

A cost-effectiveness analysis of Trastuzumab Emtansine versus Trastuzumab for the Adjuvant Treatment of Patients with Residual Invasive HER2 Positive Breast Cancer in Portugal

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1 - Background and Objectives:

– Breast cancer (BC) is the most common cancer and the leading cause of cancer death in women worldwide. [1] HER2 positive disease represents about 15 to 25% of all breast cancer cases. [2,3]

– In Portugal, according to data from the Registo Oncológico Nacional (RON), in 2010 there were 6.608 new cases of BC. It represented 14% of all cancer cases diagnosed in that year, being the most frequent malignancy.

– Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets HER2 containing humanized anti-HER2 immunoglobulin G1, trastuzumab, linked to the DM1 microtubule inhibitor (a maytansine derivative) through a stable thioether ligand of MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate).

– T-DM1 was compared directly to trastuzumab in the KATHERINE study [4], a phase III, multicenter, randomized clinical trial that aimed to investigate the efficacy and safety of T-DM1 against trastuzumab in patients with early stage HER2 positive BC. The aim of this study is to assess the cost-effectiveness of T-DM1 versus trastuzumab for the adjuvant treatment of patients with residual invasive HER2-positive BC after completion of preoperative systemic treatment in the Portuguese setting.

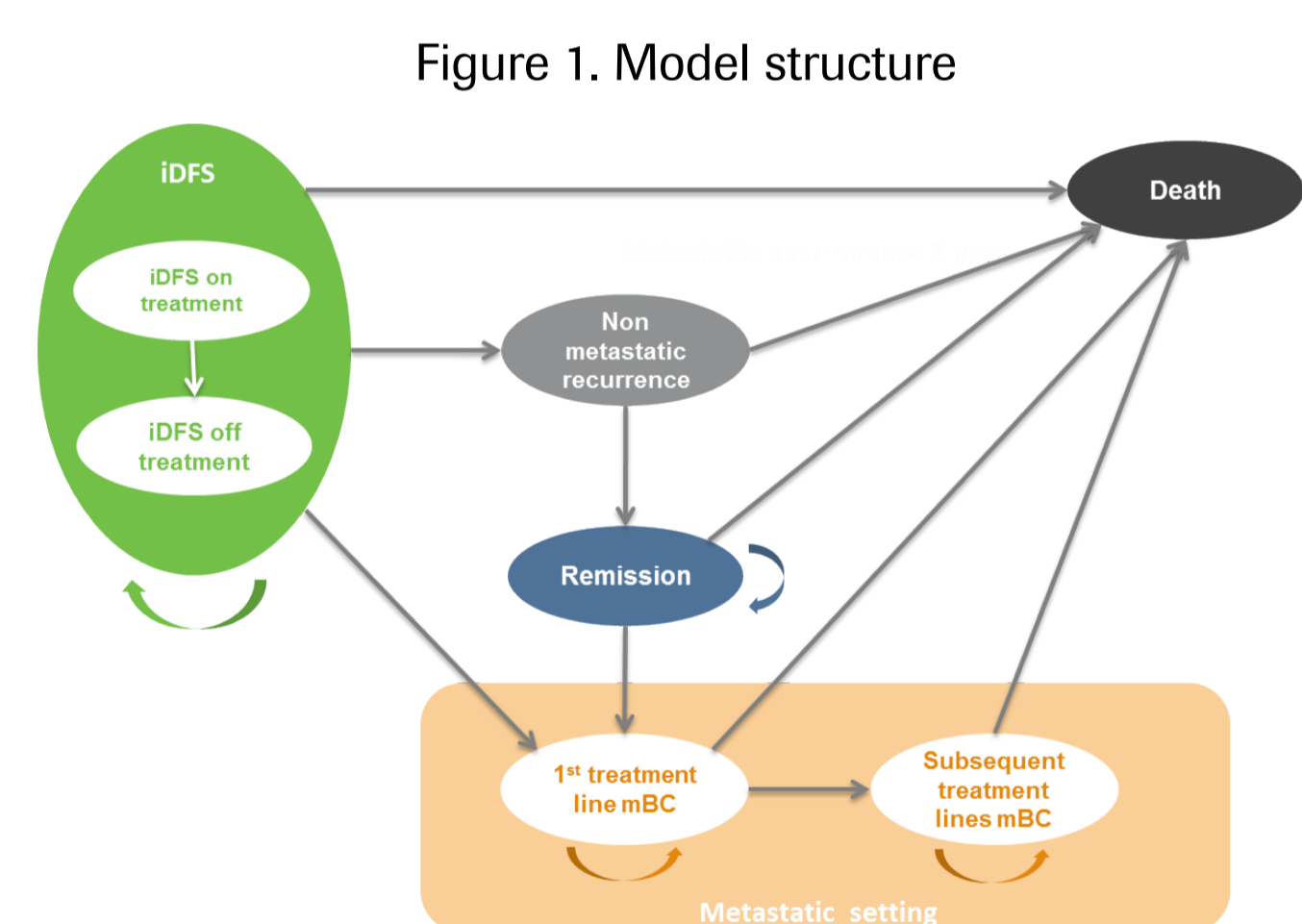
2 - Methods

Effectiveness Model:

– A Markov model was developed by Roche and MORSE Health Technology Assessment Group to estimate patients' pathway through six health stages: invasive disease-free survival (iDFS) (with distinction for patients on and off adjuvant treatment); non metastatic recurrence (includes locoregional recurrence and contralateral BC); remission from a non-metastatic recurrence; first line treatment in metastatic BC (mBC); subsequent lines of treatment in mBC; and death. (Figure 1)

– The model allows the estimation of incremental life years (LY), quality-adjusted life years (QALY) and costs associated with the use of T-DM1, compared to trastuzumab, in adjuvant treatment of cancer in adult patients with HER2 positive BC at an early stage, with residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant therapy directed to HER2 and based on taxane.

