Economic evaluation of Pembrolizumab combination therapy compared to standard of care chemotherapy as a first-line treatment for previously untreated, metastatic, non-squamous patients with metastatic non-small cell lung cancer (NSCLC)

A cost utility analysis in the Slovak perspective

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Abstract

Objective – The aim of this study is to assess the cost-effectiveness of pembrolizumab combination therapy and standard of care chemotherapy as a first-line treatment for previously untreated, metastatic, non-squamous, NSCLC patients from the Slovak healthcare system perspective.

Method - A cost-utility analysis with a partitioned survival model with cycle length of 3 weeks, time horizon of 20 years and discount rate of 5% for costs and health outcomes was constructed to assess the cost-effectiveness of pembrolizumab in combination vs chemotherapy alone. KEYNOTE-189 randomized controlled trial data was used as a foundation for extrapolating overall survival and progression free survival beyond the trial time period. Kaplan-Meier (K-M) probabilities were used for an initial period of the model, progression free survival was modeled by fitting the spline models into K-M data and overall survival was modeled by using the external data approach based on the annual mortality rates given by SEER. Costs of drug acquisition, drug administration, adverse events, disease management and terminal care were included in the model. Health outcomes measured in the model were quality-adjusted life years (QALYs) and life-years gained (LY gained).

Results - Pembrolizumab combination therapy resulted in longer expected life year gain and in QALYs gained compared to the treatment based on chemotherapy. Expected life-years were 2.91 for pembrolizumab therapy and 1.87 for chemotherapy alone. QALYs accumulated in the pembrolizumab arm were 2.09 QALYs and 1.28 QALYs in the chemotherapy arm. The total cost for the pembrolizumab in combination was € 118 093 and the total cost for the chemotherapy treatment was € 14 187. The Incremental Cost-Effectiveness Ratio of pembrolizumab combination therapy in comparison with chemotherapy was € 128 765 per QALY gained and € 99 786 per LY gained. For the willingness to pay threshold of € 37 000 the likelihood of pembrolizumab combination therapy being cost-effective was 0%.

Conclusion – The analyses provided evidence that pembrolizumab in combination is more effective, but also more costly than chemotherapy. From the health care perspective pembrolizumab combination therapy is not likely to be a cost-effective strategy in the Slovak Republic.

Keywords: metastatic NSCLC, cost-effectiveness, health economics, pembrolizumab, pemetrexed, chemotherapy, Slovakia

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Dominika Kantor

List of Abbreviations

CBA Cost-Benefit Analysis

CEA Cost-Effectiveness Analysis

CEAC Cost-Effectiveness Acceptability Curve

CUA Cost-Utility Analysis

EU European Union

EQ-5D Euroqol Five-Dimensions Questionnaire

EVPI Expected Value of Perfect Information

EVPPI Expected Value of Perfect Information for Parameters

GDP Gross Domestic Product

HRQoL Health-related quality of life

ICER Incremental Cost-Effectiveness Ratio

KM Kaplan-Meier

MOH Ministry of Health

NMB Net Monetary Benefit

NSCLC Non-Small Cell Lung Cancer

OS Overall Survival

PFS Progression Free Survival

QALY Quality-Adjusted Life Year

RCT Randomized Controlled Trial

RR Relative Risk

VOI Value of Information

WHO World Health Organization

WTP Willingness to Pay

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Declaration of Oath

Declaration in lieu of oath

With this declaration, the student confirms having written the thesis him or herself without any outside help. Others' thoughts and ideas are clearly marked as such and the master thesis has not been handed in during the course of another program and has not yet been published. Each master's thesis needs to contain such a declaration and has to be signed by the student in person. An electronic signature cannot be accepted. Exact formulation of this declaration:

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1. INTRODUCTION

Cancer is one of the leading causes of death in the world and one of the main contributors to the global economic burden. The majority of deaths caused by cancer take place in low and middle income countries. Lung cancer is the primary cause of cancer death worldwide, accounting for 1.76 million deaths in 2018 (1). Data from the Statistical Office of the Slovak Republic in 2017 showed that lung cancer was the fourth leading cause of death in the whole population (2227 deaths), the third leading cause of death in men (1603 deaths) and the eighth leading cause of death in women (624 deaths). The proportions of newly diagnosed patients with non-small cell lung cancer (NSCLC) by stage is according to the last publication from 2011: stage I 0.86%, stage II 4.93%, stage III 25.98%, stage IV 55.35%, and 3.88% in unknown (2).

NSCLC accounts for 80-85% of all lung cancers (3). Incidence and mortality of lung cancer are closely associated with varying trends in cigarette smoking and air quality. Age, genetics and occupation are secondary lung cancer risk factors (4).

In recent years, first-line treatment options for lung cancer in stage III and IV have successfully evolved. The success of genome-driven treatments with targeted agents offer new hope to NSCLC patients. Immunotherapy results in better overall survival and progression free survival compared to any platinum-based doublet with third generation agents (5). However, platinum-based chemotherapy continues to be the main treatment for lung cancer patients in the Slovak Republic, in spite of the fact that immunotherapy is getting greater results in improving results in treating cancer patients (6). An often-discussed problem is the accessibility of innovative treatments for Slovak patients. It might be challenging to implement an innovative drug into the Slovak health care system, due to its usually high price and Slovakia's low purchasing power. Also, lack of human and financial resources, makes wider use of managed entry agreements for pharmaceuticals between manufacturers and payers impossible (7).

Slovakia has so far categorized an immunotherapeutic drug called pembrolizumab only for patients with malignant melanoma. Unfortunately, patients suffering NSCLC do not have pembrolizumab among their treatment options. The objective of this analysis is to critically assess the cost-effectiveness of pembrolizumab in combination with platinum-pemetrexed

chemotherapy versus platinum-pemetrexed chemotherapy alone in the first-line treatment in previously untreated adults with metastatic NSCLC in the Slovak Republic.

2. BACKGROUND

2.1. Overview of Slovakia's health care system

Health care system in Slovakia is based on a compulsory health insurance scheme. Three health insurance companies (one public and two private) are operating in the country. A basic benefit package and universal population coverage is offered by the country. Insurance companies are competent to freely contract with providers, as well as individually negotiate prices and volumes. The Slovak Ministry of Health represents the main function in the governance of system and controls the activities of all health insurance companies (8). The health status of the Slovak population lags behind the EU average.

2.2. Lung Cancer

During the 20th century, lung cancer has become the world's leading cause of death in men and in some parts of the world even in women. The main reason for this incidence increase is proven growth in smoking. Even though tobacco use is decreasing in some developed countries, in the remaining parts of the world it is still evolving, causing an increase in the new lung cancer cases and deaths. Lung cancer deaths are expected to grow up to 3 million cases until 2035 worldwide (9).

Lung cancer is the uncontrolled growth of abnormal cells in lungs. This growth forms tumors and restricts the lung function. Lung cancer is traditionally classified into two main types: small cell lung carcinoma and non-small cell lung carcinoma (NSCLC). NSCLC is most frequent histological type accounting for 80-85% of lung cancers and is further categorized into squamous-cell carcinoma, adenocarcinoma, and large-cell carcinoma (10). Prognosis of lung cancer is poor with a 5-year overall survival rate around 18.6%, which can be explained by the fact that almost 50% of patients are diagnosed with the advanced stage of the disease (11).

2.3. NSCLC Treatment

Type, size, localization, stage of the lung cancer and the person's health status determine the treatment option of the patients with NSCLC. In order to treat NSCLC, treatments such as: surgery, radiation, chemotherapy, immunotherapy alone or in combination are available (12).

2.3.1. Current therapeutic options for first-line treatment of metastatic NSCLC

In Slovakia, there are no officially published treatment guidelines for NSCLC patients. In order to determine comparators for the analysis, we used a qualitative survey, which was conducted by experts of the NSCLC patient-management in the previous CEA for pembrolizumab monotherapy (13). In this survey experts assessed the proportions of treatment regimens in the first-line treatment for NSCLC patients in stage IV. According to the survey results, platinum doublets are most likely to be used (58%) as a treatment regimen in subjects with metastatic NSCLC. Other options are platinum doublets in combination with bevacizumab (14%), monotherapy with either vinorelbine, gemcitabine, pemetrexed or docetaxel (21%) and as a combination of cisplatin, pemetrexed and bevacizumab (6%) (60). One meta-analysis (14) has assessed the effect on survival of chemotherapy versus supportive care in advanced NSCLC. Results showed a significant benefit of chemotherapy. Chemotherapy reduced risk of death by 23%, improved 1-year survival by 9%, increased overall median survival by 1.5-months and improved quality of life. There have been very few improvements over the past twenty years and the efficacy of chemotherapy remains poor. Therefore, in order to combat NSCLC, there is an existing unmet medical need for implementing new treatments.

2.3.2. Immunotherapy in the treatment of metastatic NSCLC

Immunotherapy has recently become the breakthrough treatment in oncology and has revolutionized cancer therapy, which mainly can be attributed to the success of immune-checkpoint blockade. Recent research has provided better understanding of the host immune system and its interaction with tumors (15). It has led to the development of multiple treatments that are able to boost host immunity as a cure against tumor cells. As a result, immunotherapy nivolumab and pembrolizumab for the treatment of advanced NSCLC has recently been approved by the federal agency of the United States Food and Drug Administration (FDA).

Pembrolizumab, as a drug of interest, is a humanized monoclonal antibody that binds to programmed cell death receptor 1 (PD-1) and blocks its interaction with PD-L1 and PD-L2 ligands. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab develops T-cell responses, including anti-tumor responses, by hindering the binding of PD-1 to PD-L1 and PD-L2, which

are expressed by antigen-presenting cells and can be expressed by tumor cells or other cells in the tumor microenvironment (16).

Pembrolizumab has been approved both as a monotherapy and as a combination therapy combined with platinum-pemetrexed chemotherapy. As a first line monotherapy, pembrolizumab can only be used in patients with advanced or metastatic non-squamous NSCLC, with PD-L1 expression Tumor Proportion Score (TPS) ≥50% of tumor cells, with no epidermal growth factor receptor (EGFR) or anaplastic large-cell lymphoma kinase (ALK) (17). As a first-line treatment, pembrolizumab can be used in combination with platinum-pemetrexed chemotherapy to treat patients with metastatic non-squamous NSCLC who have not previously been treated for advanced disease, regardless of subjects' PD-L1 score, and in whom EGFR or ALK-directed therapy is not indicated (18).

3. THEORETICAL FRAMEWORK

3.1. Economic Evaluation

Health economics is a type of economics focused on efficacy, effectiveness and value in the delivery and consumption of health and healthcare. The scarcity of health care resources and budget constrains require priority setting between interventions, where cost-effectiveness is used to rank interventions.

The past decades, development of new technologies and treatments has been rapid and expansive. Improvements in biomedical research have stimulated the development of many effective medical treatments. However, their interpretation into practice has raised complex medical, economic, and social issues. In addition, patients' health needs are increasing and so is the ageing population. All these aspects are rising the urge for systematic methods of quantitative analysis (19).

Economic evaluation has become a widely used tool to inform decisions of policy makers. It results in answers to which alternative policies, services or interventions should be adopted into the country specific health care system and funded by its available resources. This comparative analysis identifies, measures and values all the available alternatives on costs and consequences (20). Unfortunately, it is not possible to implement all beneficial health technologies to all who need it or want it, due to the limited budgets. Therefore, economic evaluation is used to provide evidence for the most favorable option of health care interventions. The decision makers are then able to maximize populational health with the available resources.

3.1.1. Types of Economic Evaluation

Methods of the economic evaluation can be selected from the three most common forms, depending on the characteristics of the observed clinical problem; Cost-Effectiveness Analysis (CEA), Cost-Utility Analysis (CUA) and Cost-Benefit Analysis (CBA). All three types are similar with regard to costs, which are expressed in monetary units, but differ in terms of outcome measurement (20).

CEA measures the benefit in natural units, e.g. life-years gained or disability days saved. This type of analysis is acceptable for interventions targeting the same diseases and syndromes.

CUA presents outcomes in units of health. Health-related quality of life (HRQoL) and quality-adjusted life-years (QALYs) gained are essential features in the CUA. The QALY calculation is based on utilities obtained from patients filling in a generic utility-generating HRQoL questionnaire. Utilities are measured on a scale from zero to one, where zero is death and one is perfect health. Utilities are typically measured by some instrument which depends on different dimensions and different disease severity measures such as European Quality of Life Five-Dimensions questionnaire (EQ-5D) and direct measures such as time trade-off (TTO), standard gamble (SG) and visual analog scale (VAS) method (21). The change in utility value is then multiplied by the period of time (in years) to give the number of QALYs gained. The cost/QALY approach allows decision makers to make comparisons across various conditions and disease areas (20).

