university of groningen / faculty of science and engineering / biomedical engineering

# The clinical use of Pembrolizumab as immunotherapy in treatment of PD-L1 positive non-small-cell lung cancer patients: a cost effectiveness analysis in the Netherlands

Nazanin Mir Derikvandi

s3047334

Period: 01/03/2020 - 21/09/2020

Master thesis

Supervisor: Prof. dr. Maarten J. Postma

Mentor: Prof. dr. ir. G. J. Verkerke, University of Groningen

**Abbreviations**

AE: Adverse event

ALK: Anaplastic lymphoma kinase

CEA: Cost-effectiveness analysis

CUA: Cost-utility analysis

DSA: Deterministic sensitivity analyses

EGFR: Epidermal growth factor receptor

EQ-5D: EuroQoL Five Dimensions Questionnaire

HRQoL: Health-related quality of life

LY(G): Life-Year (Gained)

NSCLC: Non-small cell lung cancer

NICE: National Institute for Health and Care Excellence

OS: Overall survival

PD-L1: Programmed death-ligand 1

PFS: Progression-free survival

PF/SD: Progression-free/stable disease

PP/PD: Post-progression/progressive disease

QALY: Quality-adjusted life year

WTP: Willingness-to-pay

ZIN: National Health Care Institute (Zorginstituut Nederland)

# 1. Abstract

*Objective:*

The purpose of this study was to investigate the cost-effectiveness of pembrolizumab as treatment in non-small lung cancer (NSCLC) versus platinum-based chemotherapy with paclitaxel plus cisplatin, with use of decision analytic modelling considering the long-term effects. However, the cost-effectiveness of pembrolizumab as treatment in NSCLC has not been yet assessed in the Netherlands. The aim of this study was to assess the potential cost-effectiveness of the two years treatment based on the recently published results of the Keynote-024 trial.

*Methods:*

A Markov decision analytic model with progression-free, progressive disease and death states was constructed to compare the quality-adjusted-life years (QALYs) and costs of pembrolizumab versus platinum-based chemotherapy with paclitaxel plus cisplatin in a 10year time horizon and from a healthcare perspective. Clinical parameters were informed by the KEYNOTE-024 trial. Univariate sensitivity analyses were performed to explore the robustness of the decision analytic model. The main outcome measure is the incremental cost effectiveness ratios (ICERs).

*Results:*

Estimates based on the model show that patients receiving a pembrolizumab higher cost-effective treatment, presented as high QALYs, and have higher health care costs compared to chemotherapy. According to the sensitivity analysis, showed that pembrolizumab was associated with increased life expectancy of patients by 166,402 LY, and 1.57 QALY for an incremental cost of € 90,872 compared with platinum-based doublets. The ICER of pembrolizumab versus platinum-based chemotherapy with paclitaxel plus cisplatin was € 149,272/QALY calculated from higher gains in QALYs with higher health care costs will not necessarily be considered cost-effective. Initial costs for immunotherapy (pembrolizumab) and chemotherapy (platinum-based doublets), and the utility in overall survival had the largest impact on the result found.

*Conclusion:*

The results of this study confirm results reported in other studies that pembrolizumab improves overall survival and cost increasing for first-line treatment of PD-L1-positive (50%) metastatic NSCLC patients in the Netherlands. In the case base analysis, probability that pembrolizumab is not cost-effective compared to chemotherapy, assuming with a willingness to pay of €80,000.

## 2. Introduction

Lung cancer, with highest incidence rate among patients, and is the leading causes of death world-wide [21]. It accounts for 1.4 million case per year [15]. In the Netherlands, approximately 11,669 patients are diagnosed, of which 10,555 death are annually registered (www.ikc.nl). Lung cancer is a highly aggressive neuroendocrine tumor, which is characterized by rapid growth and early tendency to widespread metastasis. Clinical onset is often associated with heavy symptomatic burden, as well as a rapid decline of overall health [25]. Survival rates for metastatic lung cancer including non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are poor, with 5-year survival of less than 5% [21]. Unfortunately, life expectancy for NSCLC patients has not been significantly improved, during the last three decades, resulting in NSCLC being defined as a recalcitrant cancer.

The molecular characterization of lung cancer has changed the classification as well as treatment of these tumors, and becomes an essential component of pathologic diagnosis and oncologic therapy decisions in clinics [13]. Among different biomarkers used to diagnose NSCLC patients, epidermal growth factor receptor mutations (EGFR) and anaplastic lymphoma kinase translocations (ALK) can identify those, who will? benefit from targeted therapies [32].

To this end, patients with NSCLC, during the stage III or IV of their disease, are treated with both targeted therapy or immunotherapy, after surgery. Targeted therapy, is a new therapy in which drugs are calibrate to attack cancer cell only. Approximately 10% to 30% of patients, with NSCLC, have an EGFR-gene mutation, which is a leading cause to excessive cell growth [33]. Thus, EGFR-inhibitors are used to slow down this process in treated patients. Among EGFR-inhibitors, Gefitinib, Erlotinib, and Afatinib are used in combination with other chemotherapy to treat NSCLC tumor at the stage IV. The immunotherapy is also used to treat stage III tumor, which is shown to improve survival and quality of life in NSCLC patient.

PD-L1 expression has been previously investigated as predictive biomarker to assess treatment response in NSCLC patients [26]. Immune checkpoint inhibitors (ICIs) of programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) are used as immunotherapy in treatment of patients with advanced NSCLC [20]. These ICIs inhibit pathways which restrain the immune response in cancer treatment. However, the expression of PD-L1 blocks PD-1 receptor, and promotes tumor growth in NSCLC

patients [10]. Thus, NSCLC patients with positive PD-L1 expression exhibit clinicopathologic features, such as no squamous, which is typically seen in those who are young and non-smoker [26].

Because brain metastases are seen in approximately 30% to 40% of NSCLC patients with advanced PD-L1 positive expression, the activity of PD-L1 expression is important to consider [18,22]. In these patients, PD-L1 expression is confirmed with molecular or histological tests. Treatment of patients with PD-L1-inhibitor antibody, such as Pembrolizumab and Nivolumab, are generally limited to those with PD-L1-expression [26]. Pembrolizumab is used in patients with PD-L1 expression > 50% [12]. However, treated patients eventually develop resistant to chemotherapy, which reduce the penetration of drug into cancer tissue.

Pembrolizumab, commercially known as Keytruda, and nivolumab are used as immunotherapy to treat lung cancer. Pembrolizumab associate with the programed death-1(PD-1)-receptor on T-cells [19]. T-cells recognize antigens on surface of tumor cells [2]. However, tumor cells produce a protein called PD-L1-expression, which is bind to T-cell's PD-1 immune checkpoint [2]. This interaction block PD-1 receptor and deactivated T-cell attack on tumor cells. To this end, Pembrolizumab prevents this inhibition. It binds to PD-1-receptor on the T-cell, allowing it to avoid attachment with PD-L1 [19]. Thus, the effectiveness of pembrolizumab in patients depends on the PD-L1-expression on the surface of tumor. There is an association between EGFR mediated signaling and PD-L1 expression [28]. Mutant EGFR signaling increases PD-L1-expression. In this contact, the activation of PI3K-AKT and MEK-ERK signaling has been shown to upregulate PD-L1 expression and thus blocks the PD-1 receptor in tumor cells [9,28]. Since pembrolizumab prevent from activation of EGFR-mutation, this immunotherapy became effective as first-line treatment against NSCLC in stage III patients [11,7].

After 2016, the Dutch guidelines for non-small cell lung cancer (NSCLC) management has been changed. The new treaty recommend pembrolizumab treatment as first-line setting in the prevention of progression of NSCLC (www.zorginstituutnederland.nl). However, in other countries, pembrolizumab treatment is still recommended in a large proportion of the patients with advance NSCLC. This study focusses on a systemic review of cost-effectiveness analysis in immunotherapy of NSCLC patients, wherein previous pharmacoeconomic analyses on the prevention of NSCLC metastases show that the immunotherapy, including pembrolizumab is cost-effective in patients with advanced NSCLC [1,6].

The Dutch Healthcare institute (ZIN) has discussed the inclusion of medicines in the drug reimbursement for NSCLC treatment. ZIN has given a negative advise over reimbursement in therapy with pembrolizumab and nivolumab, because these drug treatments are expensive. In patients with NSCLC, ZIN could be responsible for reimbursement of therapy, if the cost effectiveness is improved. Therefore, it is important to get an insight into the cost-effectiveness of pembrolizumab and nivolumab in treatment of patients with advanced NSCLC. In the present study, we performed a systemic review of cost-effectiveness analysis on pembrolizumab treatment. Using PubMed search engine, we found no study previously investigating cost-effectiveness analysis of pembrolizumab as immunotherapy of NSCLC in Dutch population. We assumed that our cost-effectiveness analysis of pembrolizumab treatment in NLCLC patients can be benefited from the sequence of PD-L1-inhibitor at different stage of cancer progression. We examine the cost-effectiveness of immunotherapy with pembrolizumab in PD-L1 positive patients. We then compared our finding in NLCLC patients who have not been treated without an PD-L1-inhibitor.

Pembrolizumab treatment and chemotherapy can be analyzed by comparing lifetime costs and gains in quality of life (QoL) associated with the two procedures based on known information regarding costs, quality of life and probabilities of clinical outcomes like overall survival and complications. Decision analytic modelling techniques also offer the potential to analyze the long-term performance of a new technology prior to the availability of long-term clinical outcome data. A Markov model is a state transition model and therefore appropriate to analyses recurrence of events [59]. The health states are defined such that, in any given cycle, a member of the cohort is in only one state. Transition probabilities define the possible movements between health states. Different utilities and costs are accumulated for each time interval spent in a particular state.

The purpose of this study was to investigate the cost-effectiveness of pembrolizumab versus chemotherapy, as a first-line treatment for patients with PD-L1 positive >50% NSCLC in the Netherlands, with use of decision analytic modelling considering the long-term effects. Outcomes will be in incremental cost-effectiveness ratios (ICERs). Results of this study could be used to help inform Alberta Health Services (AHS) in long-term policy issues regarding hip replacements in Alberta. The specific objectives of this study were (a) to evaluate the cost-effectiveness pembrolizumab compared chemotherapy, considering the long-term effects, and; (b) to explore uncertainty surrounding the estimates in the decision analytic model using a sensitivity analysis.

## 3. Material and Method

This study follows two-stage. The first stage involves scoping review of literature in order to provide a list of biomarkers they can target therapies in non-small cell lung cancer (NSCLC), and the second stage involves cost-effectiveness analysis of drug treatment to determine whether drug treatment for the prevention in diagnosed non-small cell lung cancer in Dutch population is cost effective. Making a list of biomarkers in non-small cell lung cancer (NSCLC), using PRISMA guideline and select biomarker, was done for the first stage of the scoping review, due to its ease of use and ability to give realistic results. The cost effectiveness analysis is performed by implemented Markov model and sensitivity analysis. The database for analysis used in this modelling are taken from different literatures.

According to the PICO way (**P**atient problem or **P**opulation, the **I**ntervention, the **C**omparison, and **O**utcome), our study investigates the following questions:

- Which cancer biomarkers are considered in determination of prognosis and prediction of treatment response in lung cancer?
- Which biomarkers for targeted therapies should be selected for cost-effectiveness analysis in Dutch population?
- Which treatment for primary prevention in cancer is cost-effective considering Dutch incomes?

