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USING 'COSTS STATES' IN A SEMI-MARKOV MODEL TO ESTIMATE COST-EFFECTIVENESS WITH AN ILLUSTRATION FOR METASTATIC HER2+ BREAST CANCER IN THE CZECH REPUBLIC

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Using 'Costs States' in a Semi-Markov Model to Estimate Cost-Effectiveness with an Illustration for Metastatic HER2+ Breast Cancer in the Czech Republic

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Abstract:
This paper proposes an original method for assessing costs of medical treatment. It defines states in a semi-Markov model associated with specific costs of the treatment, and not with patients' health statuses. Costs assigning to these 'costs states' is more straightforward; moreover, it allows to estimate the periods separately when no treatment is administered. This method is applied to individuals' data drawn from the Czech clinical practice in the treatment of metastatic HER2+ breast cancer. The aim is to assess the cost-effectiveness of adding pertuzumab to the combination of trastuzumab+docetaxel within first-line therapy. The Kaplan-Meier estimates of survival functions were supplemented by the Cox proportional hazard model and the accelerated failure time model that both control for patients' characteristics. Based on the employed data, the addition of pertuzumab does not result in significantly longer patients' survival. Since the treatment is associated with higher costs, adding pertuzumab is not considered to be cost-effective; however, this could be due to relatively short patients' follow-up that is available at the moment.

JEL: C24, C41, C51, D61, I13, I18
Keywords: Cost-effectiveness, costs states in semi-Markov processes, Kaplan-Meier estimator, HER2+ metastatic breast cancer, pertuzumab, clinical data, Czech Republic

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1 Introduction

Employing Markov processes is a common practice in health-economic analyses, particularly in the cost-effectiveness studies of chronic diseases, e.g. cancer (Castelli *et al.*, 2007; Karnon, 2003; Zeng *et al.*, 2012), diabetes (Gillies *et al.*, 2008), hypertension (Lovibond *et al.*, 2011; Montgomery *et al.*, 2003), or HIV (Foucher *et al.*, 2005). Markov processes are used to estimate the time spent in the defined states that is further used both for the estimation of costs and benefits of the treatment. It is thus crucial to make an appropriate choice of the states based on the therapy in question and on the available data.

Our approach to defining the transition states differs from the approaches commonly seen in the literature. We propose using 'costs states' that are connected to specific phases of treatment, i.e. specific costs. These can be based on regularly administered medication or procedures depending on the studied medical condition. Whereas in other studies, we can see health states defined based on the health condition of the observed patients, such as progression-free, progression, and death in Paz-Ares *et al.* (2008) or analogously in Castelli *et al.* (2007); or based on ranges of clinical-tests values as in Foucher *et al.* (2007). However, costs assigning to these states might not be straightforward. One health state can comprise more treatment approaches, each with specific costs per unit of time.

There are two main advantages of 'costs states' beside the straightforward costs assigning. First, we can define a *no-medication* state, or else a *no-care* state. Our clinical data show that there are long periods when no medication is administered or other care provided, and costs are therefore minimal. These periods occur not only before death but between different types of treatments as well. Not taking into account these periods assuming the patient is treated the whole time instead systematically increases the incurred costs.

The other advantage of defining 'costs states' arises in the form of averting interval censoring, described for example, by Boruvka & Cook (2016). As the change in health status (e.g. disease progression) can usually be detected only during a check-up, the exact date of transition from one health state into another cannot be determined precisely, it is only known to be within a time interval between two check-ups. Analyses that consider disease progression as an ending/starting point of consecutive states should take this interval censoring into account; otherwise the time to actual disease progression is biased (Zeng *et al.*, 2015).

We demonstrate this approach here using individual Czech clinical data on metastatic HER2+ breast cancer treatment with pertuzumab and estimate its cost-effectiveness from the perspective of health-care payers, i.e. health insurance companies. Cost-effectiveness of this medication in the Czech Republic was previously estimated by the pharmaceutical company[1] using partially a different methodology from ours, i.e. health states survival without progression, disease progression, and death (Roche, 2017). Their study takes into account the periods when no medication is administered by looking at the average treatment duration in higher lines of treatment in the clinical register. This is a suitable method if the treatment duration is derived from a register with only non-censored patients or when the censored patients are adequately modelled. This modelling is already incorporated into our Markov process, so we avoid this step.

Another methodological advancement can be seen in Durkee *et al.* (2016) who analyse US data on patients treated with pertuzumab. They consider beside three health states similar to those above also the time before death spent in a hospice. This follows the results by Chastek *et al.* (2012) that patients in hospice have 'marginally lower' costs during the last weeks of life than those who died before entering a hospice. This exclusion from the time spent in the next-line-therapy state is in accordance with our notion of costs states; unfortunately, our data do not allow us to consider this state.[2]

As suggested, states defining is heavily dependent on available data. To model time spent in each of our 'costs states', we utilise a semi-Markov process. The advantage of such a process lies, especially in its flexibility. The hazard functions in a semi-Markov process can be modelled by any suitable distribution, and the distribution parameters can differ among transitions between pairs of states. Moreover, the future evolution depends not only on the present state but also on the holding time in the current state, which we found appropriate for our data (Castelli *et al.*, 2007; Foucher *et al.*, 2005).

[1]The manufacturer, F. Hoffmann-La Roche Ltd, presented their results to SÚKL, the foremost Czech executive authority in the area of reimbursement of pharmaceuticals while asking for reimbursement. Their study is based primarily on data from the international clinical trial CLEOPATRA (CLinical Evaluation Of Pertuzumab And TRAstuzumab); some data is taken from the Czech BREAST register as well.

[2]Costs per unit of time assigned by Durkee *et al.* (2016) to the states next-line-therapy and hospice were derived from previously published studies focusing on broad population with metastatic breast cancer, i.e. not necessarily HER2+. The costs for this broader population are expected to be lower, as the authors themselves admit, and they are also less likely to take into account the specificity of periods when no medication is administered.

This paper is structured as follows: a methodology for the costs and benefits estimation is outlined in Section 2. In Section 3, we describe data on metastatic HER2+ breast cancer and present our models. Then, in Section 4, we present our results, compare them with other studies and propose further methodological advancement.

2 Methodology

2.1 Semi-Markov process for costs estimation

Let $E = \{1, 2, ..., r\}$ be a finite discrete state space. For each subject, successive states $X = \{X_0, X_1, ..., X_n\}$ are observed, where X_0 is the initial state and X_n the final state after n transitions. The times $0 = T_0 < T_1 < ... < T_n$ are the consecutive entries into the states $X_0, X_1, ..., X_n \in E$, given that $X_p \neq X_{p+1}, \forall p \geq 0$ and X_p not persistent.
The random processes $(T, X) = \{(T_n, X_n) : n \geq 0\}$ are called semi-Markovian, if the distribution of waiting times $(T_n - T_{n-1})$ satisfies:

$$\begin{aligned} &P[(T_{n+1} - T_n) \leq t, X_{n+1} = j | T_n, X_n, T_{n-1}, X_{n-1}, ..., T_0, X_0] = \\ &= P[(T_{n+1} - T_n) \leq t, X_{n+1} = j | X_n] \end{aligned} \tag{1}$$

(Castelli *et al.*, 2007; Foucher *et al.*, 2005; Ibe, 2013).
Dependence of future evolution of the random process not only on the present state but also on the waiting time in the present state is apparent from Equation 1.[3]

The probability density function of the waiting time in state i before moving into state j is given by:

$$f_{ij}(t, \theta_{ij}) = \lim_{h \to 0^+} \frac{P[t < (T_{n+1} - T_n) < t + h | (T_{n+1} - T_n) \geq t, X_{n+1} = j, X_n = i]}{h}, \tag{2}$$

where θ_{ij} is a vector of parameters of the density probability function. Values of these parameters as well as their distribution can vary across the transitions.

