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Cost-effectiveness of first-line nivolumab plus ipilimumab combined with two cycles of platinum-doublet chemotherapy compared to four cycles of platinum-doublet chemotherapy in patients with advanced non-small-cell lung cancer in a Dutch healthcare system

MASTER THESIS HEALTH ECONOMICS

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Abstract

Objectives

The CheckMate 9LA trial demonstrated a beneficial effect on survival of adding a limited course (two cycles) of platinum doublet chemotherapy (PDC) to nivolumab and ipilimumab (NIC) in patients with aNSCLC whose tumors do not harbor a sensitizing Epidermal Growth Factor Receptor (EGFR) mutation or Anaplastic Lymphoma Kinase (ALK) translocation, to improve disease control during the initial phase of immunotherapy treatment. Although this comes with an unprecedented improvement in survival, costs concerned with the treatment of aNSCLC are expected to increase. It is critical to assess the cost-effectiveness of chemo-immunotherapy combination treatment NIC compared to PDC for advanced NSCLC patient in the Netherlands, in order to inform decision making with respect to reimbursement of first-line NIC.

Methods

A three-state partitioned survival model was developed to assess whether NIC is cost-effective compared to PDC by means of a cost-utility analysis. Costs and effects were calculated from a Dutch societal perspective over a lifetime horizon, with effects being measured in quality-adjusted life year (QALY). Future effects and costs were discounted at 1,5% and 4%, respectively. The cost-effectiveness is assessed by calculating a base case incremental cost-effectiveness ratio (ICER) and compared to the societal willingness-to-pay threshold (WTP) of €80.000 per QALY gained. Deterministic (DSA), probabilistic sensitivity analysis (PSA), scenario analysis, value-of-information analysis and a budget impact analysis were conducted.

Results

Total discounted per patient costs for NIC and PDC were €225.715 and €123.729, and mean QALYs were 1,74 and 1,19 per patient, respectively. NIC resulted in €133.968/LY and €185.579/QALY gained compared to PDC. DSA showed that the base case ICER is particularly sensitive to variation in health state utilities and the price of nivolumab and ipilimumab. The PSA showed that NIC had 0% probability to be cost-effective at a threshold of €80.000/QALY. A price reduction of 60% is required for nivolumab and ipilimumab to be regarded as cost-effective at a threshold of €80.000/QALY. Use of NIC in the first-line treatment of advanced

NSCLC will be associated with costs estimated at €103.210.470 after year 2 of incorporation into the package, assuming a market penetration of 37%.

Conclusion

NIC compared to PDC is not regarded as cost-effective at the Dutch WTP threshold of €80.000 per QALY gained.

Preface

This thesis is an excellent addition to my master in Health Economics at the Erasmus University Rotterdam and a great extension to my previously obtained Bachelor degrees in Health Policy and Management, and Economics and Business Economics. With ultimately the aim of combining economic knowledge with the knowledge and passion that I have developed for healthcare. I believe the combination of economics and healthcare is more relevant than ever at the moment. Diving into cost-effectiveness gave me a feeling on working something highly relevant and challenging that will impact and improve the healthcare system. Developing a cost-effectiveness model for the first time was challenging and I learned a lot the past year. I undoubtedly consider the knowledge I have acquired in health economics, and HTA in particular, of great value.

I would like to express my gratitude to my supervisor Renaud Heine for his enthusiastic guidance and constructive feedback throughout the process. I appreciate all the advice he provided me with during the many (digital) meetings over the past year. Although my thesis work needed to be done almost entirely from home, I believe we have made the best of the situation and were able to have fruitful discussions nonetheless. Special thanks go to my family, friends and boyfriend for their interest in my thesis, unconditional support and encouragement during this busy and sometimes stressful period and their valuable comments on my initial report.

