[14]

Verma *et al.* [14] compared LAP+CAP versus T-DM1 alone and found that the latter had greater efficacy. The parameters assessed were (a) progression-free survival, (b) the objective response rate, (c) overall survival, (d) dose reduction, (e) discontinued treatment due to adverse events, (f) adverse events, complete or partial response, and (g) duration of response. Duration of response was calculated as the number of days from the objective response to the onset of

disease progression. Time to progression was defined as the number of days from the date of the first drug infusion to the onset of disease progression or the date on which the patient was considered to be progression-free. Survival was calculated from the date of randomization to disease progression or death by any cause [14]. Table 2 summarises the parameters used in the Markov model for the treatment of MBC with T-DM1 and LAP+CAP.

Table 2: Parameters of interest included in the Markov model

Intervention ^a	Efficacy data ^a (%)	Utility	Cost of chemotherapy ^c (per cycle/patient) (BRL)	Cost of tests before treatment ^c (BRL)	Cost of tests during treatment ^c (BRL)
Lapatinib+ Capecitabine	CR =0.5 PR =30.3	Stable ^b = 0.715 Death = 0	6,116.04	214.23	2,321.39
Trastuzumab emtansine	CR =1.0 PR= 42.6	Stable ^b = 0.715 Death = 0	11,300.96	214.23	2,321.39

^adata from the phase III controlled clinical trial performed by Verma *et al.* [14], ^bvalue for stable disease with no side effects–base state–according to Lloyd *et al.* [24], ^cvalues calculated by the authors based on Brazilian data

Cost survey

The costs were assessed from the perspective of the Brazilian health system and calculated in American dollars and Brazilian real. Indirect costs were not considered.

The cost of the medications was estimated based on the average price per vial and the duration of treatment. The cost of the medications included in the Albert Einstein Hospital Breast Cancer protocol was surveyed on the following databases: the Management System of the table of Procedures, Medications (Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos–SIGTAP) for 2016 and the Portal of Purchases of the Federal Government (Portal de Compras do Governo Federal–COMPASNET). The period for public bids considered was 2015/2016 [25, 26]. Relative to the tests, the period for the survey of values at the SIGTAP was April 2016. The list of tests included in the cost-effectiveness analysis was based on the suggestions by Verma *et al.* [14], Geyer *et al.* [22], and Gasparini *et al.* [23]. Based on the study by Verma *et al.* [14], the frequency and cost of tests were established for the following time points: (1) before chemotherapy;

(2) during chemotherapy, for a total of nine cycles in the LAP+CAP cohort; (3) during chemotherapy, for a total of 14 cycles in the T-DM1 cohort; and (4) after chemotherapy (30 d after the last dose of the assessed drug). The number of cycles was calculated based on the average number of months with progression-free survival in the T-DM1 (9.4 mo) and LAP+CAP (5.8 mo) groups [14].

RESULTS

Costs

The cost of the medications was based on the average price of vials and the duration of treatment. The price per unit of trastuzumab emtansine in injectable lyophilised powder (Kadcyla®/Roche) in 100 mg and 160 mg concentrations is BRL 5,650.48 and BRL 9,040.76, respectively. The cost per unit of lapatinib ditosylate in 250 mg tablets (ditosylate salt; Tykerb®/GlaxoSmithKline) is BRL 44.32. In turn, the cost per unit of capecitabine in 150 mg and 500 mg tablets (Xeloda®/Roche) is BRL 5.13 and BRL 17.41, respectively. Table 3 describes the direct costs of treatment of MBC with T-DM1 and LAP+CAP.