### 3.1.1 First phase method, study Design and Literature Search Strategy

A scoping literature review was conducted through PubMed from 2010 to the present to extract all biomarkers that are used in treatment and targeted therapies in non-small cell lung cancer (NSCLC) and its cost effectiveness. To ensure we collect all biomarkers that have been applied for targeted therapies, different combination of keywords with the MeSh term was used: biomarkers in lung cancer' OR 'biological marker in lung cancer' AND 'biomarker in lung carcinoma' AND 'biomarker in treatment' OR 'biomarkers in diagnosis' OR ' biomarkers for prediction' OR

'biomarkers for prognosis' AND 'cost analysis' OR 'cost-benefit analysis' OR 'cost-effectiveness analysis'.

### 3.1.2 Identification of Relevant Literature and Eligibility Criteria

We included all original publication that were written in English language if they met the following criteria: (1) participant: human studies in which the patients with lung cancer and non-small cell cancer, we ignore the tumor stage. There is no restriction on gender and age. (2) intervention: studies that evaluate biomarker, all biomarkers that are used for targeted therapies in lung cancer, biomarkers that are used for diagnosis non-small cell lung cancer, or one biomarker combines with other biomarker. (3) outcome: for selecting biomarker we considered on sensitivity, specificity, and their respective 95% confidence intervals as the primary outcomes. The first screen of literature was based on articles' title and keywords. If those articles were relevant, then we selected to review the abstracts. After the initial selection, the selected article in full text was assessed based on inclusions and exclusions. We analyze the selected articles in full text, then we included them to our study if that article was eligible for research study, otherwise they were excluded. The following criteria was used for inclusion or exclusion of articles:

*Inclusion criteria*:

- Studies that discuss biomarkers and its role in treatment in non-small cell lung cancer (NSCLC).
- Studies that provide sufficient data to extract.

*Exclusions criteria*

- Studies that do not report data on a biomarker for lung cancer; and
- Incomplete studies; and
- Animal research; and
- Summaries of review articles.

### 3.1.3 Included studies

We checked the name of extracted biomarkers in the different studies to select biomarker for cost-effectiveness analysis. In the next step, the extracted biomarkers were reviewed. Thus, for each biomarker, we considered the biomarker for targeted treatment of no-small cell lung cancer (NSCLC) and the drug treatment that was assessed. The articles related biomarkers were reviewed and biomarkers for targeted therapies in NSCLC were extracted. In this stage, all biomarkers were listed regardless of other biomarkers which belong to the prediction of diagnostic NSCLC. If a biomarker for targeted therapies was used in a different type of cancer, the outcome measure of the biomarker was selected for NSCLC. The biomarkers were divided between two groups: Target therapy and Immunotherapy.

In this study we provided an informative pool of biomarkers for the selection of biomarker and its cost effectiveness. All biomarkers in targeted therapies for NSCLC were arranged in the Appendix 1, the biomarkers were classified under their drug treatment, indication, prevalence in NSCLC, and type of treatment. Also, literatures for biomarkers in targeted therapies of NSCLC and cost-effectiveness of selected biomarker were arranged in the Appendix 2 to create a clear and brief overview.

### 3.1.4 Predict biomarker for therapy

The role of most biomarkers in NSCLC is described from different studies which are presented in Appendix 3. In this table, different indication, the line treatment, the drug treatment, and type of therapy are shown. Looking at appendix 3, it is visible that most of the biomarkers are referring to targeted therapy. ROS, ALK, BRAF, and EGFR used as predict biomarkers response in Tyrosine kinase inhibitors (TKIs) treatment and almost all them included as first-line therapy in stage IV of treatment. Epidermal growth factor receptor (EGFR)-mutation, it is a tyrosine kinase inhibitor (TKI) that inhibit the EGFR protein in cell. The EGFR mutation is a predictive biomarker in first-line or second -line in stage IV of treatment for patients with advanced NSCLC [33]. gefitinib, erlotinib, afatinib, and dacomitinib are in first-line treatment. Osimertinib

is another drug treatment that indicated for patients has resistance on first-line treatment, it uses in second-line treatment with combination chemotherapy.

Anaplastic lymphoma kinase (ALK), Patients with ALK- positive can be treated with ALK inhibitor such as alectinib, crizotinib, and ceritinib in first-line or second-line treatment [17]. Crizotinib is used in stage IV of treatment as the first-line treatment [31]. Alectinib and certinib can be used in second line treatment in the case of progression disease after crizotinib treatment [31]. Proto-oncogene tyrosine-protein kinase (ROS), *ROS1* rearrangements occur in approximately 1% to 2% of NSCLCs with nonsquamous histology [14]. Patients with positive ROS are treated with criztonib in first-line therapy and are assessed for response to therapy [5]. Second-line option for patients who are resistance to criztonib. In those patients, cabozantinib with combination chemotherapy are used [16]. BRAF-gene mutation, leading to excessive cell growth in tumor cell. BRAF inhibitor including dabrafenib and trametinib inhibitor the cell growth in NSCLC [24]. In the stage IV, patients can be treated with a chemotherapy and BRAF inhibitor as first-line treatment [3].

A big group of people with NSCLC (24% to 60%) have a rare genetic expression in Programmed death-ligand 1 (PD-L1), it leads to constitutive expression in cell that promotes tumor growth. PD-L1-inhibitor including pembrolizumab and nivolumab are referred to immunotherapy and are used in stage III treatment of advanced NSCLC as first-line therapy.

### 3.1.5 Included studies for cost effectiveness analysis of nivolumab and pembrolizumab

In this stage, selecting articles for cost effectiveness in pembrolizumab was done.

According to PICO way, our study investigates the following questions in cost effectiveness:

- What is the cost-effectiveness of programmed death ligand-1 PD-L1 expression in patients with non-small lung cancer (NSCLC) who have progressed on PD-L1-inhibitor during treatment?

| | |
|---|---|
| Population | Adult patients with PD-L1 positive NSCLC who have not previously been treated with anti PD-L1.<br>Adult patients with PD-L1 positive NSCLC who disease of patients has treated with anti PD-L1. |
| Intervention | Anti-PD-L1 (Pembrolizumab) |
| outcomes | Cost-effectiveness (e.g. ICER, cost/QALY) |
| Study design | Economic evaluation |

*Table 1: selection criteria*

We review the articles that were selected for cost-effective of Pembrolizumab. In the first level of screening, literature was based on article's title and keyword. From the relevant articles, we reviewed the abstract and relevant literature and decided whether to include them or not. The relevant articles selected to review the abstract and relevant literatures were assessed for inclusion. Appendix 1 presents the PRISMA flowchart of the study selection. The final selection of full-text literature was based on the inclusion criteria presented in table 1.

### 3.1.6 Exclusion Criteria

We excluded literatures if they not meet the selection criteria from table 1. Excluded literatures using another cost-effectiveness analyses than Costs/QALYs. Literatures were excluded if they were not published in English, and articles without access to the full text. Also, review articles were excluded.

### 3.2.1 Second phase of method

This study employed a Markov model to analysis cost-effectiveness (CEA) and cost utility (CUA) of pembrolizumab in treatment of patients with PD-L1 expression >50% in NSCLC in the Netherlands by capturing data from multiple sources. The decision tree used in this study in order to choose and subsequent consequences of two primary treatment alternatives; Pembrolizumab and platinum-based chemotherapy, in which each alternative is represented as a Markov state with mutually exclusive health states (figure 1).

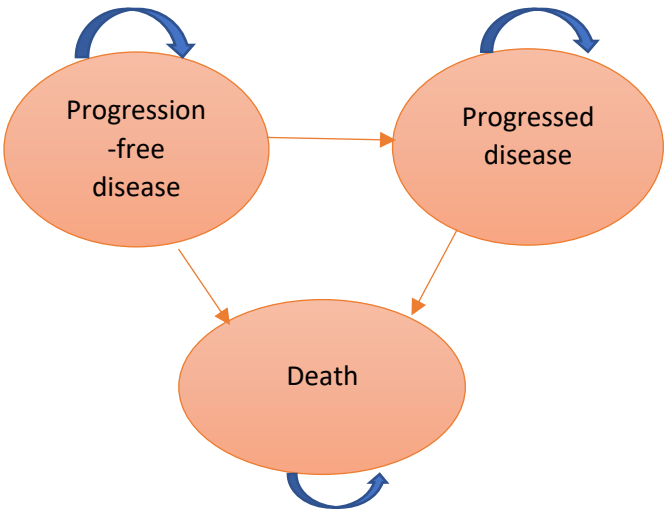



*Figure 1: Model structure and transitions.*

### 3.2.2 Model structure

The Markov model was used with outcomes within three different health states. Namely the progressive-free (PF), the initial state of patient until progression, the progressive disease (PD), the health state after progression, and the death or absorbing state. This model was used with 305 PD-L1-expression positive patients and run 174 cycles over a period of three weeks, resulting in a time horizon of 10 years [34,35]. The relative short time horizon was chosen because both treatments are end-of-life treatments for patients with a prospect of near death, it was assumed that most patients were not alive anymore after 10 years. After the primary treatment, patients' first cycles started in progressive-free pembrolizumab or chemotherapy in health state. Thereafter, patients were able to move to different states, as determined by the annual transition probabilities or remain in a state.

The cycle length of pembrolizumab and platinum-based chemotherapy is 21 days because both pembrolizumab and chemotherapy were administrated every three weeks [34]. The model assumes that the patient is always in one of the finite number of states of health. In each state during each yearly interval, patients experience a quality of life and possibly incur medical costs. Transitions associated with revision chemotherapy or major complications not requiring chemotherapy are associated with a short-term decrement in quality of life (QoL) and an increase in medical costs. State transitions occurred at the beginning of the first year of treatment and therefore a half cycle correction was applied. In health care, effects and costs often occur for different durations of time and over different time periods. Therefore, the costs were discounted with 4% per year and the effects were discounted with 1,5%, according to the Dutch standard [36]. With the incremental discounted costs and QALYs the incremental cost-effectiveness ratio (ICER) of pembrolizumab was established. This ICER was compared to the Dutch willingness to pay (WTP) for end-of-life treatments (€80.000/QALY) [34,36].

### 3.2.3 Study population for base case analysis

The data for model generation was extracted primarily from a large cohort study. The project was completed using data from the KEYNOTE-024 trial. The population of interest comprised of people under 65 years of age, with stage III or IV NSCLC, who did not undergo previous systemic chemotherapy, are diagnosed with metastatic NSCLC and high PD-L1 expression (TPS > 50%), without EGFR mutations or ALK translocations [34].

Across the KEYNOTE-024 trial, 12 percent of patients obtained paclitaxel and 47 percent obtained cisplatin [34]. This selection and comparable ones are also included in this cost-effectiveness study since the OS and PFS results included were focused on these drugs. In this trial the effect of pembrolizumab every three weeks for 35 cycles with a dose of 200 gm/kg bodyweight was compared to platinum-based chemotherapy (paclitaxel plus cisplatin) for four to six cycles in a dose of 135 mg/m2 and 75 mg/m2 body surface administered intravenously for 60 minutes [34,37]. In the Netherlands, a dose of 200mg was administrated every 3 weeks for 30 minutes [37,38]. In this study's model, the cost-effectiveness of pembrolizumab versus platinum-based chemotherapy is established, with a dose of respectively 200 mg/kg for pembrolizumab, 135 mg/m2 and 75mg/m2 for paclitaxel plus cisplatin every three weeks like in the model of the NICE [39].