– The analysis was conducted from the Portuguese National Health Service perspective, assuming a 4% annual discount rate for costs and consequences.



iDFS, invasive disease-free survival; mBC, metastatic breast cancer.

Clinical data:

iDFS

– The probability of remaining in the iDFS health state was based on the KATHERINE study.[4] Separated parametric distributions were fitted to the Kaplan-Meier iDFS data to extrapolate it beyond the observation period. Log-logistic was the parametric curve with the best fit according to goodness-of-fit criteria (AIC and BIC).

– Patients who remain in iDFS state might achieve cure. The proportion of cured patients increases linearly with time, ranging from 0% at month 36 to 95% at month 120. The cure rate was based on the study by Takeuchi et.al. (2009). [5]

– The duration of T-DM1 incremental treatment effect was maintained for 7 years and then linearly decreases (to be null at 10 years).

– Mortality risk was based on the maximum between the clinical trial and the general population.

Non-metastatic recurrence and remission

– The split between metastatic recurrence and other types of recurrences is based on the observed data in the KATHERINE study.

– Patients who experienced a non-metastatic recurrence undergo one year of treatment, entering the remission afterwards.

– Mortality risk was based on the maximum between the clinical trial and the general population.

– Subsequent recurrences are treated as metastatic. The probability of subsequent recurrence is based on Hamilton et al. (2015). [6]

Early metastatic recurrence

– Every disease recurrence observed within 18 months after initiation of adjuvant therapy is considered a metastatic recurrence.

– Progression free survival and overall survival of patients with early metastatic recurrence is based on study EMILIA. [7]

Late metastatic recurrence

– The risk of disease progression and the risk of death is dependent on treatment regimens. Probabilities were derived from EMILIA, CLEOPATRA and M77001 trial data [7,8,9].

– Treatment regimens used in metastatic setting in Portugal were defined by the expert panel.

Adverse events

– Grade 3/4 treatment-related adverse events reported in the KATHERINE trial were considered in the model.