[3] A transition into a future state of a pure Markov process is independent of the history of the process and depends only on the present state.

The corresponding survival function $S_{i.}(t)$ can be deduce from $f_{ij}(t)$:

$$S_{i.}(t) = 1 - P[(T_{n+1} - T_n) \leq t | X_n = i] = \sum_{j \in E} p_{ij}(1 - F_{ij}(t)), \tag{3}$$

where $p_{ij} = P[X_{n+1} = j | X_n = i]$ and $F_{ij}(t)$ is the cumulative distribution function of the waiting time in state i before moving into state j. The survival function in Equation 3 is defined for survival in state i, not for a specific transition between two given states (Castelli *et al.*, 2007; Foucher *et al.*, 2005).

Parameters of the chosen parametric distribution are estimated using the maximum likelihood method, separately for each possible transition.
The first $m^h - 1$ transitions of the subject h (from a sample of subjects $h = 1, 2, ..., N$) are observed. The subject h moves at times $T_1^h, T_2^h, ..., T_{m^h-1}^h$ and occupies successively the states $X_1^h, X_2^h, ..., X_{m^h-1}^h$, where $X_p^h \neq X_{p+1}^h, \forall p \geq 0$. At the last time of the follow-up, $T_{m^h}^h$, the subject h can either move into state $X_{m^h}^h$, or be censored in state $X_{m^h-1}^h$.
The resulting likelihood is a product of contributions of all the subjects' transitions:

$$L = \prod_h \left\{ \prod_{r=1}^{m^h} \left\{ \left\{ p_{X_{r-1}^h, X_r^h} f_{X_{r-1}^h, X_r^h}(T_r^h - T_{r-1}^h) \right\}^{\delta_r^h} \left\{ S_{X_{r-1}^h .}(T_r^h - T_{r-1}^h) \right\}^{1-\delta_r^h} \right\} \right\}, \tag{4}$$

where $\delta_r^h = 1$ if the transition r is observed and $\delta_r^h = 0$ when an observation is right-censored.

The different account of history in Markov and semi-Markov models can be used to differentiate which one should be employed. The Markov assumption can be verified by including a covariate representing history into the Cox proportional hazard model. A significant history covariate indicates a violation of the Markov assumption and thus use of a semi-Markov model (Williams *et al.*, 2017).

2.2 Survival functions for benefits estimation

The Kaplan-Meier estimate of the survival function is the most commonly used display of survival data that is particularly useful for a graphical comparison of several survival functions (Bland & Altman, 1998; Goel *et al.*, 2010; Jager *et al.*, 2008). This non-parametric approach is suitable for analyses consisting

of censored observations when only incomplete information about their survival times is available. We assume that censoring is independent of survival time and, additionally that the survival probabilities are independent of the time when the subjects were recruited in the study.
Total probability of survival $\hat{S}(t)$ until time t is calculated by multiplying all the probabilities of survival at all time intervals (t_{k-1}, t_k) preceding time t:

$$\hat{S}(t) = \prod_{t_k \leq t} \frac{n_k - d_k}{n_k}, \tag{5}$$

given that $n_k = n_{k-1} - d_{k-1} - c_{k-1}$, where n_k are those who are at risk prior to time t_k; d_{k-1} those who failed at time t_{k-1}; and c_{k-1} those censored between time t_{k-1} and t_k (Bland & Altman, 1998; Goel *et al.*, 2010; Jager *et al.*, 2008). The confidence interval around the Kaplan-Meier estimate can be computed according to the plain formula proposed by Greenwood *et al.* (1926).
To determine whether the estimates of the survival functions are statistically different the log-rank test is commonly used (Bland & Altman, 2004), however, in the case of (non-randomised) clinical data we have to account for possible differences in the compared groups of observations. The Cox proportional hazard model quantifies the effects of all the covariates $\mathbf{z}$ on the hazard rate $\lambda(t)$.

$$\lambda_i(t) = \lambda_0(t) e^{\mathbf{z}_i' \boldsymbol{\beta}} \tag{6}$$

Statistical significance of the regression coefficient β_i for the variable distinguishing the compared groups indicates ceteris paribus a difference between the survival curves.
The function $\lambda_0(t)$ is the baseline hazard. Satisfying the assumption developed by Cox (1972) that the hazard ratio for two observations i and i' $\lambda_i(t)/\lambda_{i'}(t)$ is independent of time t the method does not require specification of the baseline hazard (Johnson & Shih, 2012). This can be tested using Schoenfeld residuals according to Grambsch & Therneau (1994) and Schoenfeld (1982).
The accelerated failure time (AFT) model provides a parametric alternative to the semi-parametric Cox proportional hazard model. Both of these control for covariates; nevertheless, these covariates are assumed to induce different effects. Whereas in the Cox model the effect of a covariate is assumed to multiply the hazard by some constant, in the AFT model the effect of a covariate is assumed to stretch or shrink the survival curve along the time axis. This shift, determined by the 'acceleration factor' c in Equation 7, increases ($c > 1$)

or decreases ($c < 1$) the surviving time.

$$S_1(ct) = S_0(t), \tag{7}$$

$S_1(t)$ being the survival function of the studied group and $S_0(t)$ survival function of the control group, i.e. the baseline. The assumption of a constant effect of the variable distinguishing the two compared groups on the survival time has to hold. This can be checked by a Q-Q plot. The AFT model provides estimates of distribution parameters that can be further used for mean and median survival estimation (Bradburn *et al.*, 2003; Swindell, 2009).

3 Model for metastatic HER2+ breast cancer

Breast cancer is the most common cancer in women worldwide and the second most common overall.[4] In our data, we focus on metastatic HER2+ breast cancer, thus a very aggressive type of breast cancer that has spread and cannot be cured. Fortunately, modern treatment can be very effective in maximising the duration of a patient's quality time without disease-related adverse effects (Veronesi *et al.*, 2017).

In the past years, trastuzumab (distributed under the trademark Herceptin®, hereafter Herceptin) combined with chemotherapy (docetaxel) has been considered the most effective first-line treatment choice for HER2+ metastatic breast cancer. Recently, another biological therapy, pertuzumab (Perjeta®, hereafter Perjeta), suitable for first-line treatment of metastatic unresectable HER2+ breast cancer has been proposed as an addition to trastuzumab and chemotherapy.[5]

After disease progression on the first-line therapy, the majority of patients moves to the second (and then higher) line of treatment where other therapies targeting HER2+ cells are administered. Nowadays, these include Kadcyla®, hereafter Kadcyla, and Tyverb®/Tykerb®, hereafter Tyverb. Clinical practice in the Czech Republic includes Halaven®, hereafter Halaven, in subsequent treatment in higher lines as well (Cardoso *et al.*, 2017; Colomer *et al.*, 2018).

[4]Based on data from 2018, AICR (2018); WHO (2018). The most common cancer worldwide is lung cancer. Breast cancer is the fifth most common cause of cancer death.

[5]Perjeta has been given a status of a highly innovative medicinal product as it was not classified into any of the existing reference groups in the Czech Republic. It is a hospital-only pharmaceutical that only the comprehensive cancer centres are authorised to administer.