The standard treatment paclitaxel plus cisplatin were also administered intravenously for 60 minutes, while the infusion duration was 30 minutes. The dose used in Keynote-024 were respectively 135 mg/$m^2$ of body surface area (BSA) for paclitaxel every three weeks, 75 mg/ $m^2$ for cisplatin every three weeks as loading dose. These doses correspond with doses in the Netherlands [37,38]. A univariate sensitivity analysis was performed when all doses from the Keynote-024 were used. The body surface area (BSA) was from the literature, because the NICE and Keynote-024 data was confidential. This study mentioned that the mean BSA for patients with NSCLC was 1.8 $m^2$ [34,37]. According to the Keynote-024 study, patients were treated until disease progression in the standard treatment group. In the pembrolizumab group, it was possible that the patients were treated during progression, but in this analysis, treatment stops when patients flow into the PD state because this was according to the guidelines for cancer therapy.

### 3.2.4 Patients in health stage

Updated 2-year survival data, based on the cohort and treatment of the Keynote-024 trial, were used to quantify patients in various health situations. The median progression free survival PFS and overall survival OS after treatment with pembrolizumab and platinum-based chemotherapy was obtained from the Keynote-024 trial. The median PFS of pembrolizumab was 10.3 months and median of OS was 30 months [34,37]. For the platinum-based chemotherapy, the median of PFS was 6 months and the median of OS was 14.20 months [39]. According to these data, an overall-survival-curve and a progression-free-survival curve can be estimated by an exponential extrapolation, extrapolated for the 10 years. An overview of the used data is shown in the table 2.

| | Pembrolizumab | Chemotherapy | Source |
|---|---|---|---|
| **Median OS (months)** (95%-CI) | 30,0 (18.3 – not reached) | 14.2 (9.8 – 19.0) | Keynote-024 trial [34,39] |
| **Median PFS (months)** (95%-CI) | 10,3 (6.7 to not reached) | 6,0 (4.2 to 6.2) | Study of Reck M. et al. [37] |

*Table 2: The different data used for the exploration the OS- and PFS-curve.*

Exponential extrapolation is used to build the overall-survival-curve and progression-free-survival curve, in which the pembrolizumab and platinum-based chemotherapy are considered as the median overall survival (OS) and median progression-free survival (PFS). The equation is mathematically described as the following [40]:

$$S(t) = exp\ (-\lambda t)$$

Where S is the proportion of patients at the time in months (t), λ is a constant, it can be computed by using the median OS and PFS. After determination of the exponential formula, it is possible to calculate the proportion of patients in the different cycles for the PFS and OS curve for the time horizon chosen. The number of patients in the PF, PD and death state in the different cycles can then be calculated by the use of the following formula [41].

$$\%\ patients\ PFS = 305 * PFS$$
$$\%\ patients\ PD = (OS\ cycle\ - PFS\ cycle\ ) * 305$$
$$\%\ patients\ death\ cycle\ x = (1 - OS\ cycle\ ) * 305$$

305 patients are included in the model as the model starts to be analyzed. Costs and utilities have been adjusted in the model according to the number of patients at each health stage. For some of the parameters, a half-cycle correction has already been used. Assuming that the number of patients in a health state was different during the cycle than in the beginning of the cycle and that these parameters only apply for the patients in the cycle.3.2.5 Utilities

The effectiveness of pembrolizumab and platinum-based chemotherapy was based on quality adjusted life years (QALYs) associated with each procedure. For the calculation of QALYs, the values (utilities) were allocated to all health state in the model and specifically to each year of follow-up. Utilities are represented as a measurement of how a patient determines the value of a particular state of health [42]. These utilities originated from the Keynote-024 trial and had a set value for PD and PFS states. The NICE guideline define utility along a continuum with a value of 1.0 representing perfect health and a value of 0.0 representing death [34,42].

The utility values of pembrolizumab and platinum-based chemotherapy are derived from another cost-effectiveness study in UK for pembrolizumab in NSCLC, see table 3. In this study of Xiaohan Hu [44], the utility was based on conducted a quality-of-life survey in NSCLC patients in 25 hospitals in Europe, Canada, Australia, and Turkey. There was used (EQ-5D) questionnaire, with data from the Keynote-024 study [50]. The (EQ-5D) questionnaire was also approved by the ZIN for use in the Netherlands [37].
For every year the patients were getting older, 0,0039 was deducted of the (QALYs) [43]. The QALYs were put in the model with half-cycle correction, in order to only include the QALYs of the actual living people in that cycle. The utilities were transformed to QALYs by correcting the utilities for a cycle length of three weeks.

| Utilities (95% CI) | Pembrolizumab | Chemotherapy | Sources |
|---|---|---|---|
| Progressive free disease (PFS) | 0.71 (0.6035-0.8165) | 0.68(0.5780.782) | Study of Xiaohan Hu. et al. [44] |
| Progressive disease (PD) | 0.67(0.670.5695) | 0.67(0.670.5695) | Study of Reck M. et al. [34] |
| Decrement per life year | 0,0039 (0,003315-0,004485) | 0,0039 (0,003315-0,004485) | NICE report [43] |

*Table 3: Utilities Pembrolizumab and Chemotherapy from the UK data set for both PF and PD.*

### 3.2.6 Costs

The incremental cost-effectiveness of pembrolizumab versus platinum-based chemotherapy was examined from a healthcare system perspective. The costs applied in the model were direct medical cost, consisting of the drug cost, and non-drug cost like costs for AEs and subsequent treatment costs. The costs are corrected for inflation and purchase power parity (PPP) in order to get us the current value [45,46]. The drug costs are divided into drug acquisition costs and drug administration costs. Non-drug costs are divided into monitoring costs and costs for disease management. According to the ZIN guideline, the direct non-medical costs like informal costs are added in the model [47]. The only difference with the cost categories of the ZIN in this model is the use of a one-off costs for disease progression and terminal care when patients enter the PD and death state respectively, which are based on the NICE report [47]. For all total costs implemented in the model, see table 4.

| *Costs* | Value (CI – 15%) | Applied in model by multiplying with | Source |
|---|---|---|---|
| *Drug acquisition costs PEM (€)* | 5.721.12 | All patients in PFS at start cycle patients | Dutch drug prices database [46] |
| *Drug acquisition costs IPI (€)* | 2.978.748 | All patients in PFS at start cycle patients | Dutch drug prices database [46] |
| *Disease management costs PFS (€)* | 1.792.39 | Half-cycle correction of PFS patients | Miguel, L. S et al. [52], Dutch cost manual [46] |
| *Disease management costs PD (€)* | 1.281.311 | Half-cycle correction of PD patients | Miguel, L. S et al. [52], Dutch cost manual [46] |
| *AEs costs PEM (€)* | 9.708 | Half-cycle correction of PFS patients | NICE [41], Dutch cost manual [46] |
| *AEs costs paclitaxel plus Cisplatin (€)* | 44.753 | Half-cycle correction of PFS patients | NICE [41], Dutch cost manual [46] |
| *End-of-life costs (€)* | 1292.08 (1098,36-1486) | On-off death patients | HTA analysis ZIN [41] |
| *Informal care costs PFS (€)* | 280.495 | Half-cycle correction of PFS patients | HTA analysis ZIN [38,41], Dutch cost manual [46] |
| *Informal care costs PD (€)* | 467.4929 | Half-cycle correction of PD patients | HTA analysis ZIN [38,41], Dutch cost manual [46] |
| *Travel costs (€)* | 23.75 (20,18-27,31) | Half-cycle correction of PFS patients | HTA analysis ZIN [38,41] |

*Table 4: Total costs implemented in the model for every cost category.*

### 3.2.6 Drug acquisition costs

The costs/mg for pembrolizumab and costs/$m^2$ for cisplatin plus paclitaxel were obtained from [www.medicijnkosten.nl]. The costs of drug and treatment are corrected and calculated until progression. For cisplatin plus paclitaxel, the mean doses of 75 mg/ $m^2$ and 135 mg/$m^2$ were used [39]**.** The doses in mg were calculated with the use of the body surface area (BSA) [39]. Then, the doses per cycle were calculated, based on the doses regime which is mentioned in treatment and appendix. For pembrolizumab, the dose was obtained by NICE guideline, 200 mg per three weeks [43]. The patients in the PFS state without half cycle correction were used to calculate the costs. See *appendix 4: details of drug acquisition costs* for an overview of the exact costs and *table* 4 for the total acquisition costs in the model.

### 3.2.7 Drug administration costs

Drug administration units are taken from the ZIN. The ZIN reported it takes 30 minutes to administer pembrolizumab and 60 minutes to administer platinum-based chemotherapy. These costs are taken from

the NICE report and adjusted for purchasing power parity (PPP) and are then converted into euro costs by calculating inflation [48], see Appendix 5.

### 3.2.8 Monitoring costs

The frequency of monitoring costs of NSCLC patients in the PFS and PD are derived from UK study [44]. A monitoring before progression consist of a blood test and oncologist visit once in nine weeks and chest CT-scan once in three weeks. After progression, it was assumed that blood test, oncologist visit and chest CT-scan take place every 9 weeks [44]. Thyrotropin added into this state, which take place once in 9 weeks. The costs for the CT-scan, oncologist visit and blood test are derived from the cost manual from the Netherlands [51]. The patients in the half cycle of the PF state and PD state were used to calculate the monitoring costs in the model, because these costs were made in the health state. See for an overview about calculation of the monitoring costs *appendix 6: details monitoring costs* and *table 4* for the total monitoring costs in the model.

### 3.2.9 Adverse events

The frequencies of each AEs ere based on an UK study of Reck, M. et al [35]. Adverse events with grade 3-4 as reported on the frequency in Keynote-024 trial were applied in the model. These data were based on the Keynote-024 trial [34]. It assumes that the AEs for Dutch patients were quite like the AEs of the average patients of UK in these trials. The costs of AEs are derived from the package advice of the ZIN in the Netherlands [38]. The other costs which were not mentioned in ZIN, they are derived from the France study of Chouaid, C. et al [49]. The costs for AEs are calculated in Dutch cost by correction in inflation and PPP, then they are implemented in the model. See table 5: details AE costs for an overview of the calculation of pembrolizumab and chemotherapy.

| AEs | Frequency AEs of PEM (%) [35] | Frequency AEs of chemotherapy (%) [35] | Costs in france [49] | Corrected for inflation [46] | Corrected for PPP [45] | Dutch costs (€) (ZIN) [38] | Coupled | Costs for PEM PFS patients per cycles | Costs for Chemotherapy PFS patients per cycles |
|---|---|---|---|---|---|---|---|---|---|
| Fatigue | 1.3 | 3 | 586 | 597.72 | 640.99 | 723 | 723 | 9.399 | 23.859 |
| Anamia | 1.9 | 19 | 5.752 | 5.86704 | 6.29 | 1.846 | 1.846 | 0.035074 | 0.3562 |
| Pneumonitis | 2.6 | 0.7 | 5.778 | 5.89356 | 6.32 | 3.864 | 3.864 | 0.100464 | 0.0270 |
| Neutropenia | 0 | 13.3 | 93 | 94.86 | 101.72 | 1.316 | 1.316 | 0 | 0.175 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Colitis | 1.3 | 0 | 3.457 | 3.52614 | 3.78 | 0 | 3.901 | 0.050724391 | 0 |
| Diarrhea | 3.9 | 1.3 | 2.879 | 2.93658 | 3.14 | 1.82 | 1.82 | 0.07098 | 0.023 |
| Nausea | 0 | 2 | 2.052 | 2.09304 | 2.24 | 662 | 662 | 0 | 13.24 |
| Stomatitis | 0 | 1.3 | 482 | 491.64 | 527.23 | 0 | 544.027 | 0 | 7.072 |
| Diabetes | 0.6 | 0 | 7.742 | 7.89684 | 8.46 | 0 | 8.738 | 0.052429839 | 0 |
| | | | | | | | Total | 9.70867223 | 44.753 |

*Table 5: Frequencies of the different AEs and calculated costs per cycles.*

### 3.2.10 Disease management

The frequency of the different disease managements of NSCLC patients in the PFS and PD are derived from the literature. This data was based in the Portuguese study of Miguel, L. S. et al [52], which determined the health resource uses for recurrent or metastatic NSCLC patients for both the PD and PFS state. Due to lack of data in the Netherlands it was assumed that the frequency of disease management was similar to other European countries. The study of Miguel, L. S. et al was used for this model. For the costs of disease managements, some costs were not possible to find in Netherlands and for these costs the Portuguese costs were used in the model. Then, these costs were corrected in inflation and PPP [45,46]. The costs of disease managements were multiplied with patients in the PFS state, after the half-cycle-correction these data was added into the model. All data are shown in appendix 7.