Utilities

– The quality-of-life data used in the model was collected in the KATHERINE clinical trial through the EuroQol – five dimensions, 3 levels (EQ-5D-3L). The algorithm based on the preferences of the Portuguese population was used to convert the EQ-5D-3L results into utilities. [10]

– For the metastatic context, pre- and post-progression utilities were based on data published by Lloyd et al. (2006). [11]

Table 1. Utility score per health state.

Health State	Mean value (SE)
iDFS – on treatment	0.700 (0.010)
iDFS – off treatment	0.710 (0.008)
Non-metastatic recurrence	0.700 (0.010)
Remission	0.710 (0.008)
1st metastatic line of treatment	0.765 (NA)
2nd metastatic line of treatment	0.508 (NA)

iDFS, invasive disease-free survival; NA, not available; SE, standard error.

Costs

– Treatment duration in both arms is modelled as observed in the KATHERINE study (time to off treatment data).

– Portuguese-specific disease management resource use was based on an expert panel and on Portuguese 2017 DRG microdata (ACSS, 2017).

– Resources were valued according to national legislation (Portaria nº 207/2017) and official drug cost databases (Infomed and ACSS Catalog).

– he average cost per health state is presented below:

Table 2. Monthly follow-up costs.

Health State	Monthly cost
iDFS 1-2 years	48 €
iDFS 3-5 years	32 €
iDFS +5 years	23 €
Remission	35 €
Non-metastatic recurrence	2.347 €
1st line treatment for early metastatic disease – T-DM1	1.698 €
1st line treatment for early metastatic disease – Trastuzumab	2.216 €
2nd line of treatment and later lines for early metastatic disease	1.660 €
1st line treatment for late metastatic disease	1.143 €
2nd line of treatment and later lines for late metastatic disease	1.802 €
Terminal state (one-off)	2.095 €

iDFS, invasive disease-free survival; T-DM1, Trastuzumab emtansine. One-off cost.

– The average cost per adverse event is presented below:

Table 3. Adverse event cost.

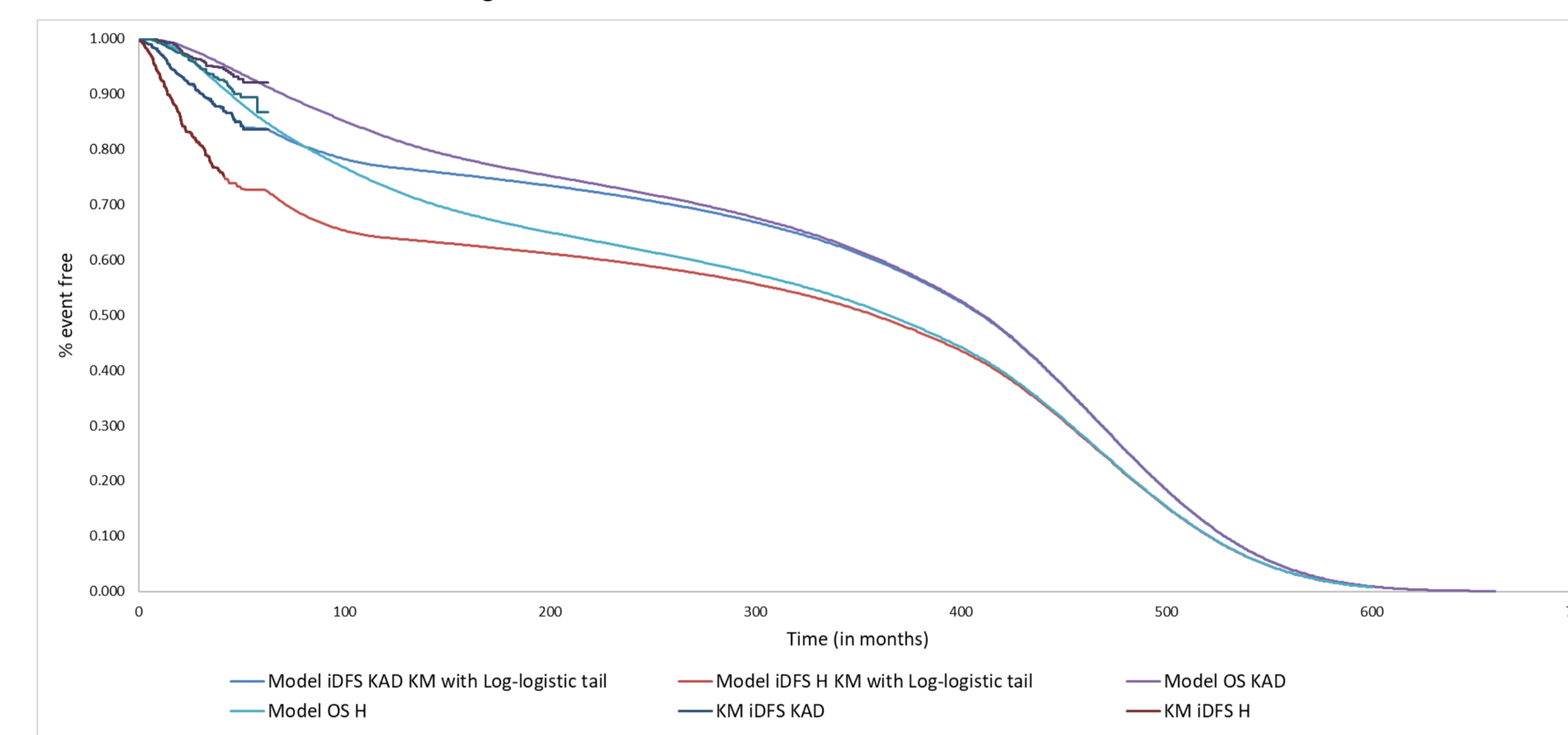
Adverse Event	Cost
Platelet count decrease	997 €
Peripheral sensory neuropathy	254 €
Neutrophil count decrease	656 €
Hypertension	53 €
Anaemia	868 €
Fatigue	231 €
Vomiting	3.830 €