In CBA, both costs and effects are valued in monetary terms, which makes them directly comparable. This technique allows the intervention to be evaluated beyond the health sector, but it is morally questionable and difficult to measure the value of health outcomes in monetary units. Therefore, CBA is unlikely to be seen in the medical literature (22).

Once a type of the economic evaluation is chosen, the results of the analysis can be presented as an incremental cost-effectiveness ratio (ICER), which reflects how much extra must be paid for each additional health gained. ICER is calculated as the ratio of the incremental change in cost of the intervention (compared to the alternative) divided by the incremental change in health outcome of the intervention (20).

$$ICER = \frac{cost_A - cost_B}{effect_A - effect_B}$$

Where $cost_A$ is the cost of the intervention, $cost_B$ is the cost of the comparator, and $effect_A$ and $effect_B$ are the consequences of the intervention and the comparator, respectively.

The ICER results of the analysis are provided and interpreted in tables or plotted on the cost-effectiveness plane (C-E plane). A typical C-E plane has four quadrants. When a new

intervention has a negative incremental costs and a positive incremental effects, the ICER is negative and the intervention is therefore a *dominant* strategy. The opposite is a *dominated* strategy (positive incremental costs and negative incremental effects). However, the most common outcome for the new technologies is that they are clinically superior at increased costs. In order to determine which outcome option is cost-effective, the willingness to pay (WTP) threshold must be defined. All ICERs that fall under the willingness-to-pay threshold are cost-effective. All ratio outcomes are summarized in figure 1.

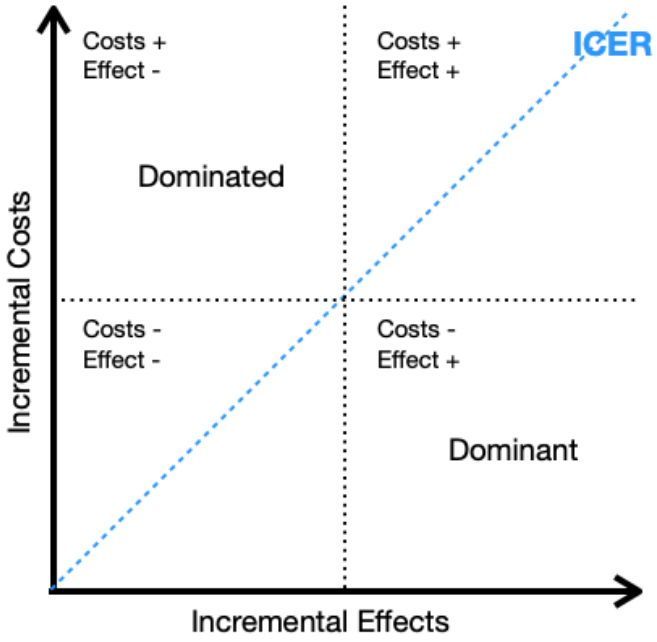

Figure 1. CE plane, incremental costs (y-axis) and incremental effects (x-axis)

3.1.2. The cost-effectiveness threshold

Decisions that concern investment in new interventions, require appropriate economic justification. The cost-effectiveness threshold (CE-threshold) sets the ceiling under which interventions are considered to be cost-effective and reflects the maximum value decision makers are willing to pay for health benefits. There is no such thing as single threshold determining acceptance of the CE ratio, it ranges greatly due to the countries' wealth and the features of the health care system (23). In Slovakia, the Ministry of Health defines two thresholds (λ1, λ2) in the reimbursement decision-making process. Lower (λ1) and upper (λ2) CE-thresholds are expressed as 35 and 41 times the average monthly salary, which is €32 000 and €37 000 per QALY (7). In comparison, the United Kingdom uses its standard threshold of

£20 000 – £30 000 per QALY (24), an informal threshold of €45 000 per QALY is commonly used in the US and the threshold in Norway varies according to severity from €30 000 to €90 000 per QALY (25).

3.1.3. Perspectives In Economic Evaluation

Cost identification is the stepping stone for every health economic evaluation. The choice of study perspective depends on the nature of healthcare system and is often specified by a decision-maker. The adopted perspective determines which costs are important and relevant for the analysis. There are three main types of perspectives, namely the *patient and family's perspective*, the *health care perspective* and *the societal perspective*. In the patient and family's perspective, relevant costs include all "out-of-pocket" expenses related to health care intervention (e.g. travelling expenses) and patient's cost of time. Costs included in the health care perspective are medication costs, material costs, hospitalization costs, costs of physicians, and all other costs which directly impact the budget of the health care sector. The societal perspective includes broad range of costs linked to all relevant stakeholders. This approach covers treatment and patient costs, and social opportunity costs, which are costs of consumed resources and productivity losses. Adaptation of this approach is very complex and not all costs can be captured due to practical reasons (20). This study is used to inform the Ministry of Health in Slovakia, and therefore the perspective of health care provider is adopted.

3.2. Decision Analytic Modelling

In the health economic evaluation, decision analytic modeling is a widely used analytical technique. The main objective of modeling is to gather all available evidence related to clinical and economic outcomes and structure them in the way that can be used to help inform a decision making process. More than one study is needed to make a well informed health care decision. Randomized controlled trials, as a center of efficacy testing, no longer provide sufficient amount of evidence needed for the economic evaluation. The modeling approach based on a single trial is limiting and might ignore the evidence from other sources. Therefore, a decision must be made based on the collection of the best available sources, such as other trials, meta-analysis, observational studies, clinical and outcome data and performance surveys (26).

3.2.1. Decision Models

The decision tree and *Markov model* are two main types of decision analytic models used in economic evaluation. In order to decide which model will be used, focus must be placed on the nature of the analysis. According to Drummond (20), the steps of building a correct decision model are as follows; to specify the decision problem, to define the boundaries of the model, to structure a decision model, to identify and combine input parameters, to handle uncertainty and heterogeneity, and to assess the value of additional information.

The decision tree is a simple form of decision model, and represents individuals following intervention pathways and their potential prognoses. The branches (pathways) are mutually exclusive series of incidents, and illustrate possible decisions and consequences. The model includes two types of nodes; a square decision node, which represents a decision point between given alternatives, and a circular chance node showing potential event alternatives, which illustrate therapy effects for the patient. The use of a decision tree helps to identify the most likely reachable strategy (20,22).

The Markov model is a transparent tool which helps to forecast different health states of patients, for example cancer progression. It has the ability to reflect time by each cycle, and shows how patients move from one health state to another. The Markov trace is central to the model and gives the basis for calculating important outputs such as costs, QALYs and life-years gained. Results from this model help to determine the potential health economic benefits. The Markov model allows decision analysis under uncertainty (20).

A partitioned survival analysis, often used in oncology, is used to track a theoretical cohort of subjects through time as they move between a set of exhaustive and mutually exclusive heath states. The number of subjects in any state is not dictated by transition probabilities, instead, the model estimates the fraction of a cohort in each state based on parametric survival equations, which are calculated from two separate survival estimations for overall survival (OS) and progression-free survival (PFS) (27).

3.2.2. Survival Analysis

Survival analysis is a statistical method for dealing with occurrences of events over time. It refers to the measurement of time between two events. Time-to-event data describe for example individuals followed from a time origin (onset of a disease) to an endpoint of interest (death due to a disease). These events must be captured in order to calculate the length of survival time (28). If $T \geq 0$ represents the time of failure (death), the survival function, proportion of subjects who are event-free at time *t* is defined as $S(t)=P(T \geq t)$. Survival curves start at point $S(0) =1$ and decline over time.

An important concept in survival analysis is the hazard function. This function is also known as the hazard rate. The hazard rate is the instantaneous probability of the event happening at time *t*, defined as: $h(t) = \lim_{\Delta t \to 0} \frac{p(t \leq T < t+\Delta t | T \geq t)}{\Delta t}$. It is related to how fast the survival function decreases over time. Thus, the lower the survival, the higher the hazard. It is important to understand that the hazard rate is an unobserved variable, yet it controls both the incidence and the timing of the events (29).

The key feature of the use of survival models is that they can handle censoring that often occurs in follow-up studies. Censoring is a form of missing data problem in which time-to event data are not observed. Right censoring appears when information about the survival time of individuals is incomplete due to some random cause (30). For example, patients could drop out of the study, die in an accident, or the study might have a cutoff point at which it finishes before individuals have experienced the event of interest.

3.2.2.1. Extrapolation

Unless survival data is complete, extrapolation techniques must be used in order to get estimates of the full survival benefit. There are number of methods available for performing extrapolation. It is often done using parametric models that smooth the Kaplan Meier curve (31), or by using more complex and flexible models (32). The different methods are likely to result in different survival estimates because of its varying functional forms. Therefore it is necessary to justify the particular extrapolation approach.

3.2.2.1.1. Non-parametric Method

Widely used non-parametric method (method without any mathematical form of the survival distribution assumed) for plotting survival functions is the Kaplan-Meier (KM) estimation (33). KM estimator provides an estimator of the survival function S(t). It is a step function with jumps at the observed times of event. These jumps depend on the number of the observed events at the event time and on the number of censored observations prior to that time. The KM estimator of the survival function S(t) is calculated as: $S(t) = \prod_{i=1}^{j}(1 - \frac{d_i}{n_i})$, where *d* is the number of deaths that occur at each of these time *t* and where *n* is the number of patients remaining in the cohort at each of these time *t*.

3.2.2.1.2. Parametric Survivor Models

Parametric survivor models are often used to incorporate survival data into health economic models. Parametric models are models where a particular form of the survival distribution is assumed. These parametric distributions are used in place of a normal distribution since the event times are positive numbers and have usually a skewed distribution, making the symmetric normal distribution not suitable for fitting the data closely. Some of the important models are exponential, Weibull, log logistic and Gompertz. Their survival functions and hazard rates, are summarized in Table 1.

Table 1. Survival Functions and Hazard Rates for Some Common Parametric Distributions (29)

Distribution	**Survival Function S(t)**	**Hazard Rate h(t)**	**Description**
Exponential $\lambda > 0$ $t \geq 0$	$\exp[-\lambda t]$	λ	λ - constant t - time
Weibull $\alpha, \lambda > 0$ $t \geq 0$	$\exp[-\lambda t^{\alpha}]$	$\alpha\lambda t^{\alpha-1}$	λ - scale α – shape
Log logistic $\alpha, \lambda > 0$ $t \geq 0$	$\frac{1}{1+\lambda t^{\alpha}}$	$\frac{\alpha t^{\alpha-1}\lambda}{1 + \lambda t^{\alpha}}$	λ - scale α - shape
Gompertz $\theta, \alpha > 0$ t ≥ 0	$\exp\left[\frac{\theta}{\alpha}(1 - e^{\alpha t})\right]$	$\theta e^{\alpha t}$	θ – shape λ - scale

The exponential distribution is the simplest parametric model as it contains a hazard function that is constant over time. In case of using the exponential distribution it is important to think whether the hazard is likely to remain constant over an entire lifetime, because the constant hazard rate seems too restrictive in health applications (31).

The Weibull distribution depends on two parameters – the shape parameter(α) and the scale parameter(λ), which make it flexible because of its ability to contain increasing, decreasing or constant hazard rates. If $\alpha > 1$ the hazard rate is increasing, if $\alpha < 1$ the hazard rate is decreasing and if $\alpha = 1$ the hazard rate is constant. If the Weibull distribution is to be used, the validity of monotonic hazards must be considered (31).

The log logistic distribution has a hazard function which can be non-monotonic with respect to time. It has two parameters – shape(α) and scale(λ). If $\alpha \leq 1$the denominator causes the hazard rate decrease monotonically with time, and if $\alpha > 1$the hazard rate increase initially to a maximum at time $[(\alpha - 1)/\lambda]^{\frac{1}{\alpha}}$ and then decreases to zero as time goes infinite. This model often results in long tails in the survivor function. The validity of non-monotonic hazards must be considered if the model is used (31,29).

The Gompertz distribution also depends on shape and scale parameters. It has a log-hazard function which is linear with respect to time and it can only be parameterized as a proportional hazards model. In order to apply this distribution, the validity of monotonic hazards must be considered (29,31).

According to the NICE guidelines (31), the choice of which distribution to use is done by comparing the model fit for a variety of different distributions. Visual examination is one of the most common "fitting" comparison methods in survival extrapolation. The comparison may be done graphically, using probability plots which will display how observed data follow an assumed parametric model. The best fit of parametric survival model is one which follows the Kaplan-Meier curve closely. A drawback of the visual inspection is that if censoring is heavy, observed data are clustered at certain points along the K-M curve and a parametric model might follow the K-M curve at one segment but not at another. Therefore, it is recommended to supplement this method with other tests. Akaike's Information Criterion (AIC) (34) and the Bayesian Information Criterion (BIC) (35) provide a useful statistical test of the relative fit of

alternative parametric models. These tests allow for numeric comparison, which may be less subjective than comparing graphs. For parametric models, the selected model must have a low AIC/BIC value to demonstrate its goodness-of-fit to the survival curve in the pre-extrapolation period (31). In addition, ex ante expectation, clinical plausibility and knowledge about the disease may also be important features to take into account when assessing the good fit of distributions.