### 3.2.11 Informal care cost

The hours of the informal care were based on the assumption of the ZIN, stating that a patient in PFS needed 6 hours per week informal care and a patient in PD state needed 10 hours per week informal care [37,38]. The costs were based on the Dutch cost's manual of the ZIN (appendix 8). The informal care was added to the model with half-cycle correction.

However, a social perspective was used and things as travel costs or informal care were included, sick leave was not included in the model. The median age of the trial was quite high (62). This together with the seriousness of the disease led to the assumption that patients in PFS will not continue or start working. A summary of the used utilities and costs is shown in table 3.

### 3.2.12 Sensitivity analysis

A 10-year time horizon was used to evaluate the incremental cost per quality adjusted life-year (QALY) for both procedures and incremental cost-effectiveness ratio (ICER), starting at time of treatment. The 10-year time horizon was chosen because reliable information from the ZIN register regarding revision rates, was available up to 10 years after treatment [37].

In the main analysis comparable groups were analyzed: patients under treatment of pembrolizumab and patients under treatment of platinum-based chemotherapy with paclitaxel plus cisplatin. Moreover, separate models were estimated for more specific two different treatment. The treatment was chosen with knowledge of the included patients under pembrolizumab (200mg per three weeks) and patients on platinum-based chemotherapy with paclitaxel plus cisplatin (135 mg/m2 and 75 mg/m2), an important source for the model. The clinical path of pembrolizumab treatment of patients is compared to the clinical path of chemotherapy treatment of patients by comparing the cumulative total QALYs and cumulative costs of pembrolizumab with the cumulative total QALYs and cumulative costs of platinum-based chemotherapy with paclitaxel plus cisplatin. Cumulative total QALYs and cumulative total costs are related to the 10-year time period of the decision model.

The measure of cost-effectiveness in this model is expressed as an incremental cost-effectiveness ratio (ICER), which is calculated by dividing the difference in costs between pembrolizumab and platinum-based chemotherapy with paclitaxel plus cisplatin by the differences in effectiveness between pembrolizumab and platinum-based chemotherapy with paclitaxel plus cisplatin: ICER $\frac{Costs\ Pembrolizumab - Costs\ Chemotherapy}{QALY\ Pembrolizumab - QALY\ Chemotherapy}$

QALY is used as the unit of measurement for effectiveness and costs are in Euro, which will result in a ratio expressed in Euros per QALY. Thresholds for medical interventions to be cost-effective are often considered as a willingness-to-pay of Dutch €80.000/QALY gained [37]. The willingness-to-pay of Dutch €80.000/QALY gained is also applied for this model.

Lastly, one-way deterministic sensitivity analysis was performed for each important variable in the model: Costs of drugs, utility values, and median of OS and PFS in pembrolizumab group and chemotherapy group. Each variable has variated with +/-15% of the mean, and was varied based on reported confidence intervals or low and high values of specific variables reported in literature. Then, these most parameters were put in a tornado diagram.

# 4. Result

## 4.1 Selected biomarker

PD-L1 expression was selected as a predictive biomarker in non-small cell lung cancer (NSCLC) treatment for cost effective analysis. This literature review found that PD-L1 expression has emerged as a predictive biomarker in response to immunotherapy in NSCLC. For cancer therapy, immunotherapy can be used in combination with chemotherapy, it may lead to cell death and better response to treatment in patients with advanced NSCLC. Immunotherapy with anti PD-L1 (Pembrolizumab) leads to inhibition of the progression of NSCLC. The assessment of PD-L1 expression need to be combined with another biomarker such as EGFR and ALK. Untreated PD-L1 positive metastatic NSCLC can be treated with the use of immunotherapy. This treatment will increase the lifespan compared to chemotherapy and target therapy. Treatment with immunotherapy that cover untreated PD-L1- positive metastatic non-small-cell lung cancer (NSCLC), these treatment increases the length time of people live compared with chemotherapy. Moreover, because anemia and hair loss are the most frequently reported side effect of chemotherapy medication, minimize toxicity and improve a quality of life were assessed for immunotherapy, compared to chemotherapy and target therapy.

Pembrolizumab is the PD-L1-inhibitor, and was used as the first-line therapy in PD-L1 positive NSCLC patients [29]. Nivolumab is another drug that was approved for first-line therapy against NSCLC.

In conclusion, pembrolizumab have been found to be effective as first-line or second-line treatment in patients who develop resistance to chemotherapy or had disease progression after chemotherapy.

## 4.2 Base case analysis

Overall, estimates based on the model show patients with treatment of pembrolizumab experience higher gains in QALYs and have higher health care costs compared to patients under treatment of platinum-based chemotherapy, see in table 6. The ICER of pembrolizumab €149,272/QALY calculated from higher gains in QALYs with higher health care costs will not necessarily be considered cost-effective. This can be explained by the cost-effectiveness table 6. The new treatment (pembrolizumab) is more effective but involves higher costs compared to the conventional treatment (platinum-based chemotherapy). The old treatment dominates the new treatment. ICERs have a positive value. The maximum ICER has been defined for this new treatment (pembrolizumab) and often differs per country (€ 148,998.24/QALY in this study), then pembrolizumab is considered cost-ineffective.

| | Treatment | Costs per patient (€) | QALYs per patient | Incremental Cost (€) | Incremental QALY | ICER (€/QALY) |
|---|---|---|---|---|---|---|
| *Base case* | *Pembrolizumab* | 166,402 | 1,57 | 90,872 | 0.608 | €149,272 |
| | *Chemotherapy* | 75,529.62 | 0,96 | | | |

*Table 6: Deterministic base case results with the ICER calculated.*

Cost-utility analysis results of pembrolizumab versus platinum-based chemotherapy with paclitaxel plus cisplatin are visible for the deterministic base case. The results show that pembrolizumab was associated with higher QALYs per patient than conventional treatment (platinum-based chemotherapy, respectively 1,57 and 0,96. Consequently, the incremental QALY was 0,608. The cost per patient for pembrolizumab group was also higher than the platinum-based chemotherapy group.

### 4.3 Deterministic sensitivity analysis

Results of the deterministic sensitivity analysis are shown in the format of a Tornado diagram (figure 2). A tornado diagram is a single graph presenting a set of one-way sensitivity analyses. A horizontal bar is generated for each variable being analyzed. ICER is displayed on the horizontal axis, so each bar represents the range of ICER values generated by varying the related variable.

The deterministic sensitivity analysis showed that the utility for pembrolizumab had most influence on the results found. For each input parameter in the model, a deterministic sensitivity analysis was conducted to assess the sensitivity of the model for each parameter. Every parameter was modified by + /-15% of the mean and the variation of the ICER is shown in the tornado diagram (figure 2). It is obvious that the utility of PD results for pembrolizumab had the greatest effect on the ICER, with an ICER ranging from €111,860/ QALY to €224,284/ QALY. Following is the effectiveness of pembrolizumab in PFS state. The ICER is between € 123,690/ QALY and €188,195/ QALY. The OS data of the platinum-based chemotherapy group has an effect on the ICER. The higher value raises the ICER value.

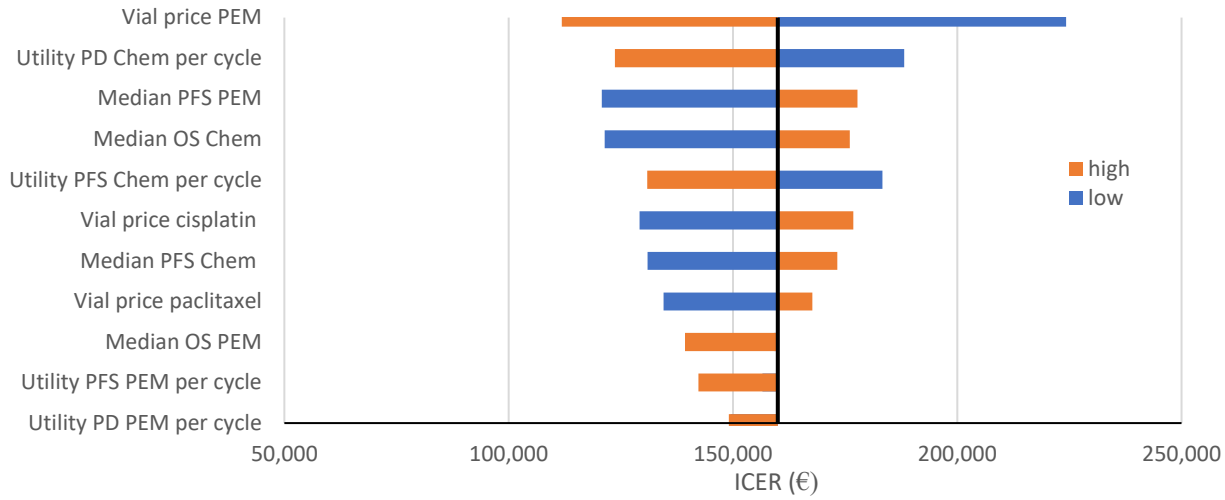



*Figure 2: in this figure a tornado diagram is visible. On the y-axis the parameters varied with a 15% interval are visible. On the x-axis the ICERs are visible. The orange bars represent the values of the ICER on the upper bound of the interval and the blue bars represent the values of the ICER on the lower bound of the interval.*

# 5. Discussion

In this economic analysis we evaluated a relatively new treatment (pembrolizumab) as immunotherapy, pembrolizumab with the conventional treatment (platinum-based chemotherapy) used as first line treatment in NSCLC. With decision analysis we were able to compare the cost-effectiveness of pembrolizumab by PFS, OS and death states. Moreover, we identified key factors that influenced the clinical effectiveness and costs of pembrolizumab compared to platinum-based chemotherapy and the uncertainty in these estimates. The potential advantages of pembrolizumab for specific patient groups were reported in literature [34]. Information derived from National Institute for Health and Care Excellence (NICE) in UK often showed higher PD-L1-expression>50% in NSCLC with pembrolizumab as immunotherapy compared to chemotherapy with paclitaxel plus cisplatin [37].