In this paper, we compare two treatment arms. First, where patients are treated in their first line with the combination pertuzumab+trastuzumab+ docetaxel (hereafter the pertuzumab arm). Second, where patients are treated in their first line with trastuzumab+docetaxel (hereafter the trastuzumab arm). The trastuzumab arm is the comparator in this study, or else the control group.
In both arms after the disease progression, patients can be treated successively with some of the medications suitable for subsequent lines of treatment, i.e. Kadcyla, Tyverb and/or Halaven.[6] Periods of various lengths when no anti-cancer medication is administered are frequent in the Czech clinical practice.

3.1 Patient's clinical data

Patients' clinical data were generated from the BREAST register by the Institute of Biostatistics and Analyses at the Faculty of Medicine of the Masaryk University, Czech Republic.[7] The pertuzumab-arm data set consists of 274 patients. These are all patients who were treated in the Czech Republic with pertuzumab within the first line of metastatic-breast-cancer palliative treatment.[8] The trastuzumab-arm data set consists of 254 patients; all patients who started first-line palliative treatment with trastuzumab after May 1, 2013.[9,10]
The following set of variables is available for all patients in both data sets: date of birth, sex,[11] health insurance company; date of diagnosis, cancer's grade, the existence of metastases*, metastases location*, cancer's stage* - all describing medical state at the time of diagnosis; underwent surgery and its type,

[6] And/or trastuzumab for the pertuzumab arm and pertuzumab for the trastuzumab arm.

[7] Generated on January 9, 2018.

[8] Fist administration of Perjeta in our data set was in May 2013. Perjeta was approved in the Czech Republic for a 24-months temporary reimbursement starting from February 1, 2014. This temporary reimbursement was prolonged by another 12-months period until February 1, 2017. Since February 1, 2018, it has been approved for permanent reimbursement. SÚKL, the State Institute for Drug Control, made this decision within the administrative proceeding SUKLS127371/2017. Only 12 patients started treatment before approval of pertuzumab's reimbursement or after its suspension on February 1, 2017. Their treatment records do not exhibit different characteristics.

[9] Nine patients experienced switch during the first-line treatment and were treated consecutively with both pertuzumab and trastuzumab as the primary medication. They were left only in the data set representing their initial medication. No patients were excluded from the data sets.

[10] More than 50% of patients in the trastuzumab arm started their treatment before approval of pertuzumab's reimbursement or after suspension of the reimbursement on February 1, 2017. Consequently, we can assume that trastuzumab treatment choice for these patients was based neither on their nor cancer's characteristics.

[11] The data set for trastuzumab arm comprises five men. They were not excluded from the analyses since their treatment records do not exhibit different characteristics from women.

underwent radiation; treatment details for each of the medications: Perjeta, Herceptin, Kadcyla, Halaven, Tyverb (line of therapy, starting/closing date of treatment, dosing, the reason for treatment cessation, date of progression, the best response to medication); date of the last check-up/last assessment of health status, patient's condition during the last check-up (alive with or without relapse, or dead).

Date of entry into the study is individual for each patient corresponding to the date of the first administration of pertuzumab/trastuzumab in the respective treatment arm. Date of exit from the study corresponds to the time of death or the date of the last check-up in the case of a censored observation.

As displayed in Table 1, the majority of patients in both data sets is subjected to end-of-study censoring since they have not reached the studied event of our survival analysis, i.e. death. Table 12 in Appendix compares the length of patients' follow-up; mean follow-up is 609 days in pertuzumab arm and 621 days in trastuzumab arm.

Table 1: Patients' living statuses at the end of the follow-up study

	pertuzumab arm		trastuzumab arm	
sample size	274	(100%)	254	(100%)
alive	204	(74.5%)	175	(68.9%)
dead	59	(21.5%)	63	(24.8%)
unknown	11	(4.0%)	16	(6.3%)

Source: Author's computation based on data from the BREAST register.
Note: Altogether, 27 patients are subjected to loss-to-follow-up censoring since the contact with them was lost.

3.2 Data on direct costs of treatment

We consider only the costs associated with the treatment of metastatic HER2+ breast cancer expended by health-care payers, i.e. health insurance companies, as it is required by SÚKL (2017).[12] These direct costs include mainly costs of medication, then medication administration and supplementary material.[13]

[12]In the Czech Republic, the majority of provided care is covered by statutory health insurance. The funds are raised from mandatory monthly payments, generally dependent on the income of policy-holders.

[13]Neither costs of check-ups, nor costs of adverse-effects treatment and end-of-life treatment are included as the data is unavailable on patients' level. These costs are relevant in a cost-effectiveness study, only if they differ across the treatment arms. If the length of treatment is shown to be significantly different across the arms, it results in a different average number of check-ups, thus different costs. We assume that the adverse-effects treat-

Medication costs per patient can be derived from the price of one pack of the applied medication, its dosing, and frequency of application. The Appendix summarises maximum reimbursement per pack of medication and standard dosing both of the primary therapy and the medication administered along with it, e.g. chemotherapy.[14] The period of medication application will be further discussed. Costs of administration include preparation of the infusion solution in an aseptic environment, cannulation of veins and infusion application (see Table 10 in Appendix).[15]
Average body weight (73.5 kg) and height (165.1 cm) of women aged 35-74 in the Czech Republic were used to compute the dosing of the medication where dosing is dependent on patient's anthropometric measurements.[16]

3.3 Modelling treatment costs

To estimate average costs per patient for the whole survival period in both treatment arms, we defined four states, each associated with the administration of a specific medication and therefore, with different costs.

3.3.1 Definition of states for the survival analysis

- State 1 - *first-line medication*:
  Patients who are in the first line of treatment administered the studied medication (Perjeta or Herceptin). These patients are alive without having experienced progression of the disease yet.[17]

ment costs per patient are similar across the arms and relatively small (Cortés *et al.*, 2013; Roche, 2017). End-of-life-treatment costs per patient are assumed not to be statistically different across the arms since no evidence supporting the contrary was found (Durkee *et al.*, 2016). Neither do we include costs associated with diagnosis or surgery, since these are both expended before entering into the study. Hospitalisation is generally not necessary for medication administration.

[14] As we compute cost-effectiveness from the health-care payers' perspective, we take the maximum reimbursement the health insurance companies are willing to pay the providers per one pack (as of October 1, 2018). We assume chemotherapy to be applied for the same period as the biological treatment; it is however often ceased before the biological treatment due to high toxicity.

[15] Additional material required for the preparation is bought by the comprehensive cancer centres in large quantities, so the unit prices are minimal and will not be included in our study.

[16] Author's computation based on data provided by the Institute of Health Information and Statistics of the Czech Republic, ÚZIS from the European Health Interview Survey 2014.

[17] **entry**: start of administration of the first-line medication; **exit**: the first from these: date of the final administration of the first-line medication increased by 20 days (a treatment cycle lasts 21 days; only six days were added to the date of the final administration when trastuzumab was administered weekly); 1 day before the start of administration of another

- State 2 - *no medication*:
  Patients who are alive but currently not administered Perjeta, Herceptin, Kadcyla, Halaven, nor Tyverb.[18]

- State 3 - *next-line medication*:
  Patients who are administered other than the first-line medication, i.e. Kadcyla, Halaven, or Tyverb, or Herceptin in case of pertuzumab arm, or Perjeta in case of trastuzumab arm.[19]

- State 4 - *death*:
  Patients who died either while being medicated or after terminating all medication.[20]

Each patient belongs to exactly one of these states at each time during the follow-up. All patients start in State 1, patients who are not in State 4 at the end of the follow-up are censored. All the transitions are displayed in transition diagrams in Figures 1 and 2. Patients can repeatedly move between States 2 and 3, so there is not a finite set of possible transition paths among the four states.