3.2.2.1.3. Flexible Parametric Survival Models

Flexible parametric function is defined by piecewise polynomials and used to model non-linear distribution in survival analysis models. The points at which the polynomials connect are called knots. In practice, the most common splines are cubic splines. If the Weibull survival curve is defined as $S(t)= \exp[-\lambda t^{\alpha}]$ (λ-scale, α-shape) and converted to the log-cumulative hazard scale $\ln [H(t)] = \ln(\lambda) + \alpha \ln(t)$, this function is linear in ln(t). This linearity can be uninterrupted by using restricted cubic splines or ln(t). In order to obtain a proportional hazard model with β-log-hazard ratios and k-knots, covariates x can be introduced: $\ln \{H(t|x)\}= s(\ln(t)| \alpha, k0) + x\beta$. Because of the ability to fit proportional hazards in to the survival models, the smooth predictions of time-dependent effects(expected mortality) can be made, which makes this approach more flexible than standard parametric models. To increase the flexibility of the model, one needs to increase the number of knots (degrees of freedom) of the spline function (36).

3.2.3. Model uncertainty

Detecting uncertainty is an important feature of every decision-analytic model in economic evaluation. This is to make sure that model results are reliable and decision-makers can have confidence in them and be guided by them. The preferred approach to detect uncertainty in decision models is to run probabilistic sensitivity analysis (PSA) (37).

3.2.4. PSA

Values used in analytical models are estimates, e.g. resource use, utilities, parameters for OS and PFS curves. All these estimates are associated with uncertainty. PSA is made by defining probability distribution for each input variable, drawing random number for each distribution, calculating the ICER, and then repeating the whole process multiple times (e.g.1000 iterations).

Making a deterministic decision model probabilistic reflects the uncertainty of all input parameters and presents the extreme diversity of outcomes and their likelihood (22). PSA offers the information necessary to quantitatively measure if the evidence is satisfactory or if additional evidence is required.

The uncertainty results from PSA are graphically summarized by cost-effectiveness acceptability curve(CEAC). The CEAC illustrates a range of willingness to pay thresholds on horizontal axis and the likelihood of a treatment being cost-effective on vertical axis. The CEAC is a useful tool for decisionmakers to understand the uncertainty associated with making a decision about approval or rejection of an intervention (20).

In order to come up with different random values for selected parameters, different distributions that best fit the properties of parameters need to be used. Normal distribution is always a candidate for any parameter, but different distributions should be preferred to improve the quality of the model. Distribution choice is not arbitrary, but rather based on the logical constraints of parameters. They reflect the standard distributional assumptions employed to estimate confidence intervals (22). An example of distributions choice used for different parameters are presented in table 2.

Table 2 . Choice of distributions for parameters

Distribution	Type of parameters example	Comments
Beta	Utilities, probabilities, proportions	Beta distribution used for values constrained between 0 and 1
Gamma	Costs, days, patient data, resource use	Gamma distribution is used for values that cannot be negative
Dirichlet	Multinomial data	Dirichlet distribution is needed when probability is multivariate: e.g. K=3

The output from PSA contains estimates of expected costs, effects and net benefit based on the simulated parametric mean sample. Decision uncertainty is then presented as the probability that each health program has the highest expected net benefit (20).

Decisions based on current evidence could be uncertain and therefore incorrect and costly, in terms of health benefits and funds spent (22).Therefore, another important feature of the analysis is to know whether a decision can be made based on the current evidence or whether there is a need to collect additional data. This can be done by using VOI analysis, which is based on two measures; *the expected value of perfect information*(EVPI), *the expected value of perfect parameter information* (EVPPI).

The expected cost of uncertainty is the EVPI. EVPI represents the maximum value of additional evidence which is needed to determine model uncertainty. The EVPI is calculated as a difference in net monetary benefit (NMB) of decision with perfect information and NMB of decision with current information: EVPI=$E_\theta \, max_j NMB\,(j,\theta) - max_j \, E_\theta \, NMB\,(j,\theta)$, where j are alternatives and θ is vector of unknown parameters (37).

EVPPI on the other hand, is more specific. It detects which parameters are sensitive to the uncertainty the most, and represents the maximum value of additional evidence needed for that specific parameter. The EVPPI is calculated as a difference in NMB of decision with perfect information on parameter(s) φ and NMB of decision with current information: EVPPIφ = $E\varphi \; max_j \, E_{\varphi|\psi} \, NMB\,(j,\varphi,\psi) - max_j \, E_\theta \, NMB(j,\theta)$, where φ is the parameter of interest, ψ is other uncertainty and j are the alternatives (37).

3.2.5. Model Transparency and Validation (A report of the ISPOR)

Transparency and validation are two central methods needed in order to succeed in building a trustworthy and confident model a decision maker can rely on. The guidelines issued by the ISPOR—SMDM Task Force on Good Research Practices define recommendations for decision model development and its validation in the field of economic evaluation (38). These guidelines present standards for model quality, including validation and its categories, purpose and design of the model, and data inputs (39). Typically when talking about validation, 3 main types are described: face validity, internal validity and external validity. Face validity refers to the extent to which a model with its assumptions is constructed and used according to current evidence and to which a model measures the variable that it is supposed to measure. Evaluation of face validity can be done by external consultants and experts. Internal validity, called verification, refers to the degree to which the mathematical calculations correspond with the model specifications, and to which these calculations are performed correctly. This validation

helps to prevent computing errors. External validation compares the outcomes of a model to real event data. Events that have occurred in a clinical trial are simulated and examined to evaluate how well the model outcomes match (38).

4. METHODS

4.1. Target population

The target population in the model was based on the inclusion criteria in the KEYNOTE-189 trial. Patients included were 18 years or older (mean age 63 years); diagnosed with metastatic NSCLC; non-squamous cell histology; previously untreated; without sensitizing EGFR or ALK mutations, and with any PD-L1 expression.

4.2. Interventions

Patients in KEYNOTE-189 trial were randomized to first line treatment. The intervention group was treated with pembrolizumab + cisplatin/carboplatin + pemetrexed, while the comparator group was treated with a regimen of cisplatin/carboplatin + pemetrexed. In the rest of the thesis I will refer to the intervention as pembrolizumab and to the comparator as chemotherapy. Both treatment arms were followed by pemetrexed maintenance therapy. All patients received pre-medications to reduce toxicity and incidence of skin reaction: folic acid, vitamin B12 supplements and corticosteroids (40). One cycle of treatment was three weeks.

Pembrolizumab arm:

- Pembrolizumab: 200mg once per cycle, total duration - 35 cycles (24months)
- Carboplatin/Cisplatin: once per cycle, for up to 4 cycles
- Pemetrexed: 500mg/m2 once per cycle, for up to 4 cycles, followed by pemetrexed maintenance therapy up to 35 cycles

vs.

Chemotherapy arm:

- Carboplatin/Cisplatin: once per cycle, for up to 4 cycles
- Pemetrexed: 500mg/m2 once per cycle, for up to 4 cycles, followed by pemetrexed maintenance therapy up to 35 cycles

Both treatments (pembrolizumab and chemotherapy) and pemetrexed maintenance therapy were continued to the maximum number of cycles or until disease progression. As observed in

the clinical trial, those patients who stopped the 1st line treatment could switch to 2nd line treatment (docetaxel).

4.3. Model Structure

To evaluate the cost-effectiveness of pembrolizumab compared to the chemotherapy, a cost-utility analysis was chosen. The results of the analysis are presented in the form of life years, QALYs, costs and ICER.

A partitioned survival model was developed in Microsoft Excel and used to assess the incremental benefits and costs associated with each regimen in the target population. The cohort simulation model was constructed with three mutually exclusive health states: (1) progression free health state (PF) defined as time from the start of regimen use to the progression or death, whichever occurs first; (2) progression disease health state (PD) defined as a time after the progression; (3) death, see Figure 2. The cycle length of the model was 3 weeks. All patients started in the PF health state. After the end of each cycle, patients who were PF could stay in PF, progress to the PD state, or die. Patients in the PD state could either remain in PD or die after each cycle. Progressed patients in PD state were not able to enter the PF health state again.

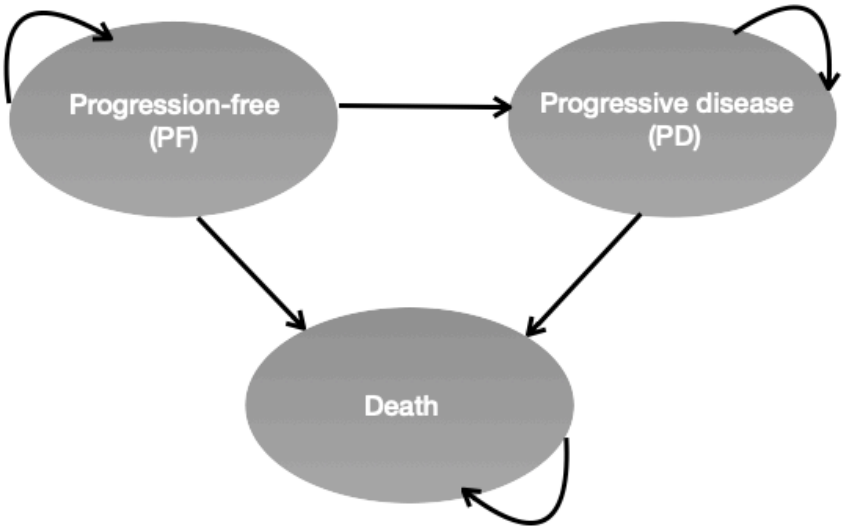

Figure 2. Model structure for cohort simulation model health outcomes

The proportions of patients in each cycle and in each health state were calculated using patient proportions in overall survival and in progression free survival, see Figure 3. The calculations for each cycle *t* were estimated based on the following equations:

$PFS_t = PFS_t * cohort$
$PD_t = (OS_t – PFS_t) * cohort$
$Dead_t = (1 – OS_t) * cohort$

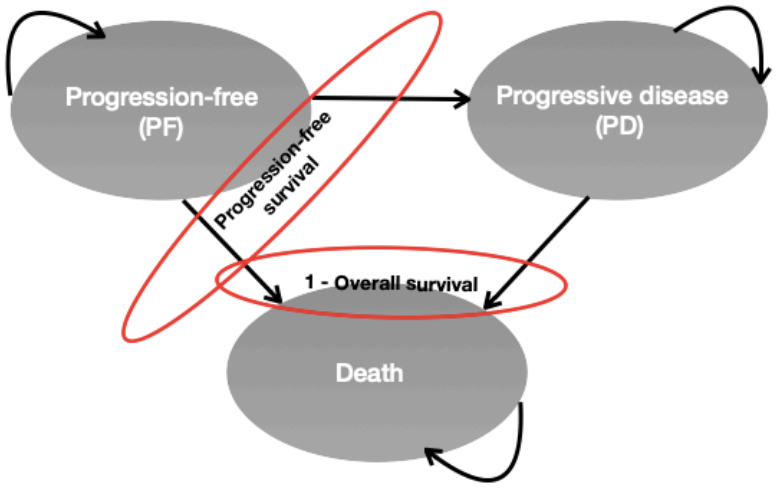

Figure 3. The cycle calculation displayed in the model structure

4.4. Time horizon

According to Briggs (22), the time horizon should be long enough to reflect all important differences in costs and outcomes between the compared treatments. A lifetime time horizon is required when the alternative technology leads to differences in survival (41). Given the chronic nature of the metastatic NSCLC disease the time horizon was set to 20 years, which represents a lifetime horizon for the patients. To reflect the short life expectancy of patients with metastatic NSCLC, scenario analyses were conducted to explore the effect of shorter time horizon (5 and 10 years).

4.5. Perspective

The setting of the analysis is from the Slovak Republic. The analysis was conducted from the perspective of a health care payer, perspective of health insurance companies, as required in the Slovak methodological guidelines for economic evaluation (42). The model therefore

included only direct medical costs such as treatment costs (medicine costs, administration and monitoring), the costs of managing the disease, as well as the costs of managing the adverse events with grade 3+ caused by the treatment. Societal costs were excluded from the analysis. The results of the analysis (costs and health outcomes) were discounted at a discount rate of 5% in accordance with methodological requirements in Slovakia (42). The impact of varying discount rates according to different countries are presented later in scenario analysis.