Our results confirm other findings reported in literature. The often-reported higher costs for pembrolizumab [53] could be seen as a problem when applying treatment of pembrolizumab in NSCLC. In older patients, generally only a very small increase in costs could ever be justified, because of the shorter life expectancy [44]. In younger patient higher costs could be justified by a longer life expectancy with a higher QoL. However, contradictory with other literature [44], higher costs pembrolizumab compared to

platinum-based chemotherapy were found in this study. As mentioned before, the higher costs of pembrolizumab (table 2), the treatment of pembrolizumab showed higher total costs. The reported higher total costs for pembrolizumab were mainly explained by the higher costs for drug acquisition and higher disease management costs. Patients who received a pembrolizumab had generally a higher length of stay; 30.0 moths for pembrolizumab group compared to 14.20 months for platinum-based chemotherapy group. We estimated costs from a healthcare perspective, as only direct hospital costs were included in the analysis. The costs of hospital treatment, however, capture most of the total costs [34].

Pembrolizumab was the first immunotherapy to show OS benefit and improved quality of life in patients with metastatic / recurrent NSCLC with platinum resistance. However, the cost of immunotherapy is high and it is therefore important to look at the economic impact of pembrolizumab in the Netherlands. In the Netherlands, pembrolizumab contributes to higher costs per patient (€166,402) than the platinum-based chemotherapy group (€75,529). It was expected due to higher drug acquisition costs for pembrolizumab and median of OS for patients treated with pembrolizumab. The cost of monitoring and disease control is also higher, as patients receiving pembrolizumab are more present in the PD state while patients in the platinum-based chemotherapy group die earlier. Informal treatment costs are also still higher, since they have mostly been incurred in the PD state. Pembrolizumab also contributes to a higher quality of life, respectively 1.57 for pembrolizumab and 0.96 for platinum-based chemotherapy group. It's just because more patients are in PD state in the group treatment of pembrolizumab, while patients are dying earlier in the group treatment of platinum-based chemotherapy. It is also related to lower AEs in the group treatment of pembrolizumab. It then raises the pembrolizumab gain in QALY. Therefore, the ICER was €149,272/ QALY, higher than the default WTP for end-of - life medications about €80,000 / QALY.

Based on the one-way sensitivity analysis, the model is most responsive to OS and PFS data, utilities and costs of pembrolizumab. the date from OS and PFS state were expected to determine the number of patients in each state of health. it was assumed that the OS and PFS state to determine the number of people in each state of health. It then has an impact on the estimation of expense and QALYs. Utilities are essential for the assessment of ICER as efficient usage of pembrolizumab improves QALYs and allows intervention more cost-effective.

Another noticeable result is difference in ICERs calculated, cost of PD and PFS state in pembrolizumab group, the price of pembrolizumab and utility of PD state in pembrolizumab group were the most influential factors in our study. There is visible is that the indeed a better utility of pembrolizumab in the PD or PF state decreases the ICER. There is visible is that the indeed a better utility of pembrolizumab in the PD or PF state decreases the ICER, while a better utility in chemotherapy increases the ICER, because

the incremental of QALYs become lower. So, based on these results it is important to use the right utilities in a cost-utility analysis, because the influence is great. These results can be referred for patients with better quality of life, which it means that pembrolizumab has higher cost-effective. At least, an increase in doses, frequency and costs of pembrolizumab increases the incremental costs and therefore the ICER. This is important to keep in mind for decision makers, because in clinical practice the costs, doses or frequency of the drug can become lower or higher and this can influence the cost-effectiveness.

### 5.1 Difference with the NICE

The NICE performed a utility decrement for the patients each period they were closer to death, suggesting the quality of life decline when patients approach death. There were no variations between states of health [43]. The NICE claimed that the usage of static utilities is not appropriate for improvements in quality of life because of the slight variation in utility levels among NSCLC patients [43]. As mentioned, this model used NICE in one of its scenario analyses using static methods. Scenario analysis of the NICE have shown that platinum-based chemotherapy has still been dominated by pembrolizumab but exact costs and QALYS are not published. The use of statist utilities instead of the utility system used by NICE would actually lead to lower incremental QALY. Since there is little difference between PD and PF in static utility values, the difference in quality of life between the two treatments cannot be underestimated without disutility and distinction between pembrolizumab and platinum-based chemical therapy. It may be too simplistic to assume the utility values in this model. With the exception of neglecting to include a decrease in quality of life in utilities, it can be challenged whether the value of both pembrolizumab and platinum-based chemotherapy for progressive disease is equal, in particular because the use of platinum-based chemotherapy results in more adverse events and disease management than the use of pembrolizumab.

The ICER in this model is different than the ICER of NICE report. In this study, the median OS and PFS were obtained from Keynote-024 trial. The survival data was extrapolated with an exponential survival curve. The exponential distribution was used for OS and PFS data while the NICE study used the generalized gamma distribution for OS data and the lognormal distribution for PFS data. One other method of extrapolation leads to another distribution of patients in PF, PD and death state, which has an effect on the estimation of ICER [43]. Compared with the other distributions, the exponential distribution is a simple and clear variant. The NICE performed a pessimistic scenario analysis which increases the ICER. Patients

survive longer with pembrolizumab than for platinum-based chemotherapy. However, if the distribution becomes more optimistic than the survival becomes higher. As a consequence, the QALYs received high value, which resulted in high incremental QALYs.

Another difference is that paclitaxel has higher administration costs in the UK than pembrolizumab [44]. Consequently, the incremental costs are higher. This could cause higher ICERs in this model. The univariate sensitivity analysis of this model indicates that the model is only sensitive to pembrolizumab costs and minimal to other costs. Thus, if the costs of pembrolizumab are higher in the United Kingdom (which is confidential), the higher ICER could result.

The NICE used a 20-year time horizon. Furthermore, which can be seen in the scenario study, the time horizon had no major effect on the ICER. It is possibly due to the patients' end of life status in the model of NICE [43]. Just few patients still were alive in the last years of the model. Over a shorter time horizon, used a 10-year time horizon, the lower ICER can cause less differences in the QALYs gained by both drugs. Because of the age decline used for the utilities, at some point QALYs was negative and possibly contributed to less in QALYs at 10 years and a higher ICER at that time. Assuming that NICE may have little impact on the different time horizon, however, this could result in higher incremental costs and QALYs.

The variation in costs also can be related to differences in hospital prices in countries and differences in prices for medicinal products. In the Univariate Sensitivity Analysis, it was obvious that the price of the vial of pembrolizumab had a major impact on the ICER [54]. The vial price of pembrolizumab could therefore not be used confidentially after the discount given by the UK pharmaceutical company [37]. However, it is appealing that the model used in this study had included social costs, such as informal care and travel costs, and therefore the overall cost of this model was expected to be higher. The implementation of a 4% discount rate for both costs and QALYs is another difference in NICE model [37]. After all, the univariate sensitivity analysis and the scenario analysis demonstrated that the discounting and societal costs had very little impact due to the short time horizon, a slightly lower cost discount rate could lead to higher costs. So, the higher QALY discount rate could also have resulted in lower QALYs. Due to the results of the univariate scenario analysis, the utility and extrapolation of the data can be assumed to have more influence than the discount rates.

Dutch costs are not only included in the model. Some of the costs used are taken from France data, Portuges data, and from British data. Data has been corrected in exchange rates and PPP, but data may be slightly different in the Netherlands. It would be obvious from the Univariate Sensitivity Analysis that

such results did not have a significant effect on the model, which makes this a disadvantage with little impact.

### 5.2 Difference with other cost-effectiveness studies

Four additional studies in pembrolizumab in recurring/metastatic NSCLC have been performed. The first study has been performed in the UK and the ICER was calculated £86,913/QALY (€87,767) in comparison with the platinum-based chemotherapy [44]. A second research was performed in France comparing pembrolizumab and calculating ICER for platinum-based chemotherapy with Pemetrexed and Bevacizuma €62,846/ QALY [49]. A third study in Chania compared pembrolizumab with chemotherapy and calculated ICER $65,322/QALY (€45,165) [56]. The last study was performed by researchers from Huang M, et al. in the USA and calculated an ICER of $97,621/QALY (€68,395) as compared to platinum-based chemotherapy [53]. For all the trials, the ICER was lower than the WTP and thus pembrolizumab was cost-effective. The WTP varies in different countries, thus whether the intervention is cost-effective or not. As the WTP can vary in different countries. Therefore, this may arise the question, that whether the intervention in NSCLC patients is cost-effective or not. It is difficult to know the exact causes of the different ICERs and the high ICERs in the Netherlands, as there is a lack of generalization between the studies and no accurate data is available in comparison to the NICE report. Cost- categories, discount rates and AE's were also varied between studies and no studies were focused on social factors. In UK research, the cost-effectiveness was calculated using a Markov model with the probability of transition.

### 5.3 Strengths

In our model is greatly improved with the usage of more updated OS data to assess PF and PD patients, which a more precise estimate of cost-effectiveness will also be provided. More updated doses for pembrolizumab were included in our model. Doses used in the cost calculation model are derived from doses in the NICE report that determine the efficacy and safety of the treatments in the Keynote-024 study [37,57]. Sensitivity study indicates that the model also isn't sensitive to AE, so it was assumed that the results would be minimally affected. According to the clinical expert analysis, different doses of pembrolizumab also have no effect on the efficacy results. These doses have therefore been used in order to have a condition that is more appropriate for the Netherlands. The new doses of pembrolizumab have

a further advantage: 200 mg for every 3 weeks, because the older dose was 3 mg / kg every 3 weeks, the model is less responsible for body weight.

This research was descriptive of the perspective to be taken in the Netherlands and was also the first thesis to be carried out in the Netherlands. The input parameters were also checked with the advice of the guideline. According to the guideline, the majority of the input parameters refer to the Netherlands. The AE used are also descriptive for the population in the Netherlands. Another strength is the representativeness of the monitoring services and the frequency for the state of PF and the state of PD according to the specialist. Considerations for the use of day-care costs for administration were also descriptive and for the use of terminal care costs for patients with lung cancer. The data is therefore more applicable to the Netherlands.

### 5.4 Limitation

Limitations of this study should be considered while interpreting the results. To complete the model, it was necessary to make a few assumptions (as described in the methods). The generalizability and variability of the results were limited by accuracy and availability of data inputs used in the decision model. Especially because pembrolizumab an immunotherapy is a relatively new treatment it is not possible to obtain information about long-term effectiveness of the procedure. Moreover, no adequate disease management measurement was reported for pembrolizumab management for pembrolizumab treatment. Therefore, disease management of melanoma cancer follow up in the Portuguese literature was the most accurate measure available to represent effectiveness. No direct estimates of all costs are from the Netherlands were available, so these values were derived from another report. Therefore, it is possible that the ICER is underestimated or overestimated. But when looking at the results the model is not very sensitive for other costs then acquisition costs and therefore it was expected that it has a low influence. For follow up, it is better that first a cost research was conducted. Another limitation is that the used utilities are not from the Netherlands. Due to lack of data, utilities from the literature were chosen with the use of a UK data set. But according to the literature, it is important to take utilities which corresponds with the country in which the cost-effectiveness analysis is taken. So, this can influence or results because according to the univariate sensitivity analysis, or model was most sensitive for the PD utility data of pembrolizumab and other utilities. For follow up investigation, it is important to determine specific utilities in the population of the Netherlands.