3.3.2 Mean time spent in each state using Markov processes

To estimate the mean time spent in each state, we apply Markov processes. First, the choice between a Markov and a semi-Markov model is made using a Cox proportional hazard model (Equation 8 below). The model assesses the effect of history. i.e. the time spent in State 1, on hazard rates of death after moving from State 1.
Then, we make an assumption about the distribution of the survival time in each state of the Markovian process, i.e. we use a Weibull distribution or an exponential distribution when the shape parameter is not different from 1.

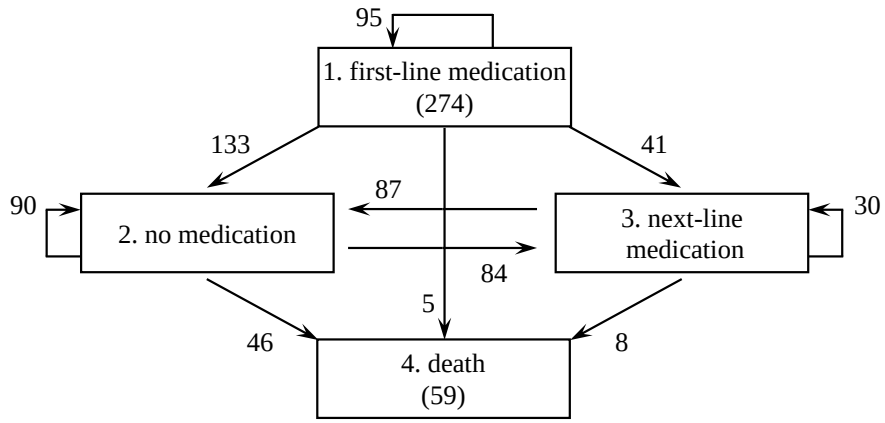
medication (as long as it is within 21 days from the final administration of the first-line medication); 1 day before the date of death (as long as it occurs within 21 days from the last administration of the first-line medication)

[18] **entry**: date of the final administration of a particular medication increased by 21 days, given that the following treatment did not start sooner nor did the death occur; **exit**: the first from these: 1 day before the start of administration of a next-line medication; 1 day before the date of death

[19] **entry**: start of administration of a next-line medication; **exit**: date of the final administration of the particular next-line medication increased by 20 days, given that the following treatment did not start sooner; 1 day before the date of death.
There were few cases of a switch within the first-line treatment between pertuzumab and trastuzumab. For our analysis, this switch was considered as a start of next-line treatment.

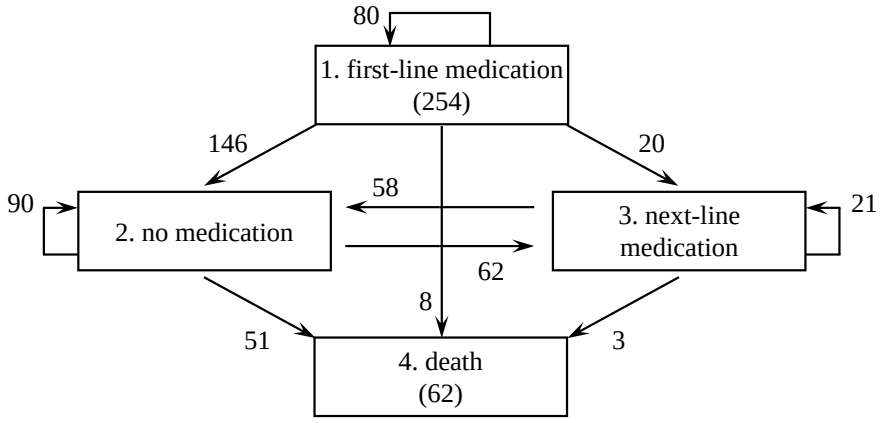
[20] **entry**: date of death

Figure 1: Transition diagram showing transitions of patients across states in pertuzumab arm



Source: Author's computation based on data from the BREAST register.
Note: The diagram displays the number of transitions, not necessarily the number of patients. Patients who are found to be in a state i at the end of their follow-up are marked by the arrow coming out of and into the state i. Bracket numbers represent the number of patients in the treatment arm (all beginning in State 1) and the number of patients who died during the study.

Figure 2: Transition diagram showing transitions of patients across states in trastuzumab arm



Source: See Figure 1.

Parameters' values are estimated for each transition separately. The estimated parameters are then plugged into the equations for the theoretical mean of the distributions to determine the mean length of staying in state i before transiting into state j.

The mean time spent in state i before transiting into any other state (not only state j) is computed as a weighted average of the mean times spent in state i

before a transition, with the corresponding number of transitions as weights. Finally, the mean time spent on average by each patient in the three states is computed. Mean length of staying in state i has to be multiplied by the number of entries into state i divided by the number of patients who entered state i.[21]

$$\begin{aligned}\lambda_i(t) = \lambda_0(t)exp\Big(&\beta_1(treatment\,arm)_i + \beta_2 age_i + \beta_3 metastases_i + \\ &+ \beta_4 surgery_i + \beta_5(grade = 1)_i + \beta_6(grade = 3)_i + \\ &+ \beta_7(time\,after\,diagnosis)_i + \beta_8(history)_i\Big)\end{aligned} \tag{8}$$

3.3.3 Mean costs expended per patient

Costs associated with the States 1 and 3 can be computed in the following steps. Costs of State 2 are disregarded as the patients are not administered any of the medication considered in States 1 and 3.

1. estimating costs associated with one treatment cycle for each state:
   (a) determining average medications' doses and the corresponding number (integer) of packs based on dosing in the data, using average body weight and height,[22]
   (b) determining shares of used medication, i.e. share of the two forms of Herceptin's administration, and shares of various medication in State 3,[23]
   (c) multiplying the average used number of medication packs by their prices and summing with the respective shares (weights),
   (d) determining administration costs (computed according to the shares),
2. multiplying costs for one treatment cycle by the estimated number of cycles (derived from the mean time of one patient spent in the state),

[21] According to the pertuzumab- and trastuzumab-arm data sets, patients who entered State 2 did it on average 1.31 and 1.26 times respectively. State 3 is entered on average 1.26 and 1.19 times respectively.

[22] The DuBois & DuBois formula (1916), was used to compute body surface area.

[23] The data set suggests approximately 55-45 division of patients treated with Herceptin 150 mg and Herceptin 600 mg. The mean survival is not statistically different for the two forms of Herceptin's administration. Thus, the mean survival is not statistically different for these groups either. The average costs of treatment in State 3 have to be estimated according to shares in Table 11 in Appendix.

3. multiplying costs per patient arising from staying in State 3 by the share of patients who arrive into the state,[24]

4. summing costs expended per patient across the states,

5. discounting future costs (computing present value using 3% discount rate).[25]

3.4 Modelling benefits of treatment

Benefits are estimated in the form of the median (mean) survival time that is adjusted for the quality of life,[26] i.e. in the form of quality-adjusted life years discounted by 3% rate. Overall patient's survival is defined as a period from the first administration of the first-line therapy to death.