Table 3: Direct costs of treatment for metastatic breast cancer with trastuzumab emtansine monotherapy and the combination of capecitabine+lapatinib per patient/cycle in a 1,000-patient cohort

Technology	Costs ^a BRL/USD			
Trastuzumab emtansine 14 cycles	Chemotherapy^b	Tests before treatment	Tests during treatment	Tests after progression
Individual	158,213.44/49,909.60	214,23/67.58	1,717.18/541.70	214.23/67.58
1,000-patient cohort	158,213,440.00/49,909,602.52	214,230.00/67,580.00	1,717,180.00/541,700.00	214,230.00/67,580.00
Lapatinib9 cycles				
Individual	27,921.60/8,808.07	214.23/67.58	1,211.17/382.07	214.23/67.58
1,000-patient cohort	27,921,600.00/8,808,075.71	214,230.00/67,580.00	1,211,170.00/382,070.00	214,230.00/67,580.00
Capecitabine9 cycles				
Individual	8,774.64/2,768.03	214.23/67.58	1,211.17/382.07	214.23/67.58
1,000-patient cohort	8,774,640.00/2,768,025.24	214,230.00/67,580.00	1,211,170.00/382,070.00	214,230.00/67,580.00

^avalues in dollars calculated according to the exchange rate of 1 dollar = BRL 3.17, ^bdoses according to the phase III controlled clinical trial performed by Verma *et al.* [14] and included in the Albert Einstein Hospital protocol

Before chemotherapy, the total cost of tests was BRL 214.23 (USD 67.58) for both therapies. During chemotherapy, the total cost of tests was BRL 1,211.17 (USD 382.07) for the LAP+CAP group and BRL 1,717.18 (USD 541.70) for the T-DM1 group. After chemotherapy, the total cost of tests was BRL 214.23 (USD 67.58).

Survival

The odds of survival were higher for the individuals treated with T-DM1 compared to treatment with LAP+CAP. The increase in survival exhibited by the group treated with T-DM1 compared to LAP+CAP occurred in the first year of treatment, reaching its peak in month

13. The results mean that 113 additional patients per 1,000 patients would survive when treated with T-DM1. After that period, the odds of survival of the two hypothetical cohorts contracted. The graph in fig. 1 depicts the progression of the difference between survival probabilities according to the selected treatments.

Cost-effectiveness analysis

Incremental cost-effectiveness analysis was performed by ranking the assessed strategies in decreasing order of effectiveness. The costs were measured in Brazilian real; effectiveness was measured as overall survival.

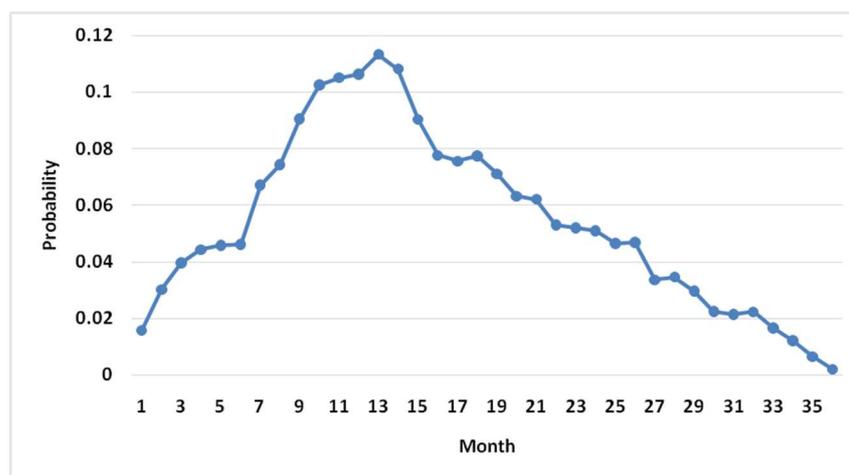


Fig. 1: Difference in survival probabilities relative to metastatic breast cancer according to the selected treatment

Table 4: Cost-effectiveness of strategies suggested for treatment of MBC

Strategies	Cost (BRL)	Incremental cost (BRL)	Effectiveness (QALY)	Incremental effectiveness (QALY)	Incremental C/E (BRL/QALY)
Lapatinib+Capecitabine	72,035.43	0.0	10.94	0.0	0.0
Trastuzumab emtansine	264,878.05	192,842.62	12.27	1.32	145,668.94