# 6. Conclusion

Pembrolizumab seems to be a safe option for patients metastatic NSCLC compared to platinum-based chemotherapy. Improved PFS and OS as indicated in KEYNOTE-024 and anticipated by the model, it will increase life expectancy, quality of living and NSCLC management costs. In our analysis shows that first-line treatment with pembrolizumab is not cost-effective compared to platinum-based chemotherapy in metastatic NSCLC patients with high levels of PDL1 (≥50%) in the Netherlands.

# 7. References


1) Aguiar, P. N., Jr., L. A. Perry, J. Penny-Dimri, H. Babiker, H. Tadokoro, R. A. de Mello and G. L. Lopes, Jr.The effect of PD-L1 testing on the cost-effectiveness and economic impact of immune checkpoint inhibitors for the second-line treatment of NSCLC. Ann Oncol**.** 2017**;** **28**(9): 2256-2263.
2) An, L., D. D. Li, H. X. Chu, Q. Zhang, C. L. Wang, Y. H. Fan, Q. Song, H. D. Ma, F. Feng and Q. C. Zhao.Terfenadine combined with epirubicin impedes the chemo-resistant human non-small cell lung cancer both in vitro and in vivo through EMT and Notch reversal. Pharmacol Res. 2017; **124**: 105-115.

3) Anguera, G. and M. Majem. BRAF inhibitors in metastatic non-small cell lung cancer. J Thorac Dis. 2018; **10**(2): 589-592.
4) Antonicelli, A., S. Cafarotti, A. Indini, A. Galli, A. Russo, A. Cesario, F. M. Lococo, P. Russo, A. F. Mainini, L. G. Bonifati, M. Nosotti, L. Santambrogio, S. Margaritora, P. M. Granone and A. E. Dutly. EGFR-targeted therapy for non-small cell lung cancer: focus on EGFR oncogenic mutation. Int J Med Sci. 2018; **10**(3): 320-330.
5) Bebb, D. G., J. Agulnik, R. Albadine, S. Banerji, G. Bigras, C. Butts, C. Couture, J. C. Cutz, P. Desmeules, D. N. Ionescu, N. B. Leighl, B. Melosky, W. Morzycki, F. Rashid-Kolvear, C. Lab, H. S. Sekhon, A. C. Smith, T. L. Stockley, E. Torlakovic, Z. Xu and M. S. Tsao. Crizotinib inhibition of ROS1-positive tumours in advanced non-small-cell lung cancer: a Canadian perspective. Curr Oncol. 2019; 26(4): 551-557.
6) Bhadhuri, A., R. Insinga, P. Guggisberg, C. Panje and M. Schwenkglenks. Cost effectiveness of pembrolizumab vs chemotherapy as first-line treatment for metastatic NSCLC that expresses high levels of PD-L1 in Switzerland. Swiss Med Wkly. 2019; 149: 20170.
7) Cabanero, M., R. Sangha, B. S. Sheffield, M. Sukhai, M. Pakkal, S. Kamel-Reid, A. Karsan, D. Ionescu, R. A. Juergens, C. Butts and M. S. Tsao. Management of EGFR-mutated non-small-cell lung cancer: practical implications from a clinical and pathology perspective. Curr Oncol. 2017; 24(2): 111-119.
8) Capizzi, E., F. G. Dall'Olio, E. Gruppioni, F. Sperandi, A. Altimari, F. Giunchi, M. Fiorentino and A. Ardizzoni. Clinical significance of ROS1 5' deletions in non-small cell lung cancer. Lung Cancer**.** 2019**;** 135: 88-91.
9) Carrizosa, D. R., K. F. Mileham and D. E. Haggstrom. New targets and new mechanisms in lung cancer. Oncology (Williston Park). 2013; **27**(5): 396-404.
10) Chalmers, A. W., S. B. Patel and W. Akerley. Immunotherapy after chemoradiotherapy in stage III non-small cell lung cancer: a new standard of care? J Thorac Dis. 2018; **10**(3): 1198-1200.
11) Chen, N., W. Fang, J. Zhan, S. Hong, Y. Tang, S. Kang, Y. Zhang, X. He, T. Zhou, T. Qin, Y. Huang, X. Yi and L. Zhang. Upregulation of PD-L1 by EGFR Activation Mediates the Immune

Escape in EGFR-Driven NSCLC: Implication for Optional Immune Targeted Therapy for NSCLC Patients with EGFR Mutation. J Thorac Oncol. 2015; 10(6): 910-923.

12) Gandhi, L., D. Rodriguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M. J. Hochmair, S. F. Powell, S. Y. Cheng, H. G. Bischoff, N. Peled, F. Grossi, R. R. Jennens, M. Reck, R. Hui, E. B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J. E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M. C. Pietanza, M. C. Garassino and K.-. Investigators. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018; 378(22): 2078-2092.
13) Henry, N. L. and D. F. Hayes. Cancer biomarkers. Mol Oncol. 2012; **6**(2): 140-146.
14) Joshi, A., N. Pande, V. Noronha, V. Patil, R. Kumar, A. Chougule, V. Trivedi, A. Janu, A. Mahajan and K. Prabhash. ROS1 mutation non-small cell lung cancer-access to optimal treatment and outcomes. Ecancermedicalscience. 2019; **13**: 900.
15) Ju, Y. S., W. C. Lee, J. Y. Shin, S. Lee, T. Bleazard, J. K. Won, Y. T. Kim, J. I. Kim, J. H. Kang and J. S. Seo. A transforming KIF5B and RET gene fusion in lung adenocarcinoma revealed from whole-genome and transcriptome sequencing. Genome Res. 2012; **22**(3): 436-445.
16) Katayama, R., Y. Kobayashi, L. Friboulet, E. L. Lockerman, S. Koike, A. T. Shaw, J. A. Engelman and N. Fujita. Cabozantinib overcomes crizotinib resistance in ROS1 fusion-positive cancer. Clin Cancer Res. 2015; **21**(1): 166-174.
17) Kwak, E. L., Y. J. Bang, D. R. Camidge, A. T. Shaw, B. Solomon, R. G. Maki, S. H. Ou, B. J. Dezube, P. A. Janne, D. B. Costa, M. Varella-Garcia, W. H. Kim, T. J. Lynch, P. Fidias, H. Stubbs, J. A. Engelman, L. V. Sequist, W. Tan, L. Gandhi, M. Mino-Kenudson, G. C. Wei, S. M. Shreeve, M. J. Ratain, J. Settleman, J. G. Christensen, D. A. Haber, K. Wilner, R. Salgia, G. I. Shapiro, J. W. Clark and A. J. Iafrate. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010; **363**(18): 1693-1703.
18) Lee, J. G., J. H. Shin, H. S. Shim, C. Y. Lee, D. J. Kim, Y. S. Kim and K. Y. Chung. Autophagy contributes to the chemo-resistance of non-small cell lung cancer in hypoxic conditions. Respir Res. 2015; **16**: 138.
19) Lim, S. H., J. M. Sun, S. H. Lee, J. S. Ahn, K. Park and M. J. Ahn. Pembrolizumab for the treatment of non-small cell lung cancer. Expert Opin Biol Ther. 2016; **16**(3): 397-406.

20) Lim, S. M., M. H. Hong and H. R. Kim. Immunotherapy for Non-small Cell Lung Cancer: Current Landscape and Future Perspectives. Immune Netw. 2020; **20**(1): e10.

21) Massarelli, E., V. Papadimitrakopoulou, J. Welsh, C. Tang and A. S. Tsao. Immunotherapy in lung cancer. Transl Lung Cancer Res. 2014; **3**(1): 53-63.

22) Melosky, B. Rapidly changing treatment algorithms for metastatic nonsquamous non-small-cell lung cancer. Curr Onco. 2018; **25**(Suppl 1): S68-S76.

23) Merlo, V., M. Longo, S. Novello and G. V. Scagliotti. EGFR pathway in advanced non-small cell lung cancer. Front Biosci (Schol Ed). 2011; **3**: 501-517.

24) Pan, J. Dabrafenib Plus Trametinib for BRAF V600E-Mutant Non-small Cell Lung Cancer: A Patient Case Report. Clin Drug Investig. 2019; **39**(10): 1003-1007.

25) Pavan, A., I. Attili, G. Pasello, V. Guarneri, P. F. Conte and L. Bonanno. Immunotherapy in small-cell lung cancer: from molecular promises to clinical challenges. J Immunother Cancer. 2019; **7**(1): 205.

26) Pawelczyk, K., A. Piotrowska, U. Ciesielska, K. Jablonska, N. Gletzel-Plucinska, J. Grzegrzolka, M. Podhorska-Okolow, P. Dziegiel and K. Nowinska . Role of PD-L1 Expression in Non-Small Cell Lung Cancer and Their Prognostic Significance according to Clinicopathological Factors and Diagnostic Markers. Int J Mol Sci. 2019; **20**(4).

27) Peters, S., D. R. Camidge, A. T. Shaw, S. Gadgeel, J. S. Ahn, D. W. Kim, S. I. Ou, M. Perol, R. Dziadziuszko, R. Rosell, A. Zeaiter, E. Mitry, S. Golding, B. Balas, J. Noe, P. N. Morcos, T. Mok and A. T. Investigators. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2017; **377**(9): 829-838.

28) Sasada, T., K. Azuma, J. Ohtake and Y. Fujimoto . Immune Responses to Epidermal Growth Factor Receptor (EGFR) and Their Application for Cancer Treatment. Front Pharmacol. 2016; **7**: 405.

29) Schulze, A. B. and L. H. Schmidt. PD-1 targeted Immunotherapy as first-line therapy for advanced non-small-cell lung cancer patients. Journal of Thoracic Disease. 2017; **9**(4): E384-E386.

30) Shaw, A. T., L. Gandhi, S. Gadgeel, G. J. Riely, J. Cetnar, H. West, D. R. Camidge, M. A. Socinski, A. Chiappori, T. Mekhail, B. H. Chao, H. Borghaei, K. A. Gold, A. Zeaiter, W.

Bordogna, B. Balas, O. Puig, V. Henschel, S. I. Ou and i. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. Lancet Oncol. 2016; **17**(2): 234-242.

31) Shaw, A. T., D. W. Kim, R. Mehra, D. S. Tan, E. Felip, L. Q. Chow, D. R. Camidge, J. Vansteenkiste, S. Sharma, T. De Pas, G. J. Riely, B. J. Solomon, J. Wolf, M. Thomas, M. Schuler, G. Liu, A. Santoro, Y. Y. Lau, M. Goldwasser, A. L. Boral and J. A. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med. 2014; **370**(13): 1189-1197.
32) Sweis, R. F., S. Thomas, B. Bank, P. Fishkin, C. Mooney and R. Salgia. Concurrent EGFR Mutation and ALK Translocation in Non-Small Cell Lung Cancer. Cureus. 2016 **8**(2): 513.
33) Van Assche, K., L. Ferdinande, Y. Lievens, K. Vandecasteele and V. Surmont. EGFR Mutation Positive Stage IV Non-Small-Cell Lung Cancer: Treatment Beyond Progression. Front Oncol. 2014; **4**: 350.
34) Reck M, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non–Small-CellLung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. Journal of Cilinical Oncology. 1 November, 2018; 37(7). 537-546.
35) Reck M, et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. The new england journal of medicine. November 10, 2016; 373(19). 1824-1833.
36) Briggs, A. Claxton, K. Sculpher, M.Decision modelling for health economic evaluation. Oxford Univerity Press. 2006
37) Moerkamp A. FFarmacotherapeutisch rapport pembrolizumab (Keytruda®) bij de behandeling van nietkleincellig longkanker met PD-L1-expressie.11 november 2016.
38) Vijgen, S.M.C. Farmaco-Economich rapport voor nivolumab (Opdivo) bij de behandeling van plaveiscel NSCLC. Zorginstituut Nederland. 23 novembre 2015.