3 - Results

Base case scenario:

– The modelled curves for each treatment arm are displayed in Figure 2.

Figure 2. Modelled curves on the base-case scenario.



– T-DM1 increases average life expectancy by 1.60 LY or 1.13 QALY. Economic analysis shows that the higher cost of the T-DM1 option is mainly due to higher treatment costs (Table 4). The estimated incremental cost-effectiveness ratios (ICER) are 11,828€/LY and 16,715€/QALY.

Table 4. Cost-effectiveness and cost-utility results for the base-case scenario.

	T-DM1	Trastuzumab	Incremental
LY	16.20	14.60	1.60
iDFS	15.46	13.23	2.22
Other health states	0.74	1.36	-0.62
QALY	11.28	10.15	1.13
iDFS	10.80	9.25	1.55
Other health states	0.48	0.90	-0.42
Costs (€)	60,492 €	41,534 €	18,958 €
Treatment	43,053 €	16,881 €	26,172 €
Treatment Administration	468 €	467 €	1 €
Follow up	16,525 €	23,631 €	-7,107 €
Adverse Events	94 €	1 €	93 €
End of life	353 €	554 €	-201 €
ICER (€/LY)		11,828	
ICUR (€/QALY)		16,715	

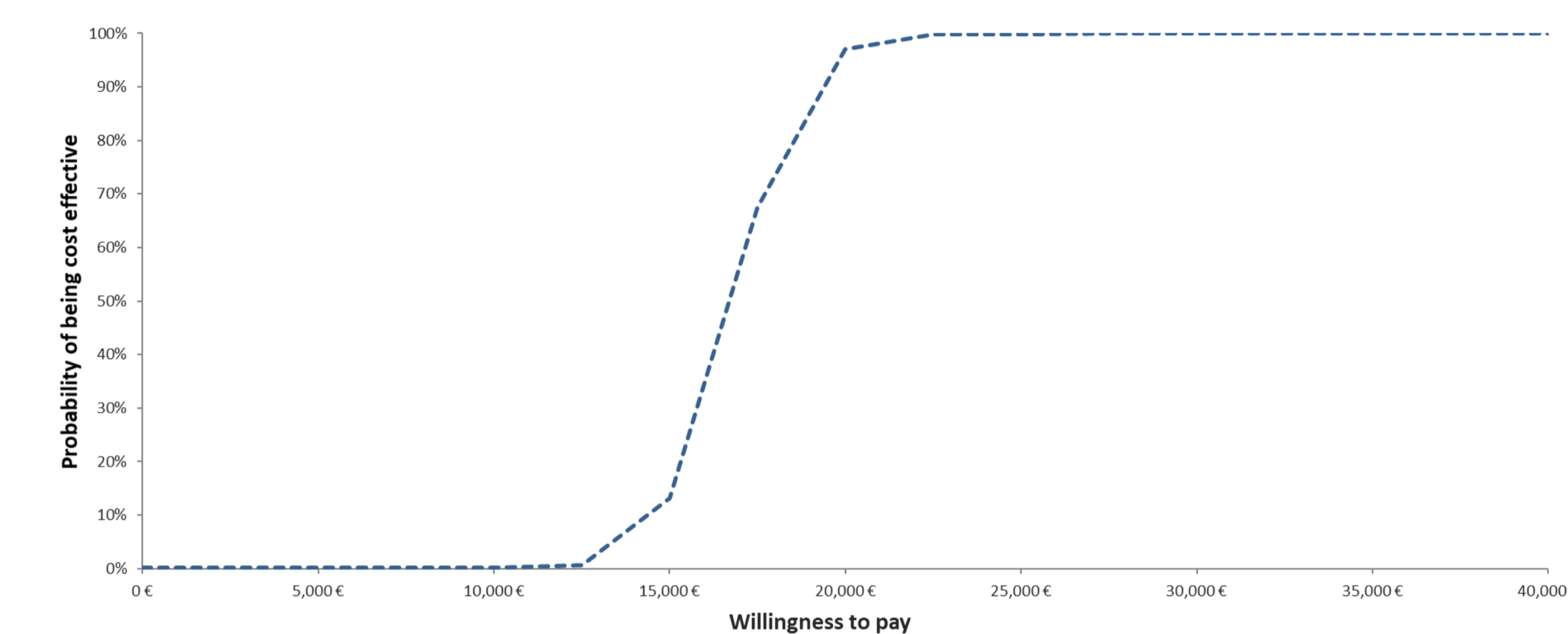
ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; iDFS, invasive disease-free survival, LY, life years; QALY, quality-adjusted life years; T-DM1, trastuzumab emtansine.

Sensitivity analysis

– Deterministic sensitivity analyses showed that the results are robust to most hypothesis and estimates, except for the options used to extrapolate iDFS and the cure rate assumed.