Source: the authors. *C/E=Incremental cost-effectiveness ratio

Treatment with T-DM1 monotherapy resulted in gains in the terms of quality of life; however, it is much more expensive than the strategy based on the use of LAP+CAP. The latter proved to be more efficient, i.e., it exhibited lower cost (BRL 72,035.43) for the treatment of women with MBC. The incremental cost of treatment with T-DM1 was BRL 192,842.62 for a mere 10% improvement in the quality of life. In addition, according to the WHO (2008), LAP+CAP is the only therapeutic strategy that may be considered cost-effective because its cost falls within the acceptability threshold, that is, up to three times the national per capita gross domestic product (GDP), of approximately BRL 30,000.00/quality-adjusted life year (QALY). In contrast, T-DM1 does not seem to be a cost-effective option because the value of BRL 145.668.94/QALY

exceeds the acceptability threshold of up to three times the national per capita GDP.

Sensitivity analysis

The assessment of uncertainty by means of an exploratory sensitivity analysis showed that the price of T-DM1 was the only variable influencing the main result of the cost-effectiveness analysis. The imprecision associated with all other parameters, within their range of value variation, was not able to significantly change the model outcomes and the interpretation of the results. The estimates described in the table below correspond to a second (alternative) scenario in which the minimum value of T-DM1 was used.

Table 5: Results of a sensitivity analysis using a variation of the T-DM1 unit cost

Strategies	Cost (BRL)	Incremental cost (BRL)	Effectiveness (QALY)	Incremental effectiveness (QALY)	Incremental C/E (BRL/QALY)
Lapatinib+Capecitabine	72,035.43	0,0	10.94	0.0	0.0
Trastuzumab emtansine	248,268.21*	176,232.8	12.27	1.32	133,122.24

Source: the authors. *Value resulting from the unit value used in the sensitivity analysis of T-DM1=BRL 5,439.63, according to the Chamber of Regulation of the Medicines Market (Câmara de Regulação do Mercado de Medicamentos-CMED) [28].

Although the ICER fell to BRL 133,122.24/QALY, it remained above the acceptability threshold of up to three times the national per capita GDP. Even after changing this parameter determinant of the results of the cost-effectiveness analysis, the results remain unfavourable to T-DM1. Reducing the unit cost of T-DM1 to BRL 4,075.00, the ICER falls to BRL 86,620.11 that is, within the acceptability threshold of up to three times the national per capita GDP, thus indicating that the drug is cost-effective.

DISCUSSION

Although ANVISA approved the commercialisation of T-DM1 in Brazil, to date, a cost-effectiveness analysis to validate its inclusion or not in the SUS has not been performed. Other studies that employed economic models to analyse the impact of treatment with

T-DM1 and other medications for MBC have reached conclusions similar to those of the present study.

In August 2014, the National Institute for Health and Care Excellence (NICE) published the results of an assessment of T-DM1 for the treatment of MBC. NICE performed a cost-effectiveness analysis using the Markov model (three-state simulation: progression-free survival, progressive disease, and death) to compare T-DM1 versus LAP+CAP. The ICER was £166,400/QALY, which is above the range considered for a treatment to be cost-effective for the British health system [29].

Another cost-effectiveness analysis conducted from the United States perspective also applied Markov models; the results showed that T-DM1 is not cost-effective compared to LAP+CAP [30]; the ICER was USD 183,828/QALY from the societal perspective and 220,385/QALY from

the payer's perspective. Nevertheless, treatment with T-DM1 may exhibit a better cost-effectiveness ratio compared to capecitabine alone.