39) Ferris RL, Blumenschein G, Fayette J, et al. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival

update of CheckMate 141 with analyses by tumour PD-L1 expression. Oral Oncol. 2018;81:45-51.

40) Ferris RL, Blumenschein G, Fayette J, et al. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumour PD-L1 expression. Oral Oncol. 2018;81:45-51.

41) Moerkamp, A et al. Package advice pembrolizumab (Keytruda®) in advanced (squamous) non-small cell lung cancer. Zorginstituut Nederland. 2015. Available via:https://www.zorginstituutnederland.nl/publicaties/adviezen/2016/12/14/pakketadvies-pembrolizumab-keytruda Accessed at 6.5.2020

42) Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-Effectiveness in Health and Medicine. Oxford: Oxford University Press, 1996.

43) McVeigh, G. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer. NICE. March 2018.

44) Xiaohan Hu, Joel W. Hay. First-line pembrolizumab in PD-L1 positive non-small-cell lung cancer: A cost-effectiveness analysis from the UK health care perspective. Journal of Lung Cancer. 10 July 2018; 166–171.

45) Purchasing power parities (PPP). [OECD] (3 june 2019) Received from: https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm assessed on 12-06-2020

46) Hakkaart-van Roijen, L. Van der Linden, N. Bouwmans, C. Kanters, T. SWAN, Tan, S. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. (2015).

47) Watson, I. Umeweni, N. Pembrolizumab for treating advanced melanoma previously untreated with ipilimumab. NICE. August 2015.

48) Werkzame stof: Pembrolizumab. [zorginstituut Nederland] Received from: https://www.medicijnkosten.nl/databank?zoekterm=PEMBROLIZUMAB&toedieningsvorm=OPLOSSING Assessed on: 29-05-2020

49) Chouaida C, et al. Cost-effectiveness analysis of pembrolizumab versus standard-of-care chemotherapy for first-line treatment of PD-L1 positive (> 50%) metastatic squamous and non-squamous non-small cell lung cancer in France. Journal of Lung Cancer. 1 November 2018; 44–52.

50) Chouaid C, et al. Health-Related Quality of Life and Utility in Patients with Advanced Non–Small-Cell Lung Cancer. Journal of Thoracic Oncology. August 2013; 8(8). 993-1003.

51) Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Tan SS. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Zorginstituut Nederland; 2015. Available via:https://www.zorginstituutnederland.nl/over-ons/werkwijzen-enprocedures/adviseren-over-en-verduidelijken-van-het-basispakket-aan zorg/beoordeling-van-geneesmiddelen/richtlijnen-voor-economische-evaluatie Accessed at 15-5-2020

52) Miguel LS, Lopes FV, Pinheiro B, et al. Cost Effectiveness of Pembrolizumab for Advanced Melanoma Treatment in Portugal. Value Health. 2017;20(8):1065-1073.

53) Huang M, Lou Y, et al. Cost Effectiveness of Pembrolizumab vs. Standard-of-Care Chemotherapy as First-Line Treatment for Metastatic NSCLC that Expresses High Levels of PD-L1 in the United States. Pharmaco Economics. 15 June 2017; 35: 831–844.

54) Zorginstituut Nederland. Pembrolizumab. [Farmacotherapeutisch kompas]. Available at: https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/p/pembrolizumab#groepsoverzicht. Accessed at 10-5-2020.

55) Zorginstituut Nederland. Paclitaxel and Cisplatin. [Farmacotherapeutisch kompas]. Available at: https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/p/paclitaxel

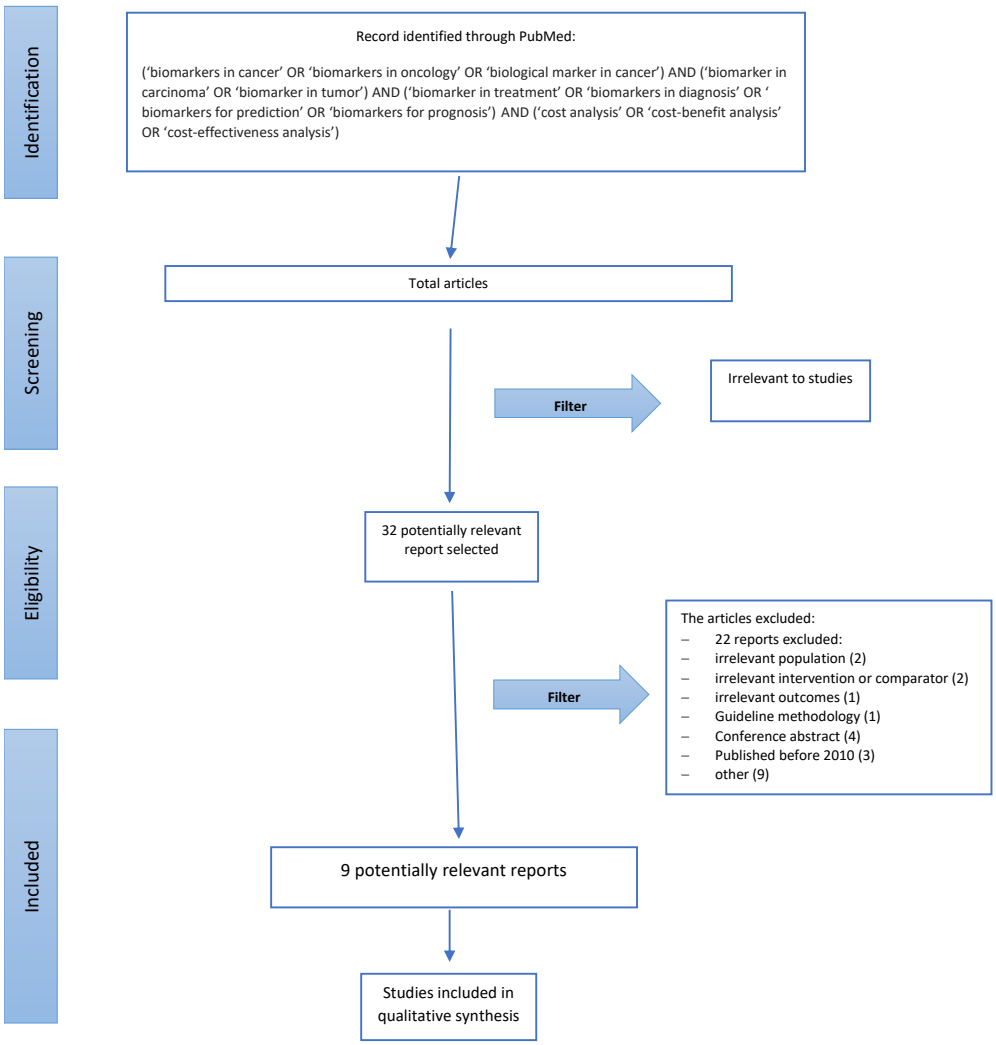
56) Zhoua K, Jiangc K, Lia Q. Cost-effectiveness analysis of pembrolizumab monotherapy and chemotherapy in the non-small-cell lung cancer with different PD-L1 tumor proportion scores. Journal of Lung Cancer. 2019; 136: 98–101.

57) Schiller J H, et al. Comparison of chemotherapy regimens for advanced non-small lung cancer. The New England Journal of Medicine. 10 January, 2002; 346(2): 92-97.

58) National Institute for Health and Care Excellence (NICE). Available via: https://webcache.googleusercontent.com/search?q=cache:KbTLVsVaxhkJ:https://bnf.nice.org.uk/medicinal-forms/paclitaxel.html+&cd=2&hl=en&ct=clnk&gl=nl. Accessed at 10-5-2020.
59) Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making 1993;13:322-38.

# Appendices

## Appendix 1: Characteristics of extracted biomarker



## Appendix 2: Included literatures for cost effectiveness

*Table 7, articles are included in cost-effectiveness for pembrolizumab, the incremental costs per patient, the incremental QALYs per patient, the ICER, the discount rate, the willingness to pay and the conclusion of each study is visible.*

| ***Reference, country, year*** | **Incremental costs per patient** | **Incremental QALY per patient** | **ICER** | **Discount rate (both costs and outcomes)** | **Willingness to pay** | **Conclusion** |
|---|---|---|---|---|---|---|
| *1) PN Aguir et al, USA, 2017.* | USD 82,201 | TPS I:0,346<br>TPS II: 0,409 | USD[1] 98,421/QALY for TPS I<br>USD 80,735/QALY for TPS II | 10% and 20% | USD 100,000/QALY | Yes, pembrolizumab is cost-effective. The parameters with most influence were bodyweight and drug acquisition costs. The cost-effectiveness increased with a higher discount rate. Pembrolizumab was more cost-effective in patients with a higher TPS. |
| *2) Min Huang et al, USA, 2017* | USD 102,439 | 1,05 | USD 97,621/QALY | 3% a year | USD 140,392–382,536/QALY<br>or<br>USD 100,000-150,000/QALY<br>USD 50,000-100,000/QALY | Yes, however AEs with an incidence rate <5% were not included. Pembrolizumab was cost-effective under USD 100,000/QALY if costs increased 3% and under USD 150,000/QALY if costs increased 59%. |
| *3) M Georgivina et al, USA, 2019* | British perspective: USD 99,000-34,000 = 65,000<br>US perspective: USD 132,000-74,000= 59,000 | In both England and the US: 1,93-1,11 = 0,82 | *(without dependency)*<br>**Without end-of-life adjustment:**<br>British perspective: USD 81,000/QALY<br>US perspective: USD 74,000/QALY<br><br>**With end-of-life adjustment:**<br>British perspective: USD 34,000/QALY | 3% a year | British threshold: USD 42,048/QALY<br>US threshold: USD 100,000/QALY | **UK:** No, only cost-effective under the assumption of no dependency<br>**USA:** Yes, pembrolizumab was cost effective in almost all sub analyses of the USA. |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | US perspective: USD 31,000/QALY | | | |
| *4) X Hu et al, USA, 2018* | GBP 72,465 | 0,83 | GBP 86,913/QALY | 3.5% a year | GBP[2] 30,000-50,000/QALT | No, the probability of pembrolizumab as cost-effective is 29,4%. The ICER is most sensitive to duration of median OS. A discount of >50% is needed to be cost-effective. |
| *5 )C Chouaid et al, France, 2018* | Squamous sub-group (only SoC): €62,032 Non-squamous subgroup: €-14,947-€47,064 | Squamous subgroup: 0,74 Non-squamous subgroup: 0,85-1,32 | Squamous sub-group: €84,097/QALY Non-squamous sub-group: €78,729/QALY | 4% a year | €100,011/QALY | Yes, Pembrolizumab has a 60% change to be cost-effective for the squamous subgroup and 70% change to be cost-effective for the non-squamous subgroup. Change of three variabilities led to signification changes in the ICER: treatment duration, second-line costs, efficacy duration of pembrolizumab. |