To estimate overall survival functions in both treatment arms, the Kaplan-Meier estimator has to be supplemented by the Cox and the accelerated failure time models. Variables representing patients' characteristics at the time of diagnosis or the beginning of the first-line therapy are included to control for their possible effects on patient's survival.

3.4.1 Non-, semi- and parametric models for overall survival estimation

First, the Kaplan-Meier estimates of overall survival functions are derived for both treatment arms using Equation 5 and the equation $n_k = n_{k-1} - d_{k-1} - c_{k-1}$.[27] The significance of the difference in survival functions for each of the treatment arms is tested using the log-rank test with the null hypothesis of no difference between the two survival curves.

The Cox model displayed in Equation 9 below is estimated to verify the results

[24] According to the patients' treatment records data, only 61.1% and 43.1% of patients entered State 3 in the pertuzumab and trastuzumab arm respectively.

[25] According to SÚKL (2017), both costs and benefits are recommended to be discounted by the simple annual rate of 3%, i.e. by the factor $1/(1+0.03)^T$, starting at year $T = 0$.

[26] We use health-related quality of life coefficients of 0.637 for the non-progressive disease (in State 1) and 0.358 for progressive disease (State 2 and higher), we base it on Cortés *et al.* (2013); Hedden *et al.* (2012); Lidgren *et al.* (2007); Lloyd *et al.* (2006).

[27] t_k = k-th ordered time of death (in days), n_k = number of patients alive (in State 1, 2, or 3) prior to time t_k, d_{k-1} = number of patients who died (transited to State 4) at time t_{k-1}, c_{k-1} = number of patients alive with follow-up period from t_{k-1} to t_k

of the log-rank test (using the significance of β_1).[28]

$$\lambda_i(t) = \lambda_0(t)exp\Big(\beta_1(treatment\,arm)_i + \beta_2 age_i + \beta_3 metastases_i + \\ + \beta_4 surgery_i + \beta_5(grade = 1)_i + \beta_6(grade = 3)_i + \\ + \beta_7(time\,after\,diagnosis)_i\Big) \quad (9)$$

To gain the parametric mean and median survival, the AFT model with the same variables is estimated using the common survival distributions.[29] The distribution with the lowest value of the Akaike's information criterion is chosen for the estimation in each treatment arm.

4 Results and Discussion

4.1 Mean time spent in the defined states

The resulting mean time spent in the defined states is summarised in Table 2. It is computed as a weighted average of the mean waiting times before a transition from the given state, with the corresponding number of transitions as weights. The mean time spent in States 2 and 3 is additionally multiplied by the average number of entries into the state (see also Table 13 in Appendix).

Table 2: Estimated mean time spent in the defined states (in days)

state	pertuzumab arm	trastuzumab arm
1	**583**	**498**
2	**278**	**451**
3	**310**	**433**

Source: Author's computation based on data from the BREAST register.
Note: These are mean times per patient who entered the given state at least once. Not everyone entered States 2 or 3.

To estimate these mean times spent in States 1, 2, and 3 above, a semi-Markov model is found to be appropriate.[30] Employing the maximum likelihood method of the semi-Markov model, the parameters of Weibull/exponential

[28] Included variables: patients' age at the time of first administration of the first-line therapy, in years; the existence of metastases at the time of diagnosis; the existence of underwent surgery; cancer's grade; years elapsed between diagnosis and first administration of the first-line therapy - proxy indicator for pre-metastatic treatment.

[29] exponential, Weibull, Gompertz, log-logistic, log-normal, gamma

[30] The variable representing history is found to be strongly statistically significant in the Cox model in Equation 8 for at least some of the transitions.

distributions are found for each of the possible transitions (see Table 14 in Appendix).[31]

4.1.1 Mean time spent in State 1 (first-line medication)

We find a significant difference in time spent in State 1 between the two treatment arms. This leads us to the conclusion that the mean (median) times are significantly different as well.

The Kaplan-Meier estimates are displayed in Figure 4 in Appendix. According to the log-rank test's p-value = 0.053, the null hypothesis of no difference between the two survival curves could be rejected on a reasonable significance level (6% and higher). This is supported by the Cox model in Equation 9. The p-value = 0.048 of the variable distinguishing the treatment arms indicates significant differences between the survival curves and consequently between the means.

Empirical median survival in State 1 can be derived from the Kaplan-Meier curves. The median length of first-line pertuzumab administration is 15.4 months (463 days), the median length of first-line trastuzumab administration is 12.8 months (383 days).[32]

4.2 Costs: Mean direct costs expended per patient

The resulting total treatment costs per patient associated with both treatment arms are summarised in Table 3. Costs for one 21-days treatment cycle in the first-line medication state are 119,747 Kč and 42,425 Kč for the pertuzumab and trastuzumab arm respectively. The numbers of treatment cycles in States 1 and 3 are derived from Table 2.

The resulting costs of 4,395,229 Kč and 2,080,195 Kč in the pertuzumab and trastuzumab arm are discounted by the 3%-rate to 4,301,506 Kč and 2,004,304 Kč respectively.[33]

[31] The variables for patients' characteristics are not included in the model as it would be computationally more demanding. Moreover, age is the only variable with statistically different mean values; however, this variable is not statistically significant according to the Cox and the AFT models.

[32] This could be considered as a lower bound approximation of the progression-free survival since not all of the patients terminate the first-line treatment with pertuzumab/trastuzumab in reaction to disease progression. Still, this is a good approximation since the majority (around 70%) of patients does.

[33] Costs related to State 1 are expended at the beginning of the survival period. Costs related to State 3 are, for the purpose of discounting, assumed to be expended uniformly within the whole remaining survival.

Table 3: Costs of medication and its administration per patient

	pertuzumab arm	trastuzumab arm
first-line medication - medication	3,415,016 Kč	1,013,380 Kč
first-line medication - administration	31,157 Kč	21,947 Kč
next-line medication - medication	942,830 Kč	1,039,458 Kč
next-line medication - administration	6,225 Kč	5,409 Kč
TOTAL mean costs per patient	4,395,229 Kč	2,080,195 Kč

Source: Author's computation based on the presented data.
Note: All non-discounted costs. Costs associated with next-line medication are already multiplied by the shares of patients who on average, enter this state in the respective arms.

4.3 Benefits: Overall survival from first-line therapy to death

The overall survival is found not to be significantly different between the two treatment arms. This is based on the results of a log-rank test and the Cox and AFT models below. Since the median overall survivals are not statistically different, neither are the median quality-adjusted life years. The results are displayed in Table 4 in terms of days spent in full health.[34]

Table 4: Overall median survival in terms of days spent in full health

state (associated HRQoL)	pertuzumab arm	trastuzumab arm
1 (HRQoL = 0.637)	295	244
2+3 (HRQoL = 0.358)	404	88
TOTAL	699	332

Source: Author's computation based on the presented data.
Note: Non-discounted. No statistically significant difference.

Resulting quality-adjusted life years (QALYs) of 23.3 months and 11.1 months in the pertuzumab and trastuzumab arms were discounted by the 3%-rate to 23.0 months and 11.1 months, respectively.