Another study that applied an economic model to assess the impact of treatment for breast cancer with T-DM1 in the Spanish health system suggests that the drug did not exhibit a satisfactory cost-effectiveness ratio [31]. The authors observe that in their analysis, they used the import price of T-DM1, which needs to be reduced for the drug to achieve the acceptability threshold. The authors conclude that € 165,588.10/QALY should be necessary, given that according to the model used, a maximum of 1,218 patients/year could be treated by the Spanish health system [31].

The data accumulated to date indicate that T-DM1 is not the best treatment to be indicated for MBC. Although there is a slight increase in patient quality of life, from the perspective of the health system, its resources would not be optimised if patients with MBC and better odds of response to treatment with T-DM1 were included because this therapy is extremely expensive.

The results of the simulation are robust and prove to be coherent with reports in the specialised literature, such as the studies by NICE [29], Le *et al.* [30], and the Spanish national health system [31]. Some limitations warrant consideration, even though none of them is likely to influence the analysis to the point of leading to a considerable change in the results. The transition probabilities and utility scores were derived from studies conducted in other countries and therefore differ somewhat from the reality in Brazil. For instance, the cost of hospitalisation may be different for each individual woman, thus diverging from the values considered in the model used in the present study.

CONCLUSION

Because estimates for breast cancer suggest that it will increase over the next 20 y and that it is the type of cancer with the highest incidence among the Brazilian female population, it is a disease with a strong impact on society. In addition to its high mortality and incidence, the currently available treatments have a high cost and a negative influence on the lives of patients.

Within this context studies, improving the treatment of MBC and minimising the suffering of patients are crucial. Treatments with softer adverse effects and that induce more considerable clinical improvement are needed.

In the model developed in the present study, T-DM1 was not associated with a significant improvement in the survival of patients with MBC. The average survival time doubles when treatment with LAP+CAP is used. In addition, because the cost/QALY of T-DM1 was above the threshold of three times the per capita GDP recommended by the WHO, it cannot be considered cost-effective. Nevertheless, T-DM1 is the most effective strategy, according to the perspective adopted in the present study.

The models of treatment for MBC based on Markov chains have almost always used the same clinical trials as basic parameters; however, these studies show considerable internal variation. No model has analysed the use of capecitabine and lapatinib.

The main limitation of the present study is that previously noted by Mosegui *et al.* [32] in a simulation using TRA with two chemotherapy agents, that is, the need for an estimate of the response data at the end of treatment with the drugs tested. As an attempt to overcome this limitation, in the present study, a sensitivity analysis was performed, varying some parameters.

The probabilities for the transition between disease states, efficacies, and utility measures were taken from the international literature and may thus diverge, in absolute terms, from the Brazilian reality. One further factor likely to influence the response to treatment for MBC, and consequently alter the cost-effect relationship, is the prices set within the Brazilian drug market.

Studies conducted in Brazil using economic models to compare the targeted therapies could not be located; therefore, the present study is innovative.

In clinical studies, T-DM1 demonstrated pharmacological superiority over other agents used for the treatment of MBC. However, the price set to it is the one variable that determines its non-inclusion in the SUS and the health systems of other countries. In light of the scarcity of mathematical models that consider the survival of this population of patients, in addition to the lack of final data on the efficacy of some drugs used for the treatment of MBC, the number of clinical studies and economic analyses of this subject needs to increase.

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AUTHORS CONTRIBUTION

Cid M. de M. Vianna and Gabriela B. G. Mosegui are the principals' investigators of economic evaluation. Marcus Paulo da Silva Rodrigues and Talita Martins Alves da Costa are leading economic evaluation activities. Paula Medeiros do Valle led efforts to determine trastuzumab emtansine effectiveness. Gabriela B. G. Mosegui conceived the idea for this paper. Gabriela B. G. Mosegui, Marcus Paulo da S. Rodrigues and Talita M. A. Costa wrote the first draft of this manuscript with editing and proofreading from all other authors. All authors read and approved the final manuscript.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest concerning the content of the present study

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