## Appendix 3: Selection of Included Studies

*Table 8, characteristics of Included biomarker*

| ***Type*** | **Prevalence in NSCLC** | **Biomarker** | **Indication** | **Drug** |
|---|---|---|---|---|
| ***Target therapy*** | 3%-7% | ALK-rearrangement | First-line treatment Second-line treatment /or after progression, stage IV | Crizotinib, Ceritinib, Alectinib, |
| ***Target therapy*** | 2%-5% | BRAF-mutation | First-line treatment, stage IV | Dabrafenib, trametinib |
| | | ATP synthase | | Citreoviridin |
| ***Immunotherapy*** | 24%-60% | PD-L1 expression | First or second-line treatment, stage III | Nivolumab, Pembrolizumab |

| | | | | |
|---|---|---|---|---|
| ***Target therapy*** | 10%-15% | EGFR- mutation | First-line treatment, in stage lllB/lV | Gefitinib, Erlotinib, Afatinib, Osimertinib |
| | | ERBB3 | | Pertuzumab |
| | | BRCA | | Gemcitabine Hydrochloride, |
| ***Target therapy*** | 1% | Ros1-rearrangement | First-line therapy, stage IV | Crizotinib, ceritinib, cabozantinib |

## Appendix 4: drug acquisition costs

*Table 9, Details of the calculation of the costs/cycled of treatment*

| ***PEM:*** | | | | **Paclitaxel:** | **Cisplatin:** | **Source** |
|---|---|---|---|---|---|---|
| | Dose(mg/kg) | 200 | Dose ($mg/m^2$): | 135 | 75 | NICE [37,57,] |
| | Average weight (kg) | 71 | Body surface area (BSA): | 1.81 | 1.81 | HTA analysis ZIN [38] |
| | Amount added (mg) | - | Amount added (mg) | 207.6 | 135.75 | - |
| | Number of vials | 4 | Number of vials | 2.076 | 1.357 | - |
| | Vial price (€) | 1,430.28 | Vial price (€) | 1.404.49 | 45.42 | Drug prices database [54,55] |
| | price per patient per three weeks (€): | 5721.12 | price per patient per three weeks (€): | 2917.090 | 61.657 | - |

## Appendix 5: drug administration costs

*Table 10, Details of the calculation of the costs/cycle for drug administration costs*

| | **Costs (Pounds)** | | **Costs corrected for inflation (pounds) [28]** | **Costs corrected for PPP (pounds) [31]** | **Costs (€)** | **Source** |
|---|---|---|---|---|---|---|
| ***Pembrolizumab*** | 184 | 197.25 | 225.02 | 198.19 | | NICE [37] |
| ***Paclitaxel plus Cisplatin*** | 561.31 | - | 647.985 | 570.74 | | NICE [37, 58] |

## Appendix 6: monitoring costs

*Table 11, The details of the calculation of the cost/cycle for drug monitoring costs*

| **Monitoring** | **Source unit** | **Unit costs** | **Frequency/cycle** | **Cost/cycle** | **Source costs** | **Total** |
|---|---|---|---|---|---|---|
| **Monitoring PF state** | | | | | | |
| Outpatient oncologist visit | NICE | €121 | 1 | €121 | Cost manual [51] | €174.61 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Blood test | NICE | €2.46 | 1 | €2.46 | Cost manual [51] | |
| Chest CT (with contrast) | NICE | €155 | 0.33 | €51.15 | Cost manual [51] | |
| **Monitoring PD state** | | | | | | |
| Outpatient oncologist visit | NICE | €121 | 0.33 | €39.93 | Cost manual [51] | €91.891 |
| Blood test | NICE | €2.46 | 0.33 | €0.811 | Cost manual [51] | |
| Chest CT (with contrast) | NICE | 155 | 0.33 | €51.15 | Cost manual [51] | |

## Appendix 7, disease management costs

*Table 12, An overview of the used disease management parameters and the corresponding frequencies and costs are shown. Frequencies and Portugese unit costs are coming from the study of Miguel et al. The Dutch unit costs, already corrected for inflation, are coming from 'het kostenregister'. The Portuguese costs are corrected for in inflation and PPP. In the last two columns the calculated costs in PFS and PD per trimester are visible.*

| *Event* | mean utilization (PFS) [52] | mean utilization (PD) [52] | Unit costs Portugal (per patient per trimester) [52] | Unit cost corrected for inflation [45] | unit costs corrected for PPP [46] | Unit costs in NL [45] | Costs for PFS patients per trimester | Costs for PD patients per trimester |
|---|---|---|---|---|---|---|---|---|
| *Outpatient visit* | 5.01 | 5.87 | 31 | 31.47 | 42.60 | | 213.43 | 250.07 |
| *Nurse visit* | 2.54 | 1.17 | 16 | 16.24 | 21.98 | | 55.84 | 25.72 |
| *psychologist/Psychiatrist visits* | 0.75 | 1.36 | 18 | 18.27 | 24.73 | 94 | 70.5 | 127.84 |
| *complete blood count* | 4.35 | 0.98 | 4.7 | 4.77 | 6.45 | | 28.09 | 6.32 |
| *ionogram* | 4.35 | 0.98 | 1.5 | 1.52 | 2.06 | | 8.96 | 2.02 |
| *biochemistry* | 4.35 | 0.98 | 11.2 | 11.37 | 15.39 | | 66.95 | 15.08 |
| *hepatic function* | 4.35 | 0.98 | 8.2 | 8.32 | 11.26 | 4,07 | 17.70 | 3.98 |
| *CT abdomen* | 0.98 | 0.15 | 199.8 | 202.87 | 274.57 | 140 | 137.2 | 21 |
| *brain CT* | 0.43 | 0.11 | 79 | 80.21 | 108.56 | 129 | 55.47 | 14.19 |
| *brain MRI* | 0.29 | 0.02 | 291.9 | 296.38 | 401.14 | 206 | 59.74 | 4.12 |
| *chest radigraphy* | 0.47 | 0.24 | 9 | 9.13 | 12.36 | 87 | 40.89 | 20.88 |
| *eco* | 0.12 | 0.71 | 16.4 | 16.65 | 22.53 | 80 | 9.6 | 56.8 |
| *bloodtransfusion* | 0.23 | 0.22 | 127.6 | 129.56 | 175.35 | 186 | 42.78 | 40.92 |
| *radiotherapy* | 4.59 | 2.19 | 104.5 | 106.10 | 143.60 | | 659.16 | 314.50 |
| *radiosurgery* | 0.02 | 0.01 | 4694.5 | 4766.65 | 6451.41 | | 129.02 | 64.51 |
| *analgesics (paracetamol)* | 54.79 | 79.08 | 0.42 | 0.42 | 0.57 | 0.52 | 28.49 | 41.12 |
| *Corticosteroids (predinisolon)* | 16.92 | 26.31 | 0.38 | 0.38 | 0.52 | 3.31 | 56.005 | 87.08 |
| *Antiemetic agents (graniesteron)* | 29.86 | 45.66 | 0.13 | 0.13 | 0.17 | 0.38 | 11.34 | 17.35 |
| *antacid agents (omeprazol)* | 53.27 | 70.11 | 0.03 | 0.03 | 0.041 | 0.03 | 1.59 | 2.10 |
| *benzodiazepines (oxazepam)* | 45.66 | 65.22 | 0.02 | 0.02 | 0.027 | 0.14 | 6.39 | 9.13 |
| *antidepressants (ssri, citalopram)* | 28.15 | 47.29 | 0.03 | 0.03 | 0.04 | 3.31 | 93.17 | 156.52 |
| | | | | | | **Total (per trimester** | **1792.39** | **1281.311** |
| | | | | | | **Total (per three weeks):** | **413.94** | **295.91** |

## Appendix 8: societal costs and informal care costs

*Table 13, In this table the travel costs (fort he used distance) and the hours of informal care for both PFS and PD stage with the corresponding costs are visible. In the last column the used sources are given*

| ***Parameter*** | | | | | **Source** |
|---|---|---|---|---|---|
| *Travel costs/cycle PFS* | **Distance (km)** | **Travel costs for this distance corrected for inflation (€)** | | | HTA analysis ZIN [37,38] |
| | 10,5 | | | | |
| | **Hours/week** | **Cost/hour(€)** | **Total costs in 2015 (€)** | **Costs corrected for inflation (€)** | |
| *Informal care PFS* | 6 | 14 | 269.82 | 280 | HTA ZIN [37,38], Dutch cost manual [46] |
| *Informal care PD* | 10 | 14 | 449.7 | 467 | - |

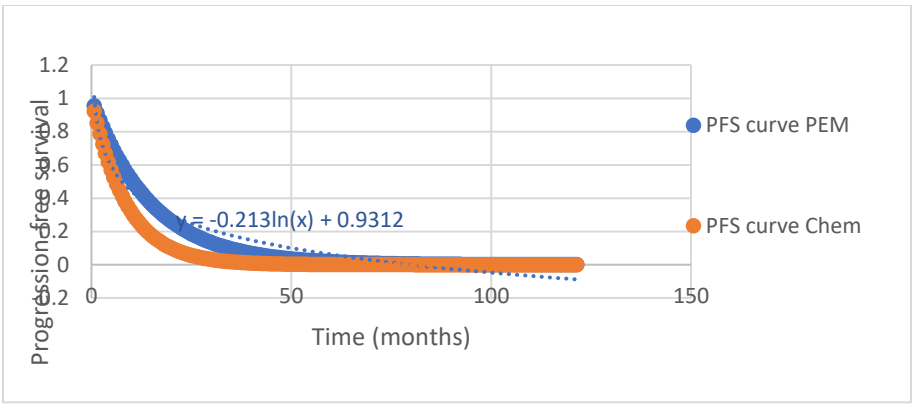
## Appendix 9: values of the most varying parameters in the univariate sensitivity analysis

*Table 14, In this table the corresponding values of the univariate sensitivity analysis are shown.*

| | **Lower bound** | **Upper bound** |
|---|---|---|
| *Utility PFS PEM* | *123,690.36* | *188,195.17* |
| *Utility PD PEM* | *111,860.34* | *224,284.74* |
| *Median PFS PEM* | *176,061.14* | *121,402.24* |
| *Median OS PEM* | *130,913.83* | *183,292.76* |
| *Utility PFS Chem* | *167,686.92* | *134,501.83* |
| *Vial price PEM* | *177,745.85* | *120,798.66* |
| *Median PFS Chem* | *142,298.28* | *156,572.16* |
| *Median OS Chem* | *173,295.03* | *130,980.55* |
| *Vial price Paclitaxel* | *139,317.45* | *159,227.06* |
| *Vial price Cisplatin* | *149,093.40* | *149,451.10* |

## *Appendix 10: OS and PFS curves pembrolizumab and chemotherapy*

*Figure 15, PFS curve of both pembrolizumab and paclitaxel plus Cisplatin. The orange line represents the curve of paclitaxel plus Cisplatin and blue line represents the curve of pembrolizumab.*




*OS curve of both pembrolizumab and paclitaxel plus Cisplatin. The orange line represents the curve of ipilimumab and the blue line represent the curve of pembrolizumab.*