– Probabilistic sensitivity analysis also shows that results are robust, with ICURs ranging between 15,715€/QALY (25% percentile) and 17,839€/QALY (75% percentile).

Figure 3. Cost-effectiveness acceptability curve.



4 - Conclusions:

– Treatment with T-DM1 resulted in increased life expectancy and quality-adjusted life expectancy compared with trastuzumab.

– The cost-effectiveness model of T-DM1 versus trastuzumab for the adjuvant treatment of patients with invasive HER2 positive breast cancer was considered valid to support a reimbursement decision in the Portuguese setting.

– T-DM1 is recommended for the adjuvant treatment of patients with residual invasive HER2-positive BC after completion of preoperative systemic treatment in the Portuguese National Health Service.

5 - Acknowledgements:

– This study was funded by Roche Farmacêutica Química, Lda. Funding was independent of the study outcomes.

– We acknowledge Administração Central do Sistema de Saúde, IP (ACSS) for providing access to the Hospital Morbidity Database in 2017 (the national diagnostic-related-group database).

– The authors would also like to thank the participation of the experts: MD Ana Rita Sousa, Centro Hospitalar Universitário de Lisboa Norte, EPE; MD Gabriela Sousa, Instituto Português de Oncologia de Coimbra Francisco Gentil, EPE; MD Margarida Brito, Instituto Português de Oncologia de Lisboa Francisco Gentil and MD Noémia Afonso, Centro Hospitalar e Universitário do Porto.

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