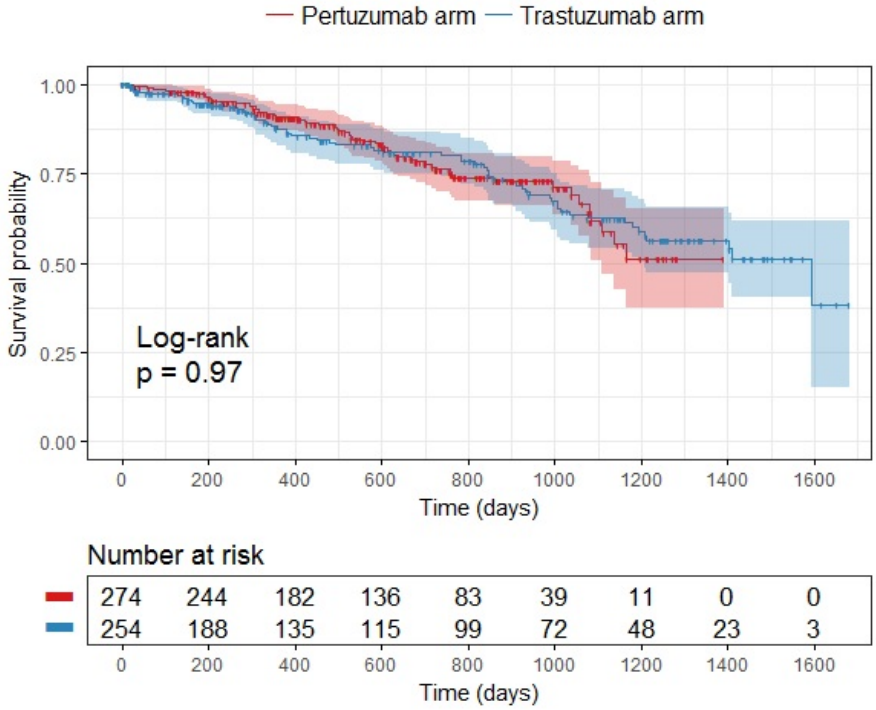
4.3.1 Testing statistical differences in overall survival

Kaplan-Meier estimates of the overall survival functions for both pertuzumab and trastuzumab arms are shown in Figure 3. The log-rank test's null hypothesis of no difference between the population survival curves cannot be rejected at any commonly used significance levels, p-value = 0.97. It can be concluded

[34]Time spent in States 2 and 3 was derived by subtracting time spent in State 1 (K-M estimation) from the median overall survival (AFT estimation).

that there is no statistically significant difference between the treatment arms. Consequently, median (mean) survival times cannot be considered significantly different either.

Figure 3: Kaplan-Meier estimates of overall survival of patients in pertuzumab and trastuzumab arms



Source: Author's creation based on data from the BREAST register using **R** packages by Therneau (2015) and Kassambara & Kosinski (2018).
Note: The tick marks indicate censoring events. Overall survival is defined as a period between the first administration of the first-line medication and death.

The empirical median overall survival has not been reached in the pertuzumab arm with $\hat{S} = 0.513$ being the last estimated survival probability.[35] In the trastuzumab arm, the empirical median overall survival is approximately 53.1 months (1,592 days).

Statistically significant differences between the survival functions are tested for various subsets of patients: according to the existence of metastases at the time of diagnosis, cancer's grade, underwent surgery, and length of patient's follow-up. The lowest p-value (0.19) is reached for a subset consisting only of patients

[35]The estimated survival function is constant at $\hat{S} = 0.513$ after 1,166 days (38.9 months) until 1,392 days (the longest follow-up in the pertuzumab arm). The confidence intervals for the median overall survival start at 1,110 and 1,206 days in pertuzumab and trastuzumab arms, respectively. The endpoints of these confidence intervals have not been reached in either of the arms yet.

who were followed up for at least 400 days since their first administration of the first-line medication.

The Kaplan-Meier estimator above does not account for patients' characteristics, so we test mean equality of these variables across the two treatment arms to see whether some of them are significantly different. Age is found to be the only significantly different variable, patients in the trastuzumab arm are on average older (59.2 in comparison to 55.7 years of age).
All the variables are included in the Cox model together with the variable distinguishing the two treatment arms to control for their possible effects on hazard rate (Table 15 in Appendix). The p-value for the variable identifying the arms reaches 0.9005, confirming the result of the log-rank test. No evidence against the proportionality assumption of the Cox model is found using the Schoenfeld residuals.
The same control variables are included in the accelerated failure model. When estimated for both arms together, the time ratio for the variable distinguishing the two treatment arms is 1.0495 indicating almost a 5% increase in survival time in the pertuzumab arm, adjusting for all the other covariates. However, this time ratio is not statistically different from 1 at the 5% significance level. Using the distribution parameters estimated by the model, we can compute the median and mean survival in both arms. However, these are not significantly different across the treatment arms either.
Based on the Akaike information criterion, the data are best fitted by Gompertz distribution (see Table 16 in Appendix). In the pertuzumab arm, the median and mean survivals are approximately 53.0 months (1,591 days) and 51.2 months (1,536 days) respectively. In the trastuzumab arm, the median and mean survivals are approximately 21.0 months (630 days) and 23.9 months (718 days) respectively.
The assumption of the AFT model of the constant effect of the variable distinguishing the two treatment arms on the survival time is checked.[36]

[36] A deviation from a line is visible for the shortest survivals. The relationship improves when both data sets are subsetted to consist only of patients who entered State 1 between 2014/02/01 and 2017/01/31 when both medications were reimbursed. When using only this subset in the AFT model, there is no statistically significant difference between pertuzumab and trastuzumab arm either.

4.4 Discussion

Our analysis finds the addition of pertuzumab to trastuzumab and chemotherapy not to significantly prolong overall survival of metastatic HER2+ breast cancer patients in the Czech Republic which is in contradiction to Roche (2017). However, it should be noted that our result is based on clinical data with relatively short follow-up periods and a high number of censored observations in comparison to the international CLEOPATRA clinical trial presented in Swain *et al.* (2015)[37] and used by Roche (2017). Baselga *et al.* (2012), in their study with shorter follow-up periods based on then ongoing CLEOPATRA did not find significant differences in overall survival either. The author is not aware of any cost-effectiveness studies based on data on Czech patients directly comparing the two treatment arms.[38]

Here, we would like to draw attention to some limitations of our data and the employed methodology related to 'costs states'. First, a challenge arises from loops between states with no medication and next-line medications. Since our data is heavily censored, we expect the number of entries into these states to be undervalued. Moreover, the share of patients who actually started administration of a next-line medication had to be estimated from a considerably reduced sample since around 33% of patients in both arms have not finished administration of the first-line medication.
Second, due to a relatively small number of patients who reached State 3 in our data set we could not have split it into four separate states (Herceptin/Perjeta in pertuzumab/trastuzumab arm, Kadcyla, Halaven, and Tyverb) which would better correspond to the notion of 'costs states'. This separation would make both our estimates of time spent with next-line treatment and costs per unit of time more precise as we would be able to model each medication individually. Third, we expect the average number of medication packs needed for one dose

[37]Swain *et al.* (2015) conducted their analysis on data with median patients' follow-up of 50 months. Their results exhibit significantly longer progression-free survival as well as the overall survival in the pertuzumab arm in comparison to the placebo arm. The median overall survival was found to be 56.5 months and 49.3 months in the pertuzumab and placebo arms, respectively. However, there are studies, such as Fleeman *et al.* (2015), that question the conclusions of Roche and offer an alternative inference building on the data from the CLEOPATRA trial.