4.6. Outcomes

The primary outcome of the model was incremental cost per QALY gained. We used the ICER to evaluate the cost-effectiveness of pembrolizumab compared to chemotherapy. We performed a cost-utility analysis (CUA) as we had QALYs as the outcome. QALYs were required in this type of analysis because treatment was likely to affect both the quality of life and the length of life. Another outcome of the model was a PSA. This was also used to estimate incremental net monetary benefits (NMB), which were used to decide whether the intervention is or is not cost-effective. Cost-effectiveness probability was then calculated from the proportions of NMBs and illustrated by using the cost-effectiveness acceptability curve (CEAC) (20).

4.7. Data inputs

To inform the model in this analysis, we have done several structural literature searches to find the input parameters. The most commonly used search engines were health and medical journals such as: PubMed, Web of Science and Science Direct. Typical search words were: non-small cell lung cancer, chemotherapy, immunotherapy and pembrolizumab.

4.7.1. Clinical Parameters

Clinical parameters as cancer mortality and disease progression rate applied in the model were derived from the KEYNOTE-189 trial's publication presenting patient-level data (43) and then digitized by using WebPlotDigitizer (44).

As an initial approach, parametric models were fitted into Kaplan Meier OS and PFS curves for both treatment arms. Data beyond the trial time horizon were extrapolated by parametric

functions. Models chosen to incorporate monotonic and non-monotonic hazards were the Weibull, the exponential, the lognormal, the log-logistic and the Gompertz distributions. The fitting of most preferred survival curve was carried out in line with the NICE guidelines (31). The most suitable parametric function was chosen based on the lowest values of the statistical tests AIC and BIC combined with visual inspection. Finally, the clinical plausibility of the extrapolated results was taken into account in the final model distribution selection. Based on these "fitting" methods we had to reject the use of parametric distributions in both overall and progression free survival. To test the impact of different parametric distributions a structural analysis was performed.

4.7.2. Progression Free Survival

For progression free survival, the KM probabilities form KEYNOTE-189 trial were used directly until week 39 in the pembrolizumab arm and week 21 for the chemotherapy arm, with parametric functions fitted thereafter. This was because of the first imagining assessments were performed at week 6, which resulted in PFS drop between week 6 and 7. The specific cut-off points were identified by the Chow test (45) in a previous analysis (46). Following the statistical criteria for the best parametric fit, the log normal distribution was chosen for both treatment arms, but did not provide a good visual fit to the observed KM data for the PFS outcomes. Progression-free survival based on the parametric approach is shown in Figure 4 for the pembrolizumab arm and in Figure 5 for the chemotherapy arm.

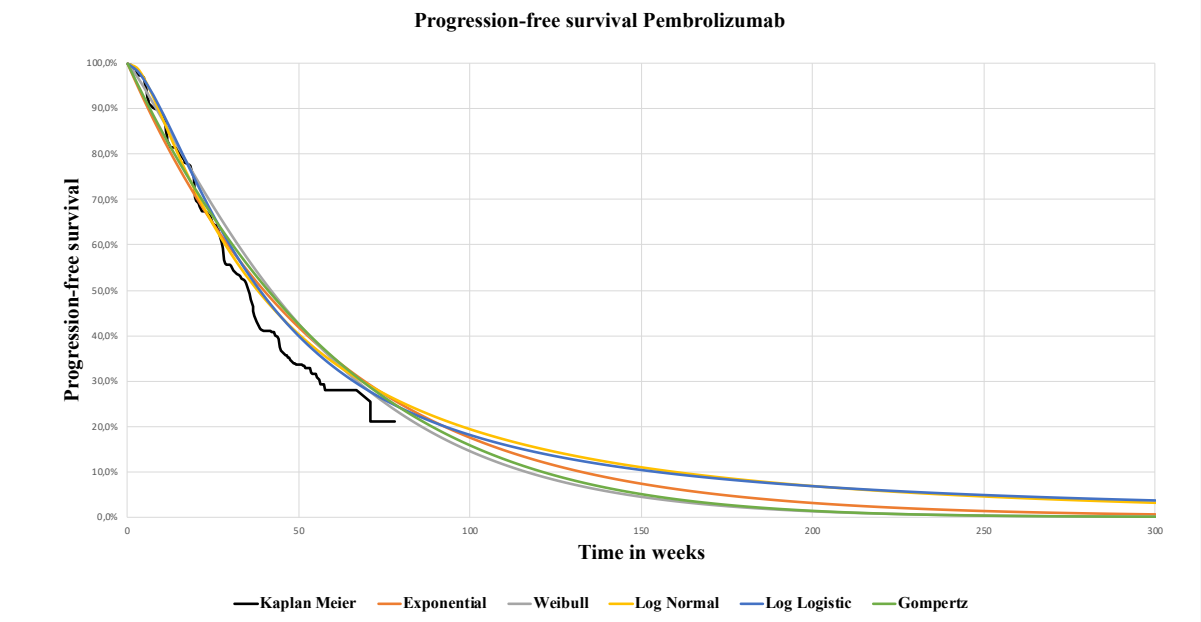

Figure 4. Progression-free survival in the pembrolizumab arm according to different parametric survival specifications

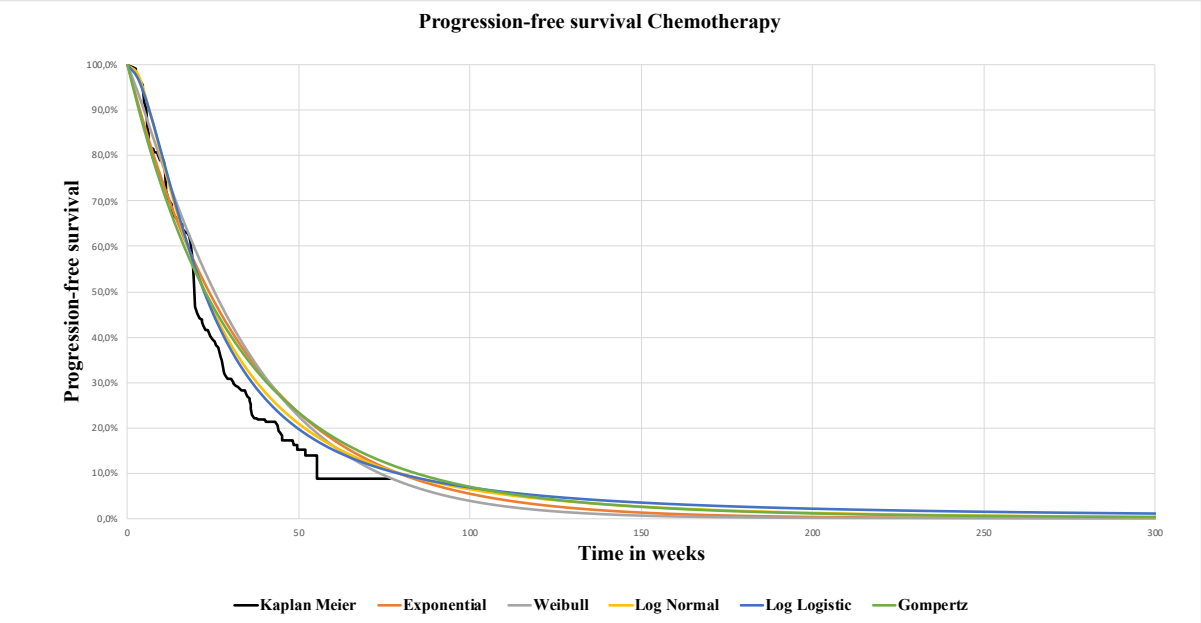

Figure 5. Progression-free survival in the chemotherapy arm according to different parametric survival specifications

As an alternative, flexible parametric models, known as a spline models by Royston and Parmar (47), were applied to extrapolate data beyond the trial period (Figure 6.) with the use of a statistical software *STATA15* (48) and command *Stpm2*. This command uses restricted cubic splines and allows the fitting of flexible parametric models and data postestimation. To model time-dependent effects of the treatments used 5 knots. Stata output (AIC, BIC, coefficients and knots) for both treatment arms is presented in Table 3.

Table 3. STATA progression free survival output of spline models in both treatment arms

	Pembrolizumab	Chemotherapy
AIC	1147.287	560.9614
BIC	1167.368	577.5028
coeficients (SE)		
_rcs1	1.157 (0.065)	1.161 (0.080)
_rcs2	0.083 (0.055)	0.237 (0.062)
_rcs3	0.048 (0.031)	-0.003 (0.038)
_rcs4	0.032 (0.014)	0.069 (0.023)
const	-0.681 (0,065)	-0.611 (0.091)
knots		
1	-0.559	0.539
2	2.824	2.448
3	3.391	3.030
4	3.834	3.405
5	4.328	4.080

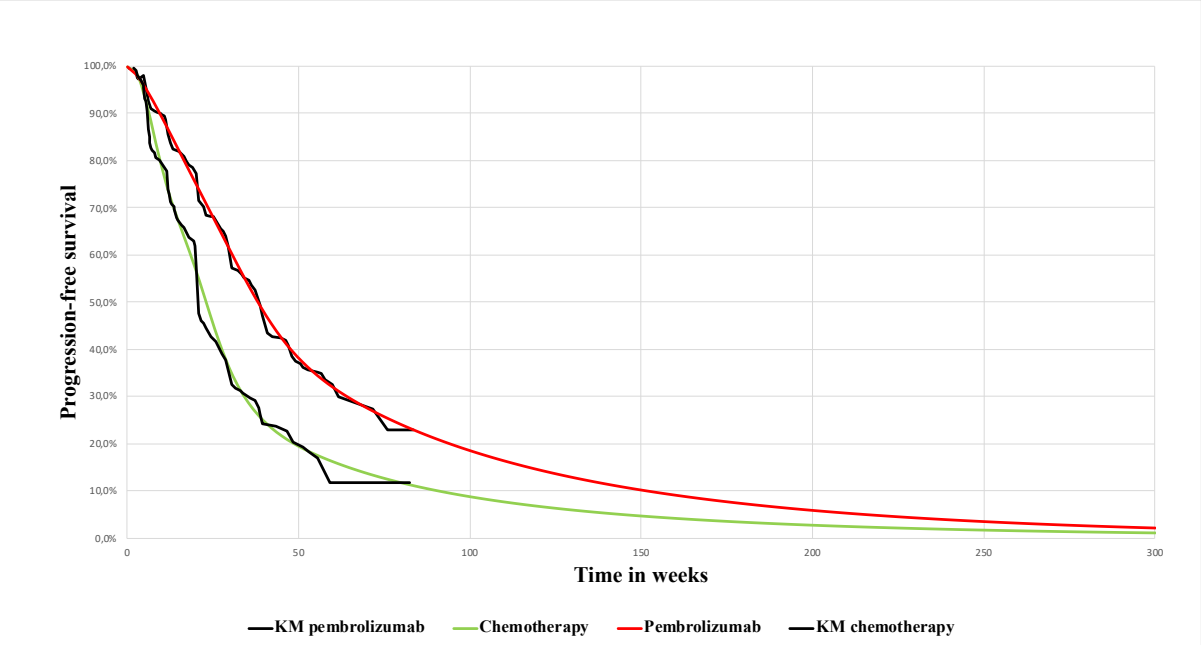

Figure 6. modeled spline models fitted into KM data for progression-free survival for the overall trial population

4.7.3. Overall Survival

For the overall survival, the standard parametric extrapolation method was conducted up to year 20. Based on the lowest AIC and BIC values, log normal distribution was selected to model survival for the chemotherapy arm, and Gompertz distribution for the pembrolizumab combination arm. However, based on the clinical plausibility, the extrapolated OS was highly overestimating the outcomes due to its flat long-term survival curves (Figure 7. and Figure 8.).