[38]Benefit are presented in Studentova *et al.* (2018). The median overall survival is not evaluated since it has not been reached; the survival probability reported by Hejduk *et al.* (2016) and used by Studentova *et al.* (2018) was 86.6% (95% CI 75.7%-92.9%) after 18-months.

to be undervalued because of using average body weight and height instead of unavailable individual data. Owing to rounding up to integer packs, a small increase in body weight and height can result in a higher number of medication packs, and this cannot always be expected to be balanced by patients with lower-than-average weight.[39] The utilisation of average weight and height is seen in other studies as well, e.g. Roche (2017).

Moreover, there is an inbuilt limitation connected to the definition of 'costs states'. Health-related quality of life is commonly surveyed only for health states. Even though our 'costs states' largely overlap with health states, assigning these HRQoL values to our states is not accurate.

Further suggestions can be made for the methodology of cost-effectiveness analyses required by SÚKL (2017) for pharmaceuticals in the Czech Republic. The inclusion of indirect (social) costs not expended from public health budgets has been discussed in literature (Verguet *et al.*, 2016), as well as suggestions to cease discounting of benefits in analyses which take the perspective of public health budgets (Attema *et al.*, 2018).

[39]For example, a patient with only 2 kg of body weight above the average theoretically needs one extra pack of Herceptin 150 mg for each 3-weekly dose. At the same time, women would have to weight less than 50 kg (more than 20 kg below average body weight) to drop one medication pack for each dose.

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Appendix

Table 5: Prices and dosing summary for Perjeta treatment

			initial loading dose		maintenance dose	
	pack	price per pack	dose	regime	dose	regime
Perjeta	420 mg	77,322.40 Kč	840 mg	-	420 mg	3-weekly
Herceptin	150 mg	13,287.53 Kč	8 mg/kg	-	6 mg/kg	3-weekly
Docetaxel	20 mg	366.01 Kč	75 mg/m^2	-	75 mg/m^2	3-weekly

Source: Author's creation based on data from SÚKL (2018) and EMA (2018d).
Note: Perjeta 420MG INF CNC SOL 1X14ML, Herceptin 150MG INF PLV CSL 1, Docetaxel Accord 20MG/1ML INF CNC SOL 1X1ML.
The regime is irrelevant for the initial loading dose. Dosing of Herceptin and Docetaxel for each patient is determined depending on her body weight and height. It is assumed in this study that Docetaxel is administered during the whole treatment period with pertuzumab.
The average numbers of medication packs needed for one 21-days treatment cycle are: Perjeta 420 mg - 2/1 (initial/maintenance dose); Herceptin 150 mg - 4/3 (initial/maintenance dose); Herceptin 600 mg - 1; Docetaxel® 20 mg - 7.

Table 6: Prices and dosing summary for Herceptin treatment

			initial loading dose		maintenance dose	
	pack	price per pack	dose	regime	dose	regime
Herceptin	600 mg	39,862.70 Kč	600 mg	-	600 mg	3-weekly
Herceptin	150 mg	13,287.53 Kč	8 mg/kg	-	6 mg/kg	3-weekly
Herceptin	150 mg	13,287.53 Kč	4 mg/kg	-	2 mg/kg	weekly
Docetaxel	20 mg	366.01 Kč	75 mg/m^2	-	75 mg/m^2	3-weekly

Source: Author's creation based on data from SÚKL (2018) and EMA (2018b).
Note: Herceptin Herceptin 600MG INJ SOL 1X5ML, Herceptin 150MG INF PLV CSL 1, Docetaxel Accord 20MG/1ML INF CNC SOL 1X1ML.
The three possible regimes of Herceptin occurring in the data are listed. It is assumed in this study that all patients who were treated in one of the Herceptin's regimes were treated with Docetaxel, in the same regime and for the whole treatment period. Herceptin 150 mg is administered intravenously within ambulatory care, Herceptin 600 mg is administered subcutaneously.
The average numbers of medication packs needed for one 21-days treatment cycle are: Herceptin 150 mg - 4/3 (initial/maintenance dose); Herceptin 600 mg - 1; Docetaxel® 20 mg - 7.

Table 7: Prices and dosing summary for Kadcyla treatment

	pack	price per pack	dose	regime
Kadcyla	100 mg	46,787.85 Kč	3.6 mg/kg	3-weekly
Kadcyla	160 mg	74,349.65 Kč	3.6 mg/kg	3-weekly

Source: Author's creation based on data from SÚKL (2018) and EMA (2018c).
Note: Kadcyla 100MG INF PLV CSL 1, Kadcyla 160MG INF PLV CSL 1.
Kadcyla treatment is a monotherapy; no chemotherapy is administered with it.
The average number of medication packs needed for one 21-days treatment cycle is: Kadcyla 100 mg - 3.

Table 8: Prices and dosing summary for Halaven treatment

	pack	price per pack	dose	regime
Halaven	0.88 mg	10,006.21 Kč	1.23 mg/m^2	days 1 and 8 of every 21-day cycle

Source: Author's creation based on data from SÚKL (2018) and EMA (2018a).
Note: Halaven 0,44MG/ML INJ SOL 1X2ML.
Halaven treatment is a monotherapy.
The average number of medication packs needed for one 21-days treatment cycle is: Halaven 0.88 mg - 6.

Table 9: Prices and dosing summary for Tyverb treatment

	pack	price per pack	dose	regime
Tyverb	70 x 250 mg	26,525.83 Kč	5 x 250 mg	daily
Capecitabine	60 x 150 mg	553.36 Kč	4 x 500 mg/m^2	days 1-14 in 21-day cycle
Capecitabine	120 x 500 mg	3,689.11 Kč	4 x 500 mg/m^2	days 1-14 in 21-day cycle

Source: Author's creation based on data from SÚKL (2018) and EMA (2018e).
Note: Tyverb 250MG TBL FLM 70, Capecitabine 150MG TBL FLM 60X1 II, Capecitabine 500MG TBL FLM 120 II.
Capecitabine is administered by the patients themselves twice a day: 2000 mg/m^2/day. One dose of Capecitabine was rounded to 1800 mg (taken twice a day). It is assumed in this paper that all patients who were treated with Tyverb were treated with Capecitabine for the whole treatment period.
The average numbers of medication packs needed for one 21-days treatment cycle are: Tyverb 250 mg - 1.5; Capecitabine 150 mg+500 mg - 0.93+0.7.

Table 10: Costs of medication preparation and administration for one treatment cycle of one patient

	price per performance	number of performances for 1 treatment cycle			
		Perjeta	Herceptin	Kadcyla	Halaven
preparation in aseptic environment	477.46 Kč	1	1	1	1
application of anticancer therapy (ID 42520, 189 points)	194.67 Kč	3	2	1	1
cannulation of peripheral veins including infusion (ID 09220, 57 points)	58.71 Kč	1	1	1	1
TOTAL costs of 1 cycle		1,120.18 Kč	925.51 Kč	730.84 Kč	730.84 Kč

Source: Author's computation. ID, as well as the points assigned to the given performance, come from the Act 134/1998 Coll. (actualized on October 1, 2018). Value of 1 point was set at 1.03 Kč for 2018 according to the Decree 353/2017 of the Ministry. Charge for preparation in an aseptic environment is based on the Price Directive 1/2013/FAR of the Ministry. Number of performances for 1 treatment cycle results from the description of treatment procedures in EMA (2018a;b;c;d;e).
Note: All is administered intravenously within ambulatory care. The number of performances for one treatment cycle corresponds to the administration of the primary therapy in combination with other relevant treatment, e.g. chemotherapy. Tyverb treatment is not included since it is administered at home by patients themselves. Cannulation is charged twice for the initial dose of Perjeta. Costs of medication preparation and administration are the same for Herceptin 150 mg and Herceptin 600 mg (cannulation has to be performed to administer chemotherapy). Costs of administration are generally supposed to cover the expenses on the medical staff.