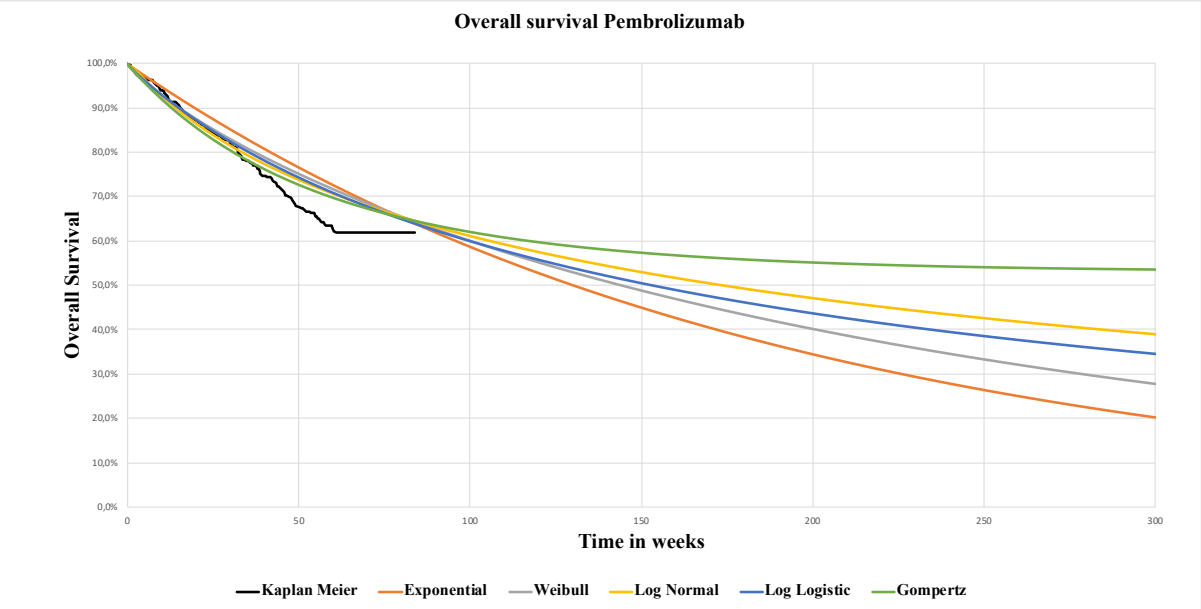

Figure 7. Overall survival in the pembrolizumab arm according to different parametric survival specifications

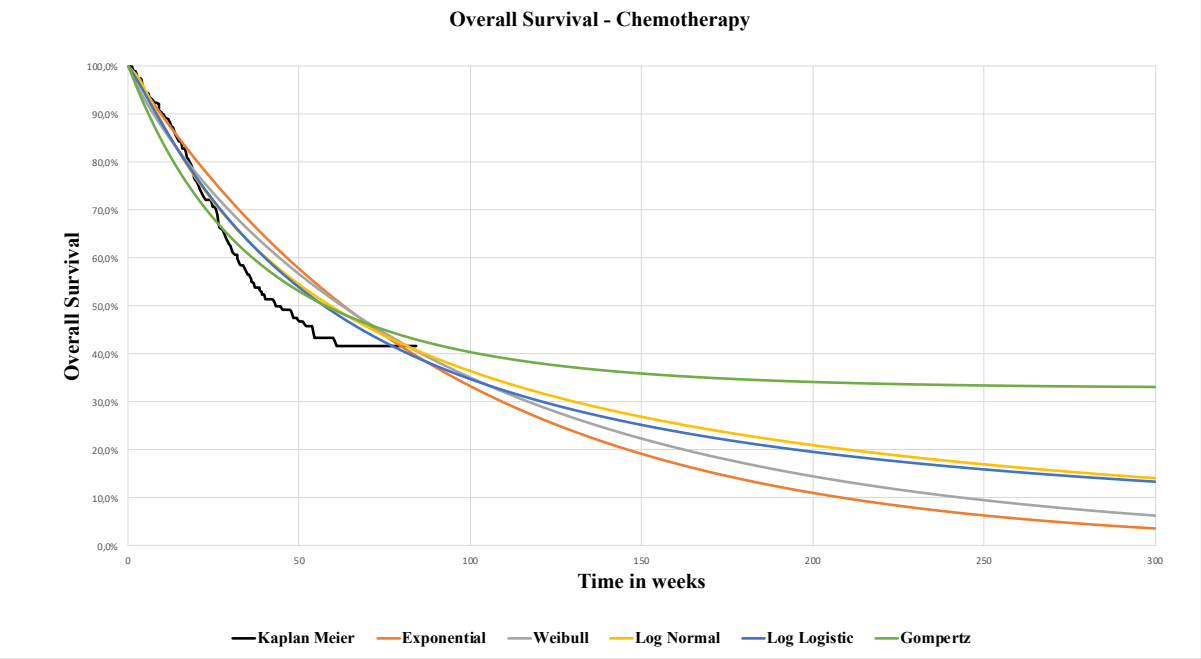

Figure 8. Overall survival in the chemotherapy arm according to different parametric survival specifications

The spline models were not relevant as an alternative approach, because there was already an external data source available. An external data (population-based) approach was chosen to model OS, instead of parametric extrapolation method (Figure 9.). To reflect the real mortality trends, long term external data for patients with metastatic NSCLC from the Surveillance, Epidemiology and End Results (SEER) database (49), were applied to the OS model after

month 12, see Table 4. Month 12 was selected as a cut-off point because of a representative sample size in both trial arms.

Overall survival for patients treated with chemotherapy regimen was calculated based on the KM proportion of alive patients up to month 12, followed by annual mortality rates given in SEER database. Annual mortality rates were adjusted to 3 week cycle length (22).

The overall survival in the pembrolizumab arm was modeled as a combination of KM data up to month 12, followed by SEER mortality rates adjusted by relative risk (RR) given in the KN-189 trial (RR=0,58) up to year 5, and SEER mortality risks were applied beyond year 5. The long-term survival trend among the lung cancer patients is assumed to not be dependent on the type of treatment they receive.

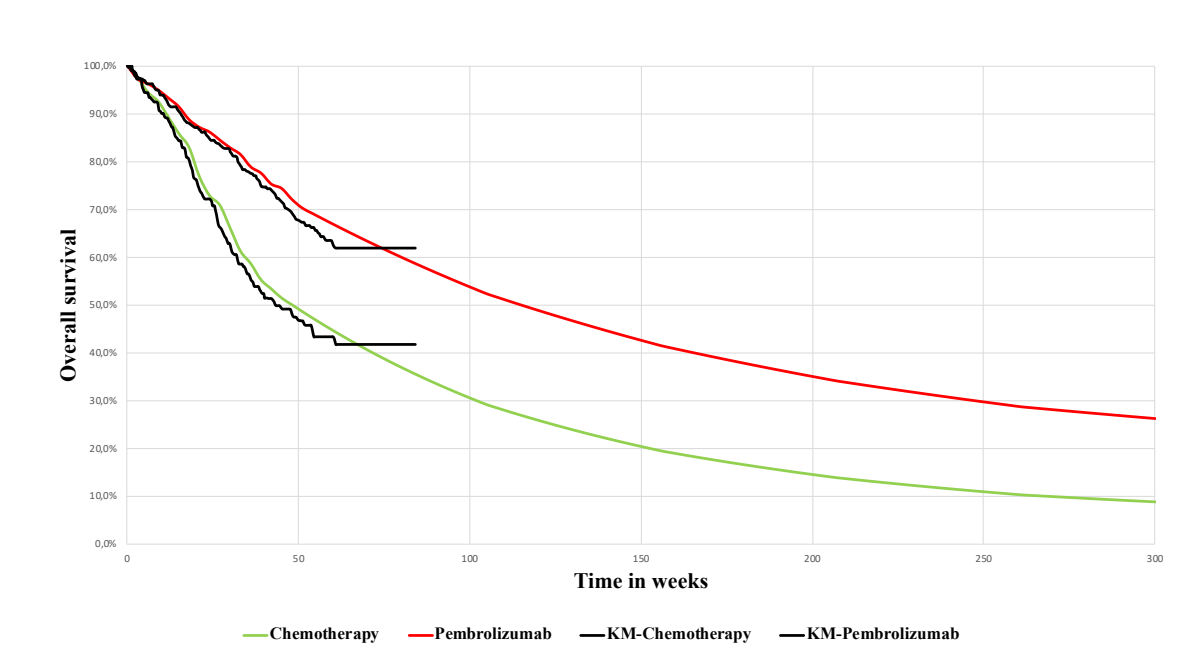

Figure 9. Overall survival based on the SEER annual mortality rates

Table 4. SEER annual mortality rates, mortality rates per cycle and mortality rate with relative risk per cycle (49).

Year	Annual mortality risk (SEER)	Instaneous rate converted to a probability per cycle	RR = 0.58 applied to instaneous rate up to year 5 in pembrolizumab arm
2	47.6%	2.8%	1.63%
3	39.7%	2.4%	1.37%
4	33.2%	2.0%	1.14%
5	27.9%	1.7%	0.96%
6	19.9%	1.2%	
7	19.3%	1.2%	
8	17.8%	1.1%	
9	13.8%	0.8%	
10	17.2%	1.0%	
11	11.4%	0.7%	
12	9.0%	0.5%	
13	12.0%	0.7%	
14	9.1%	0.5%	
15	6.9%	0.4%	
16	9.4%	0.6%	

4.7.4. Adverse Events

The model included adverse events (AEs) of any cause of grade 3 (fatal or life threating) (18). In the pembrolizumab arm, only AEs with a frequency greater or equal to 5% are included. To make both treatments equally comparable, patients in the chemotherapy arm experienced the same AEs regardless low incidence. All the treatment-related AEs occurred during the trial period or within 30 days thereafter. Defined AEs included anemia, asthenia, diarrhea, fatigue, neutropenia, nausea, and thrombocytopenia. Per patient risks of AEs used in the model are shown in Table 5.

Table 5. Key adverse events (≥ grade 3) observed in the KEYNOTE-189 study (18)*

Adverse Events	Pembrolizumab (n=405)	Chemotherapy (n=202)
Anemia	16.3% (66)	15.3% (31)
Asthenia	6.2% (25)	3.5% (7)
Diarrhea	5.2% (21)	3% (6)
Fatigue	5.7% (23)	2.5% (5)
Neutropenia	15.8% (64)	11.9% (24)
Nausea	3,5% (14)	3.5% (7)
Thrombocytopenia	7.9% (32)	6.9% (14)

* Listed are all adverse events that occurred during the trial period or within 30 days thereafter

4.7.5. Health Utility Data

Utility data used in the model were based on EQ-5D-3L questionnaire data collected in the KN-189 trial. The questionnaire was administrated at each of the first 5 treatment cycles, then every 3rd cycle for the reminder of year 1 and every 4th cycle thereafter as long as patients were on the treatment, then at the treatment discontinuation visit and at a 30-day post-treatment safety follow-up visit. To define health states utilities, two approaches was compared in the model: progression-based approach and time-to-death approach.

The most commonly used progression-based approach reflects the health utilities in each modelled health state. Time, which patients spent in pre- and post- progression health states was weighted by utility values to calculate overall QALYs. Utility weights are presented in Table 6. and were used for the base-case analysis.

Table 6. Utility values by progression status KN189, n- Number of patients with at least one valuable record (50)

Health state	Pembrolizumab		Chemotherapy	
	n	Mean Utility (95% CI)	n	Mean Utility (95% CI)
Progression Free	389	0.768 (0.759, 0.777)	187	0.757 (0.742, 0.771)
Progressive Disease	114	0.710 (0.682, 0.740)	65	0.645 (0.600, 0.689)

The time-to-death approach (TTD), explained by Hatswell (51), reflects decreasing utilities based on the time remaining until death. Time-to-death mean utility scores were divided into four categories and are reported in the Table 7. These utility values were used further in the scenario analysis.

Table 7. Utility values by time to death in KN189, n- number of patients with at least one valuable record (50)

Health state (days before death)	Pembrolizumab		Chemotherapy	
	n	Mean Utility (95% CI)	n	Mean Utility (95% CI)
≥360	136	0.79 (0.772, 0.808)	48	0.787 (0.762, 0.812)
[180, 360]	58	0.706 (0.677, 0.736)	36	0.712 (0.669, 0.756)
[30, 180]	91	0.627 (0.597, 0.657)	76	0.662 (0.631, 0.693)
<30	19	0,548 (0.411, 0.684)	13	0.449 (0.276, 0.621)

4.8. Resource Use - Costs

Costs included in the model were direct medical costs: treatment costs (medicine costs, administration and monitoring), costs of managing the disease (GP visits, hospital admissions), costs of managing adverse events caused by the treatment, and end-of-life care costs. Resource use was based on the dosing schedule described in the KEYNOTE-189 trial. Costs of the pharmaceuticals were calculated from the recently updated *List of Categorized Medicines* provided by Ministry of Health of the Slovak Republic (52). Costs per patient per cycle were derived for each regimen. The costs of diagnostic procedures, disease management costs, costs of adverse events and end of life costs were retrieved from the previous cost-effectiveness analysis, where pembrolizumab monotherapy was compared to a platinum-based chemotherapy in patients with advanced NSCLC in the Slovak Republic (13). Indirect costs were not included in this analysis. The impact of costs on the outcome of the CUA was demonstrated in the sensitivity analysis.

4.8.1. Regimen Related Costs

In Slovakia, the current list price for Keytruda (pembrolizumab) 100 mg single-vial is € 3 100. According to the summary of product characteristics, pembrolizumab is administered to NSCLC patients without prior treatment at a dose of 200mg once in three-week cycles, regardless of their weight. One patient therefore needs to be given 2 vials per cycle, which represents a cost of € 6 201 per cycle per patient. According to the KEYNTE-189 trial, the average dose for carboplatin per patient was 550mg, and the average dose for cisplatin per patient was 75mg. The cost of carboplatin was € 52.54 per dose and the cost per dose of cisplatin was €44.36. Due to the randomization of the chemotherapy groups in the trial, the

regimen related costs for both chemotherapy groups were calculated as a weighted average cost based on the number of patients in each chemotherapy regimen. The current list price for a 100mg vial of pemetrexed is € 87.21. Using the estimated body surface area of 1.82m2 (SD=0.22m2) of KEYNOTE-189 patients, the drug cost for each treatment cycle is € 872.10.

Table 8. Medication costs per cycle per patient (52) *Numbers in €.*

Drug	Dose	Cost per vial	Cost per cycle
Pembrolizumab	200mg	3 100	6 200
Pemetrexed	500mg/m2	87.21	872
Cisplatin (1x100 ml)	75mg/m2	22.18	44.36
Carboplatin	550mg/patient	40.82	52.54

4.8.2. Premedication costs

The usage of premedication was incorporated in the model(Table 9.). Patients received premedication with folic acid, vitamin B12, and glucocorticoids administered according to local treatment guidelines (53). The unit costs were obtained from the Slovak List of *Categorized Medicines* and estimated per cycle for carboplatin, cisplatin and pemetrexed use.

Table 9. Pre-medication costs per cycle per patient (52) *Costs in €.*

Pre-medications	Strength	# of doses	cost per vial	cost per cycle
Carboplatin regimen				
Aprepitant	285 mg	1	28.95	28.95
Dexamethasone	4 mg	3	0.57	1.72
Cisplatin regimen				
Aprepitant	285 mg	1	28.95	28.95
Dexamethasone	4 mg	13*	0.57	7.45
Pemetrexed regimen				
Vitamin B12 injection†	1000 mcg	1	2.41	2.41
Dexamethasone	4 mg	6+	0.57	3.44

*3 doses on day 1, 2 doses on day 2, and 4 doses on days 3-4; + 6 doses administered every 3rd cycle that pemetrexed was given

4.8.3. Drug Administration Costs

All drugs were administered intravenously. The administration cost for intravenous infusion in general is €6.10 per infusion, despite the administration time.

4.8.4. Disease Management Costs

The average management costs were divided into pre-progression and post-progression costs. The management costs included hospitalization costs, specialized outpatient care costs, laboratory costs and costs of symptomatic treatment. Cost per average patient are expressed per week and summarized in Table 10.

Table 10. Management costs per cycle in progression free and progressed health states (13) *Numbers in €.*

Type of care	Management cost per cycle in progression free health state	Management cost per cycle in progressed health state
hospitalization	77	45
specialized outpatient care	1.18	1.29
laboratory and therapeutic components	17.28	31
symptomatic treatment	4.47	4.70
SUM/patient/cycle	100	82

4.8.5. Terminal Care Costs

The end of life cost associated with the terminal stage, expressed as cost for the last month of patients' lives, equals to €1 145 (13).

4.8.6. Adverse Events Management Costs

The proportion of the patients hospitalized for each AE was provided by the KEYNOTE-189 trial. Per event costs were obtained from the previous pembrolizumab-monotherapy CEA in Slovakia (13) and is presented in Table 11. Overall cost of AE was based on the estimated incidence multiplied by per-event cost associated with each AE. The total average cost per patient for managing AE in each trial arm was included in the model as a one-time cost within the first treatment cycle.

Table 11. Per event costs of adverse events (13) *Numbers in €.*

Adverse Event	Cost per event
Anemia	1 070
Asthenia	377
Diarrhea	791
Fatigue	377
Neutropenia	640
Nausea	944
Thrombocytopenia	729

4.8.7. Second Line Treatment

According to the KN-189 trial, 45.8% of the patients in the pembrolizumab arm and 56.5% patients in the chemotherapy arm were estimated to receive second-line therapy. The Slovak national guideline recommends use of monotherapy docetaxel administered intravenously once every 3 weeks, with dose of 100mg/m2 per cycle, at maximum of 6 cycles as a second-line treatment of patients with NSCLC after the failure of initial systematic therapy.

The model was based on the assumption that each newly progressed patient, in both treatment arms, was treated with docetaxel with the maximum number of cycles. Adverse events were ignored. Newly progressed patients were counted in each cycle *t*. We assumed that all progression-free patients had to progress before they died. Therefore in order to get an exact number of newly progressed patients we used the difference of patients between two cycles in progression free state *PFS(t-1) - PFS(t)*.

4.8.8. Sensitivity Analysis

Two types of sensitivity analysis were conducted to assess the influence of uncertain factors on the final results of the model, and to determine how the final cost-effectiveness changed under different assumptions.

One-way deterministic sensitivity analysis (DSA) was performed first. The analysis tested the effect of changes in the key parameters on the base-case scenario ICER. The variables included are: OS and PFS in both arms; utilities; disease management costs; cost of subsequent therapies; adverse event management costs; end of life care cost. The modeled drug cost for pembrolizumab are based on the list price published by the Slovak Ministry of Health, which

does not vary and therefore this cost is not included in the sensitivity analysis. Table 12 describes the range of all tested parameters.

Table 12. Parameters Ranges For Deterministic Sensitivity Analysis

Model Parameter	Base-Case Value	DSA Range
Utilities based on PD and PF health states	0.71 (PD) 0.76 (PF)	+/- 20%
Disease management costs in PF	€ 100	+/- 25%
Disease management costs in PD	€ 82	+/- 25%
Cost of pemetrexed	€ 872	+/- 25%
AE management cost in combination arm	€ 559	+/- 50%
AE management cost in chemotherapy arm	€ 410	+/- 50%
End of life care cost	€ 1 145	+/- 25%

AE = adverse event; CI = confidence interval; KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival; RR = relative risk; SEER = Surveillance Epidemiology and End Results

In addition to the deterministic sensitivity analysis, a probabilistic sensitivity analysis was performed as a second uncertainty analysis including all model parameters. NICE stipulates that "Sensitivity analysis should be used to explore the impact that potential sources of bias and uncertainty could have on model results" (54). Following the Slovakian HTA guidelines, the standard deviation of each parameter used in the PSA was 30% (42). The type of distribution was selected according to characteristics of the parameter and is presented in Table13 for base-case parameter values.

Standard error was estimated to reflect uncertainty for values which were lacking SE or 95%CI. The overall survival of patients in the Markov model was based on the external population data, which were assumed to have little uncertainty, and therefore the SE for SEER data was set at 20% in the PSA. The progression free survival based on the spline models was tested with 20% uncertainty.

According to the methods stated by Briggs (22), Monte Carlo simulation was performed in Excel2020. To display a range of plausible costs, effects(QALYs, LYs) and ICERs a 1 000 iterations were used. The output from the PSA was plotted into a cost-effectiveness plane. To

make sure that the standard errors were the same, we tested the model with 3 000 iterations as well.

Table 13. PSA Distribution Models for Base-case Parameter Value

Model Parameter	Base-Case Value	PSA Range
OS - combination arm	KM first 12 month, followed by SEER mortality risks adjusted by RR to year 5, followed by SEER mortality risks	Beta distribution for the SEER data with the SE set at 20% of the base-case value
OS - chemotherapy arm	KM first 12 months, followed by SEER mortality risks	Beta distribution for the SEER data with the SE set at 20% of the base-case value
PFS - combination arm PFS - chemotherapy arm	Spline models Spline models	Beta distribution with the SE set at 20% of the base-case value
Utilities based on PD and PF health states	0.71 (PD) 0.76 (PF)	Beta distribution using the SE estimated from the KN189 trial
Disease management costs in PF Disease management costs in PD	€100 €82	Gamma distribution with the SE set at 30% of the base-case value
Cost of pemetrexed	€872	Gamma distribution with the SE set at 30% of the base-case value
AE management cost in: pembrolizumab arm chemotherapy arm	 €559 €410	Gamma distribution with the SE set at 30% of the base-case value
End of life care cost	€1 145	Gamma distribution with the SE set at 30% of the base-case value

AE = adverse event; SE = standard error; KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival; RR = relative risk; SEER = Surveillance Epidemiology and End Results

Finally, by using the PSA results from our model, we performed a value of information analysis by calculating the patient EVPI, population EVPI and the EVPPI. This was done in an online version of the Sheffield Accelerated Value of Information (SAVI) application (55). We assumed that the number of people affected by the decision per year in Slovakia was 1000 and the relevance time horizon was 10 years

5. RESULTS

5.1. Deterministic Results

Pembrolizumab treatment resulted in a longer expected life year gain and in QALYs gained compared to the treatment based on chemotherapy. Discounted outcomes are presented in Table 14. Expected life-years were 2.91 for pembrolizumab therapy and 1.87 for chemotherapy alone. In terms of QALYs, QALYs accumulated in the pembrolizumab arm were 2.09 QALYs and 1.28 QALYs in the chemotherapy arm. Costs related to treatments were higher in the pembrolizumab arm compared to the chemotherapy arm in the base-case scenario. As a result, the total cost for the pembrolizumab treatment was € 118 093 whereas the total cost for the chemotherapy treatment was € 14 187. Based on these results, the Incremental Cost-Effectiveness Ratio of pembrolizumab in comparison with chemotherapy was € 128 765 per QALY gained and € 99 786 per LY gained.

Table 14. Cost-effectiveness of treatment of pembrolizumab in combination with chemotherapy vs chemotherapy in metastatic NSCLC patients: base-case scenario with 20 year time horizon

	Pembrolizumab	Chemotherapy	Incremental pembrolizumab vs chemotherapy
Life Years Gained	2.91	1.87	1.04
Time in PFS	1.15	0.73	0.42
Time in PD	2.61	1.14	1.47
QALYs	2.09	1.28	0.81
Total Costs	€ 118 093	€ 14 187	€ 103 906
Drug acquisition cost	€ 110 820	€ 9 609	€ 101 211
PFS management cost	€ 1 994	€ 1 260	€ 734
PD management cost	€ 3 729	€ 1 631	€ 2 098
AEs cost	€ 439	€ 381	€ 58
2nd line treatment cost	€ 2 18	€ 275	- € 57
Terminal care cost	€ 892	€ 1 031	- € 139
ICER			
Cost per LY gained			€ 99 786
Cost per QALY			€ 128 765

5.2. Scenario Analysis

The alternative scenario analyses were performed to determine the impact of different values for the input parameters on the final ICER.

The first scenario analysis was performed to find the price of pembrolizumab being cost-effective at given € 37 000 willingness to pay threshold in Slovakia. As a result, the break-even price of pembrolizumab was € 725.

The second scenario analysis was based on the time horizon of the model and is presented in Table 15. Costs associated with the pembrolizumab combination treatment were higher compared to the chemotherapy in all alternative scenarios. The smallest incremental QALYs and LYs gained were in the scenario 1 (two years horizon), which was equal to the observation period of the trial. When survival data were extrapolated up to 5 years (scenario 2), the incremental QALYs and LYs gained more than doubled. The highest ICER was within the first two years of the treatment, due to the high treatment cost of pembrolizumab and small difference in effects.

Table 15. Cost-effectiveness of pembrolizumab vs chemotherapy in metastatic NSCLC patients: scenario analyses based on the length of survival data

	Pembrolizumab	Chemotherapy	Incremental pembrolizumab vs chemotherapy
Scenario 1: 2 years survival data			
QALYs	1,05	0.75	0.29
LY gained	1.4	1.06	0.34
Costs	€114 238	€12 735	€101 502
ICER (euro/QALY)			€346 055
Scenario 2: 5 years survival data			
QALYs	1.75	1.05	0.7
LY gained	2.38	1.51	0.87
Costs	€115 955	€13 598	€102 357
ICER			€146 132
Scenario 3: 10 years survival data			
QALYs	2.3	1.2	1.1
LY gained	3.14	1.74	1.4
Costs	€117 165	€13 987	€103 178
ICER			€94 183

A third scenario analysis was based on the different discount rates, see Table 16. The base-case scenario corresponds to Slovak HTA recommendations with costs and effects both discounted at a rate of 5%. Other countries (Netherlands, France, UK-NICE) use different discount rates, and sometimes different rates for costs and benefits. The impact on the ICER with the use of different discount rates confirmed that discounting is quite influential in economic evaluation. The ICER was lower with the use of the Dutch discount rate, which differed for costs and benefits and the greatest ICER was in the base-case scenario.