Table 11: Patients treated with next-line medication according to medication shares

	pertuzumab arm				trastuzumab arm			
	N	average duration (days)	average patient-days	%-share	N	average duration (days)	average patient-days	%-share
Perjeta	-	-	-	-	10	374	3,740	2.4%
Herceptin	29	171	4,959	22.3%	-	-	-	-
Kadcyla	79	176	13,904	62.6%	54	210	11,340	72.8%
Halaven	8	100	800	3.6%	8	132	1,056	6.8%
Tyverb	22	116	2,552	11.5%	17	165	2,805	18.0%

Source: Author's computation based on data from the BREAST register.
Note: N is the number of patients who were treated with the given medication. The average duration of treatment, according to medication, was computed only from a subset of patients who ended the particular treatment. In both arms, 73% of treatment periods have been terminated.
Perjeta (pertuzumab) is administered in the pertuzumab arm only in State 1. Herceptin (trastuzumab) is administered in the trastuzumab arm only in State 1.

Table 12: Duration of patients' follow-up (in days)

	Min	1st qrt	Median	Mean	3rd qrt	Max
pertuzumab arm	2	351	596	609	872	1392
trastuzumab arm	1	188	465	621	1069	1682

Source: Author's computation based on data from the BREAST register.

Table 13: Estimated mean length of one staying in each state before transiting

	pertuzumab arm			trastuzumab arm		
transition	N	mean (days)	weighted average (days)	N	mean (days)	weighted average (days)
$1 \to 2$	133	553		146	540	
$1 \to 3$	41	740	583	20	308	498
$1 \to 4$	5	93		8	194	
$2 \to 3$	84	63	212	62	467	358
$2 \to 4$	46	484		51	224	
$3 \to 2$	87	245	246	58	331	364
$3 \to 4$	8	257		3	1000	

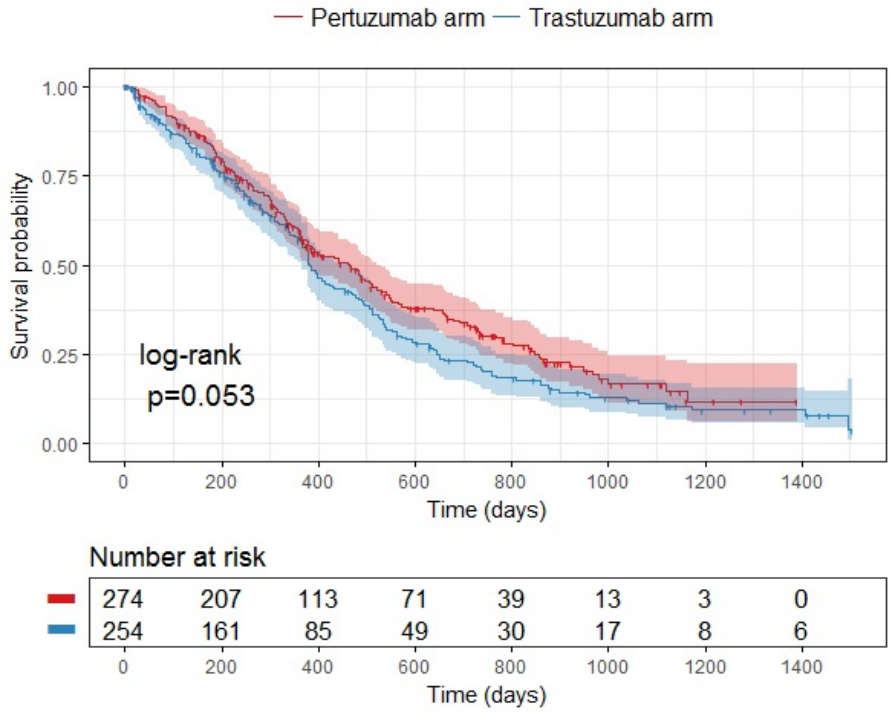
Source: Author's computation based on data from the BREAST register using an **R** package by Król & Saint-Pierre (2015) and Jackson (2016).
Note: N is the number of transitions between the two states. This is the mean length of one staying in the states, not mean time of one patient spent in these states. States 2 and 3 can be entered repeatedly.

Table 14: Weibull and exponential parameters derived from the semi-Markov model

	pertuzumab arm		trastuzumab arm	
transition	scale parameter	shape parameter	scale parameter	shape parameter
$1 \to 2$	598.800	1.306	580.874	1.256
$1 \to 3$	740.039		307.672	
$1 \to 4$	93.347		194.493	
$2 \to 3$	56.915	0.825	297.477	0.581
$2 \to 4$	483.737		190.954	0.763
$3 \to 2$	261.284	1.21	330.728	
$3 \to 4$	257.271		1000.000	

Source: Author's computation based on data from the BREAST register using **R** packages by Król & Saint-Pierre (2015).
Note: When the shape parameter was not statistically different from 1 in Weibull estimation, exponential distribution was fitted for the particular transition (only the scale parameter is listed).

Figure 4: Kaplan-Meier estimates of survival in State 1 (treatment with pertuzumab/trastuzumab in the respective arms)



Source: Author's creation based on data from the BREAST register using **R** packages by Therneau (2015) and Kassambara & Kosinski (2018).
Note: The tick marks indicate censoring events. This is not progression-free survival. It displays the length of treatment with the first-line medication. The table below the graph shows the numbers of patients who are at 'risk' of the event at time t, i.e. who are known to be still in State 1 at t. Only around 35% and 31% of patients are censored in State 1, in pertuzumab and trastuzumab arms respectively.

Table 15: Cox proportional hazard model

	coef	exp(coef)
treatment = pertuzumab	0.024	1.024
age (years)	−0.001	0.999
grade = 1	0.875*	2.399
grade = 3	0.449**	1.567
metastases	−0.681**	0.506
surgery	−0.541*	0.582
years after diagnosis	−0.108**	0.897
R^2	0.045	
LR Test	24.296*** (df = 7)	

*p<0.1; **p<0.05; ***p<0.01

Source: Author's computation based on data from the BREAST register using an **R** package by Therneau (2015).

Note: Hazard rate is the response variable. For example, grade-3 cancer (faster-growing and more-likely-to-spread cancer) increases the hazard by 56.7%, ceteris paribus. Consequently, having grade-3 cancer is associated with poorer survival.

Table 16: Accelerated failure time model following Gompertz distribution

	pertuzumab arm		trastuzumab arm	
	coef	exp(coef)	coef	exp(coef)
shape parameter	0.001520*		0.000796*	
rate parameter	0.000103*		0.000848*	
age (years)	0.019	1.019	−0.003	0.997
grade = 1	−0.413	0.662	1.443*	4.233
grade = 3	0.735*	2.085	0.151	1.164
metastases	−0.201	0.818	−1.149*	0.317
surgery	−0.281	0.755	−0.688	0.503
years after diagnosis	−0.134	0.875	−0.127*	0.881

*p<0.05

Source: Author's computation based on data from the BREAST register using an **R** package by Jackson (2016).

Note: Logarithm of survival time is the response variable.

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