Table 16. Deterministic ICER based on different discount rates (56)

	Costs	QALYs	ICER
Base-case scenario Slovakia	5%	5%	€ 128 765
Netherlands	4%	1,5%	€ 87 779
France	4%	4%	€ 116 246
NICE	3.5%	3.5%	€ 110 438

And the last scenario analysis was based on two different utility approaches, see Table 17. First, health state utility approach reflected in QALYs gained and the second, time-to-death utility approach reflected in TTD QALYs. Different scales led to different QALY values. The time-to-death approach and using the TTD QALYs resulted in higher absolute QALYs and an increase in incremental QALYs, which resulted in reduction in the ICER.

Table 17. Deterministic ICER based on different utility approach

Approach	Pembrolizumab	Chemotherapy	ICER
QALYs	2.09	1.28	€ 128 765
TTD QALYs	2.30	1.37	€ 112 724

5.3. Uncertainty Analysis

5.3.1. Structural Uncertainty

Structural uncertainty was based on the use of different parametric survival models. Two parametric extrapolation methods were applied. The two specifications with the lowest AIC and BIC were chosen for the cohort survival scenario assessment. The OS was based on the log normal distribution and the PFS was based on the log logistic distribution for both treatment arms. Results are presented in Table 18, where the ICER is equal to € 75 623 per QALY and € 58 182 per LY gained. To compare these results with the base-case scenario, see Table 13.

Table 18. Structural analysis, model results based on different extrapolation methods: OS – log normal and PFS -log logistic

	Pembrolizumab	Chemotherapy	Incremental pembrolizumab vs chemotherapy
Life Years Gained	4.16	2.35	1.81
QALYs	2.99	1.59	1.40
Costs	€ 120 227	€ 14 686	€ 105 541
ICER			
Cost per LY gained			€ 58 182
Cost per QALY			€ 75 623

5.3.2. Deterministic Sensitivity Analysis

An additional scenario analysis in form of the DSA was conducted to examine the impact of the parameter value variation on the base-case ICER (128 882 €/QALY). The utility values differed in both treatment arms. Therefore, for the purpose of this analysis, utility values were assumed to be the same in both treatment arms and varied individually by values presented in Table 11. The greatest impact on the ICER was the PD utility, which relates to overall survival in both treatment arms, see Figure 10.

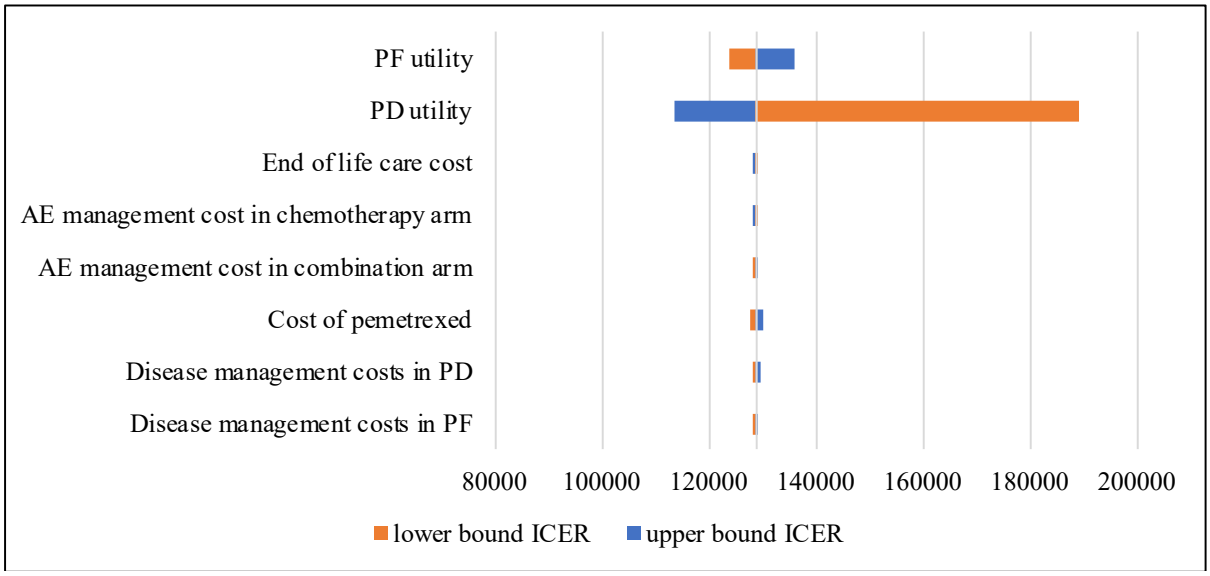

Figure 10. Tornado diagram for ICER of pembrolizumab vs chemotherapy using the health state utilities; PD: progressed disease, PF: progression free, AE: adverse events

5.3.3. Probabilistic Sensitivity Analysis

The results of the PSA were based on 1000 simulations, which was sufficient in order to have stable standard errors. In the PSA, parameters were varied simultaneously using a priori defined distributions summarized in Table 13. Table 19. shows the values of deterministic base-case scenario, mean of PSA, and lower and upper limit of 95% credibility interval. In this case mean probabilistic values were higher than deterministic values. As a result, the mean ICER of the PSA was 128 633 € per QALY gained, which is slightly higher than the ICER in the deterministic mode.

Table 19. Results of the Probabilistic Sensitivity Analysis

	Costs Pembro	Costs Chemo	LYs Pembro	LYs Chemo	QALYs Pembro	QALYs Chemo
Deterministic	€118 093	€14 187	2.91	1.87	2.09	1.28
PSA						
Mean	€118 185	€14 295	2.92	1.88	2.11	1.29
2,5th percentile	€107 512	€9 572	2.51	1.64	1.82	1.13
97,5th percentile	€129 260	€20 168	3.36	2.17	2.42	1.48

Pembro = pembrolizumab; Chemo = chemotherapy

The cost-effectiveness (CE) plane was used to visually represent the differences in costs and health outcomes between the two alternative treatments, by plotting the costs against effects on a graph, see Figure 11 (57). All the simulations on the CE plane were located in the North-East quadrant, in which the new intervention generates more health gains but is more expensive.

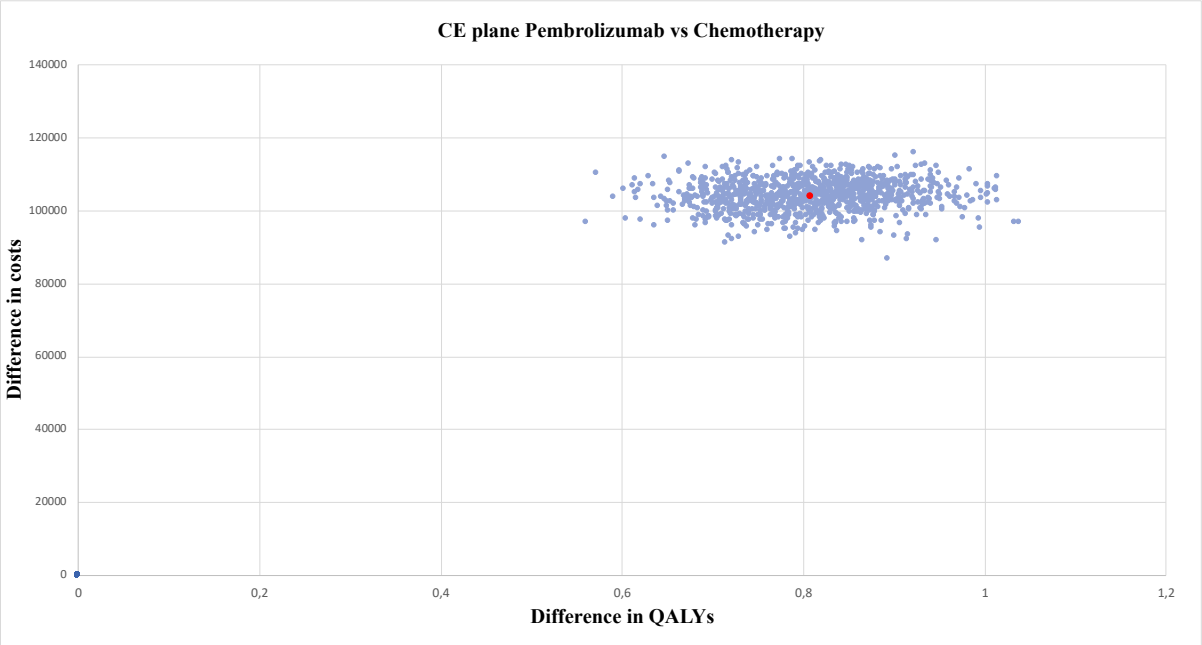

Figure 11. Cost-effectiveness plane based of Pembrolizumab vs Chemotherapy

The CEAC on Figure 12 presents the probability of the treatments being cost-effective at varying willingness-to-pay (WTP) thresholds and shows that as the threshold value increases, the probability of treatment with pembrolizumab being cost-effective is higher. Currently, the Slovak republic applies a threshold of € 32 000 – € 37 000 per QALY gained. At a WTP threshold of € 37 000/QALY, the probability of pembrolizumab being a cost-effective treatment compared to chemotherapy is 0%. The probability of pembrolizumab being cost-effective was lower than the probability of chemotherapy up to the WTP equal to ICER (128 765 €/QALY). Above this point, the probability for pembrolizumab was higher than for the comparator.

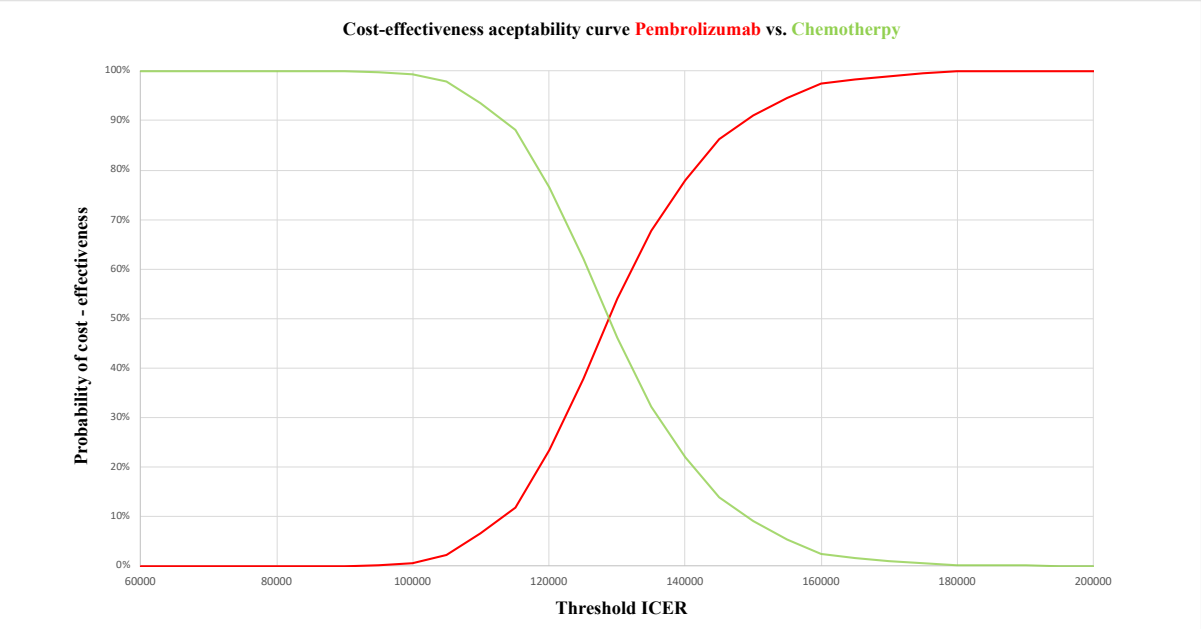

Figure 12. Cost Effectiveness Acceptability Curve of Pembrolizumab vs Chemotherapy

5.4. Expected Value of Perfect Information Results

Value of information analysis was undertaken for the cost-effectiveness model by calculating the patient EVPI, population EVPI and the EVPPI associated with the subset of all model parameters.

The EVPI estimates in the Table 19 presents the expected value to decision makers within the power of removing all existing decision uncertainty at thresholds of € 37 000 and € 128 765. Table 20 presents the outcomes for the overall EVPI per person and population EVPI per year per 1000 patients according to varying WTP thresholds and different costs of pembrolizumab.

With the base-case pembrolizumab price of € 3100 and the WTP threshold equal to the ICER (128 765€ /QALY), it is 50% likely that pembrolizumab is a cost-effective alternative. The population EVPI per year is € 4 462 000. Given the WTP threshold of € 37 000 and the break-even price of € 725 (50% likely that pembrolizumab is cost-effective) the population EVPI per year is € 1 220 000.

The likelihood of pembrolizumab being cost-effective at its base-case price of € 3 100 and a WTP threshold of € 37 000 is 0% and decision makers would not recommend the intervention.

The uncertainty at the break-even pembrolizumab price € 725 and WTP threshold of € 128 765 is 0% and decision makers would recommend the intervention.

Table 20. The overall EVPI per person affected by the decision and population EVPI according to different willingness to pay thresholds and different price of the treatment.

Pembrolizumab cost per vial	WTP threshold	The overall EVPI per person	Population EVPI per year (n=1000)
Base case: € 3 100	€ 37 000	€ 0.00	€ 0.00
	€ 128 765	€ 4 462	€ 4 462 000
Break-even value: € 725	€ 37 000	€ 1220	€ 1 220 000
	€ 128 765	€ 0.00	€ 0.00

With the price reduction from € 3 100 to € 725 and a WTP of € 37 000, the distribution becomes steeper (Figure 13.) than in the base-case (Figure 14.). Even though there is no uncertainty in the low price of pembrolizumab, the decision uncertainty is still there because there is still uncertainty regarding other parameters.

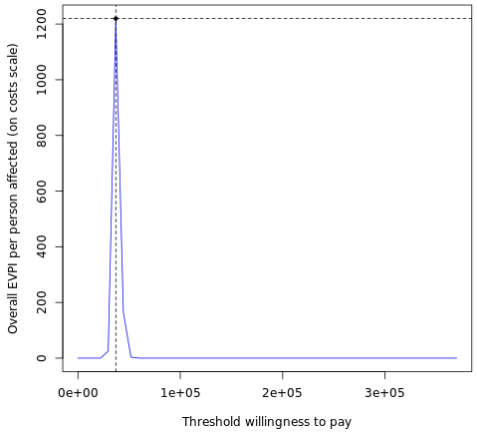

Figure 13. Overall EVPI with the WTP threshold of € 37 000 and pembrolizumab price €725.

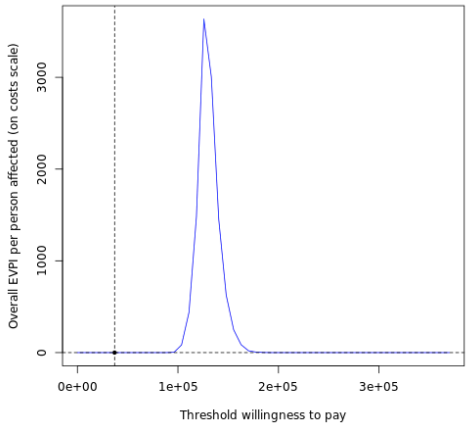

Figure 14. Overall EVPI with the WTP threshold of € 37 000 and pembrolizumab price €3100.

EVPPI presents different group parameters which caused the most of the decision uncertainty in the model. To see the impact of the parameters the cost of pembrolizumab was reduced to € 725 and WTP threshold remained € 37 000. The EVPPI estimates for different groups of parameters are illustrated in Table 21. The groups include all parameters associated with: disease management costs in progression free state and progressed disease state, costs of AEs for both treatment arms, SEER annual mortality data and utility values. For example, to reduce

uncertainty in the utility group decision makers would have to use a maximum value of € 525 per person per year on further research to inform this set of parameters.

Table 21. Group parameter EVPPI

Parameters	**Per Person EVPPI (€)**	**EVPPI for Slovakia Per Year (€)**	**EVPPI for Slovakia over 10 years (€)**
PF Disease management costs	€ 55	€ 55 496	€ 554 966
PD Disease management costs	€ 94	€ 94 851	€ 948 519
AE costs chemotherapy arm	€ 135	€ 135 637	€ 1 356 371
AE costs combination arm	€ 59	€ 59 646	€ 596 468
SEER data	€ 714	€ 714 799	€ 7 147 993
Utilities	€ 525	€ 525 845	€ 5 258 459

6. DISCUSSION

Health economic modelling helps to inform stakeholders involved in health care decisions about the value of a particular health intervention. The purpose of the analysis was to assess the cost effectiveness of pembrolizumab combination therapy compared to standard of care chemotherapy as a first-line treatment for previously untreated, metastatic, non-squamous, NSCLC patients from the Slovak health care perspective. The model was based on the KEYNOTE-189 study and was following the methodological guidelines from the Slovak Republic. The findings should be reflected in the context of assumptions made in the model.

According to our knowledge, this was the first analysis trying to explore the cost-effectiveness of pembrolizumab in combination in the Slovakian setting. Additional scenario analyses were performed to test the impact of costs, effects, discount rates and time horizon. The probabilistic sensitivity analysis was conducted to validate the performance of our model, and the model results were compared to other related studies.

6.1. Related Studies and Further Research

A partitioned survival model with 3 health states, 2-year treatment stopping rule and a lifetime treatment effect was developed to assess the incremental benefits and costs associated with the treatment of pembrolizumab in combination with chemotherapy and chemotherapy alone. The ICER from the base-case model was € 28 765 per QALY gained and € 99 786 per LY gained. Given the Slovakian threshold, pembrolizumab in combination with chemotherapy is not cost-effective compared to chemotherapy alone.

A PSA was conducted to address the problem of uncertainty. Results of the PSA confirmed what was found in the deterministic analysis, at a threshold of € 150 000/QALY gained, pembrolizumab has a probability of 91% of being cost-effective. At € 37 000/QALY, which is the upper bound of the standard threshold in Slovakia, pembrolizumab combination therapy has 0% probability of being cost-effective.

The cost-effectiveness of pembrolizumab with pemetrexed and platinum chemotherapy compared to standard of care platinum chemotherapy was assessed in other studies as well.

First, the NICE Technology Appraisal Guidance TA557 (58) did not recommend routine use of pembrolizumab with pemetrexed and platinum chemotherapy as an option for treating untreated, metastatic, non-squamous non-small-cell lung cancer patients. The deterministic base-case of pembrolizumab combination therapy compared to chemotherapy gave an ICER below £ 50 000 per QALY gained. This ICER was significantly lower than the estimated ICER in our model. The reason of this significantly lower ICER in the UK setting might be that the NICE model used the confidential commercial agreement price for the treatment drug pembrolizumab, which was the main cost driver of the analysis. This resulted in lower price of the pembrolizumab combination arm, decreased the ICER and made the treatment more likely to be cost effective. The second reason could be that the model was based on a new patient access scheme discount, which lowered the treatment costs in both arms. Our model on the other hand reflected full treatment costs. The third reason might be the fact that the estimated 5-year overall survival rate for non-squamous patients was between 5% to 11%. Our model produced relatively higher mortality rates, which resulted in longer overall survival and consequently higher treatment cost.

The second study, a study by Insinga (46) evaluates the cost-effectiveness of pembrolizumab in combination with chemotherapy versus chemotherapy and pembrolizumab monotherapy in the first-line treatment of squamous non-small-cell lung cancer in the US. The estimated ICER of pembrolizumab plus chemotherapy vs chemotherapy was $ 104 823 per QALY gained and cost per life year gained was $ 87 242. This analysis also resulted in a lower ICER compared to our analysis (128 765 €/QALY and 99 786 €/LY gained). Difference in the final ICERs could be explained by the fact that the US study used a parametric modeling approach, fitting the Weibull distribution in progression-free survival for both comparators, which was not the case in our model. Our model used a cubic spline model approach. The US model showed greater incremental QALYs and LY gained, which are some of the main cost-effectiveness ratio drivers and result in a lowered final ICER.

To sum up, there were differences in terms of ICER between the above mentioned studies and our analysis for different reasons. First, the data sources, mainly costs, were different in all three analyses which of course influenced the ICER. Second, there was a difference in the

setting, as each country has country specific guidelines, standards and requirements. In the NICE TA557 report, the company made the analysis in the UK setting, which could eventually lead to different calculations for costs and benefits. The Study by Insinga was made in the US setting and the variation in ICER could be explained by method differences in the cost-effectiveness calculations. Third, each economic model was constructed by using many different assumptions. Therefore, the choice of assumption made in each model, surely impacted the final ICER. Fourth, the use of a different extrapolation approach resulted in big outcome differences. Finally, transferability and different factors, such as factors affected by the patient population, factors associated with the healthcare system and factors associated with the analytical requirements and approach, led to varying ICERs within different countries (20).

6.2. Limitations

We made several assumptions in the development of our model to simulate the whole patient experience of living with metastatic non-small cell lung cancer.

First, major limitation of our model is a limited availability of data. Our analysis used the OS and PFS data from the KENOTE-189 study to estimate the survival benefits. The trial population was based on the "heathier" sample of NSCLC patients since the patients with comorbidities were excluded from the RCT. Therefore, we assumed that patients in Slovakia gained a similar relative survival benefit over standard chemotherapy as did patients in KN-189. The average patient population may result in shorter survival time due to their higher comorbidity levels, which may lead to a small decrease in costs of treatment and higher ICER because the treatment may not be as effective as with the trial population.

Second, data for OS in KN189 trial did not reach the median, thus the uncertain estimates for overall survival were substantial. Due to a lack of data for cancer specific mortality rates in Slovakia, the extrapolation of overall survival was based on the SEER-Medicare annual mortality data. Therefore, these data might have not be representative of the patient population in Slovakia.

Third, utilities for progression free and progressed disease were the same whether the patient recently had progressed, or whether he/she was at the tenth cycle after progression. Patients in PFS should be assigned the utilities, which decreased over time and not the constant number. If a patient is assigned a lower utility value after certain number of cycles after progression, it may decrease the number of QALYs in the model. Consequently, a treatment with worse post-progression survival may become even less cost-effective. In addition, health state utilities may not capture the full experience of patient's utility but time-to-death utilities may do so, because they are more specific. The results in cost-effectiveness models may rely on how long patients live in a post-progression state. As a result, the use of less specific utilities over some period of time may cause that an intervention may result in a lower likelihood of being cost-effective.

Fourth, our analysis did not estimate the costs for all adverse events, which might have led to underestimation of AEs costs. Nevertheless, considering the low incidence of some AEs, we assumed that the presence of all AEs would not change the final result of the evaluation. Furthermore, we tested the variation of these parameters with sensitivity analysis and the results were not affected.

Fifth, the lack of standard errors for our input data led to the SE assumptions. We used 20% for the OS and PFS survival, because we wanted to incorporate greater variation among population. This seemed to be an appropriate assumption, however the choice of standard error has quite an important impact on uncertainty in the PSA, therefore it would be better to gather the SE values from the original data.

The final limitation was the assumption that all patients had to move to the progressed-disease state before they died in order to capture and model the second line treatment. It is obvious that some patients could have died while in progression-free. This assumption led to overestimation of costs, and the ICER would probably be lower if we had more information on how patients move between the different health states.

6.3. Strengths

First, the use of a partitioned survival model based on the primary trial data is a strength of our model. This approach is recommended and often used in cost-effectiveness evaluations for the oncological drugs (59).

Second, modelling PFS with the flexible models was challenging, but these models resulted in a very smooth fit and therefore could be considered as a useful feature to the analytical instruments available to assess survival in immuno-oncology.

Third, the model used different utility values according to different treatments. This could be considered as a reasonable approach because patients should not reach the same utility, especially after disease progression, since there was a big difference in treatment effects.

6.4. Policy implications

The cost-effectiveness results from this analysis point to the importance of reasonable drug pricing. To limit the budget impact of pembrolizumab combination treatment, the Slovak Ministry of Health could negotiate volume-price agreements with Merck & Co., the manufacturer. This would reduce the uncertainty on budget impact. Another potential solution would be to engage in a performance-based scheme where reimbursement would depend on success of the treatment.

The focus should be placed on performing clinical trials with longer follow up time and more representative NSCLC patient populations. This would be useful to understand the true overall survival benefit of immunotherapies, which would allow for a better assessment of their cost-effectiveness.

In addition, focus should also be placed on gathering local data for the Slovakian setting. Often only multinational clinical data are used for cost-effectiveness models, which raises a concern that the trial population is not representative enough for the patients in Slovakia. More specific data would therefore benefit the future cost-effectiveness studies in the Slovak Republic.

7. CONCLUSION

Pembrolizumab in combination with pemetrexed and platinum-based chemotherapy showed an improvement in OS and PFS versus pemetrexed and platinum-based chemotherapy alone in a first-line treatment for eligible metastatic non-squamous NSCLC patients. From a perspective of the Slovak republic, the presented analysis suggested that pembrolizumab in combination with chemotherapy does not represent a cost-effective strategy compared to standard of care chemotherapy at the current Slovak price. As the immunotherapy treatment is starting to become more popular, extra attention should be focused on defining a reasonable price that could make these effective treatments more affordable.

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