A.F. de Jong
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List of abbreviations

AIC	Akaike information criteria
aNSCLC	Advanced stage non-small cell lung cancer
BIC	Bayesian information criteria
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CPI	Consumer price index
CUA	Cost-utility analysis
DSA	Deterministic sensitivity analysis
EVPI	Expected value of perfect information
HTA	Health technology assessment
HRQol	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
INMB	Incremental net-monetary benefits
NIC	Nivolumab plus ipilimumab plus platinum doublet chemotherapy
NICE	National Institute for Health and Care Excellence
NMB	Net-monetary benefit
NSCLC	Non-small cell lung cancer
NSQ	Non-squamous histology
OS	Overall survival
PDC	Platinum doublet chemotherapy
PEVPI	Population-based expected value of perfect information
PFS	Progression-free survival
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
SCLC	Small-cell lung cancer
SQ	Squamous histology
WTP	Willingness-to-pay
ZIN	Dutch National Health Care Institute

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1. Introduction

Lung cancer is one of the most frequently diagnosed cancers and is the leading cause of cancer-related death (with 18% of the total) worldwide (WHO Globocan, 2020). The World Health Organization (WHO) divides lung cancer into 2 major classes based on its biology, therapy and diagnosis: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for more than 85% of all diagnosed lung cancer cases (IKNL, 2021). In the Netherlands the estimated number of new cases of lung cancer in 2020 was 13.500 with 11.188 estimated deaths (WHO Globoscan, 2020,). Half of patients with NSCLC are diagnosed with advanced-stage (stage IV) cancer (aNSCLC) owing to inadequate screening programmes and late onset of clinical symptoms (Gridelli et al., 2015; Alexander, Kim & Cheng, 2020; IKNL, 2021). Consequently, most of the patients with advanced-stage are ineligible for surgical resection (IKNL, 2020). Median overall survival and 5-year survival rate for patients with aNSCLC have historically been poor. Treatment with platinum-based chemotherapy as first-line therapy for patients with aNSCLC has a median survival of approximately 10 months, and a 5-year survival rate of less than 5%. (IKNL, 2021; Ettinger et al., 2012). The landscape for treatment options for aNSCLC has been largely extended over the past years by new strategies through the addition of advances in targeted therapy and immunotherapy (Lim, Hong & Kim, 2020; Xia, Liu & Wang, 2019; Melosky, 2018). The introduction of these novel agents resulted in improved outcomes in terms of 5-year survival. The 5-year survival rate now when treated with immunotherapy is 15% (Garon, Hellmann, Rizvi et al., 2019; Rocco, Gravara, Battiloro & Gridelli, 2019; Chen et al., 2020). However, even with these agents the prognosis of patients affected by aNSCLC still remains poor.

Different possibilities are being explored to improve survival outcomes, with chemo-immunotherapy combination therapies being one of the most promising. Recent development of immune checkpoint inhibitors, such as pembrolizumab, nivolumab, ipilimumab and atezolizumab, have attracted attention for their unprecedented effect on progression-free (PFS) and overall survival (OS) (FMS, 2020; IKNL, 2020; Melosky, 2018). However, improved disease control is needed during the initial phase of immunotherapy treatment to enhance clinical benefit (Paz-Ares et al., 2021). The Checkmate 9LA clinical trial

demonstrated a beneficial effect on survival of adding a limited course (two cycles) of chemotherapy to nivolumab plus ipilimumab in patients with aNSCLC whose tumors do not harbor a sensitizing Epidermal Growth Factor Receptor (EGFR) mutation or Anaplastic Lymphoma Kinase (ALK) translocation.

1.1 Treatment scheme for patients with aNSCLC

For most patients with aNSCLC, the aims of treatment are to prolong survival and improve quality of life. Patients with aNSCLC are candidates for systematic therapy consisting of chemotherapy, targeted therapy, or immunotherapy (Ettinger et al., 2012). The goals of systematic therapies are to shrink the cancer, relieve discomfort caused by the cancer, prevent the cancer from spreading further, and lengthen a patient's life (Cancer.net, 2021). Treatment selection within systematic therapy is usually based on histology or biomarkers, i.e. driver mutations or Programmed Death-Ligand 1 (PD-L1) expression (a protein on the surface of cells). Until recently, the standard of care for aNSCLC was platinum doublet chemotherapy for 4-6 cycles (Melosky, 2018). Development of respective targeted treatments in the first-line setting and in subsequent lines represent an improvement over conventional chemotherapy for patients with known driver mutations, such as genetic alterations in the EGFR, ALK and Ros1 protooncogene receptor tyrosine kinase (Chan & Hughes, 2015). Whilst impressive clinical benefits have been observed for aNSCLC with a known driver mutation, for the vast majority of patients no known drivers are detected. For patients without known driver mutations treatment therapies that incorporates immunotherapy, either as a single agent or with chemotherapy, can be offered (Nassar, Gorenberg & Agbarya, 2020). Threshold levels of PD-L1 expression are used to determine which immunotherapy treatment is suitable. The success of PD-1/PD-L1 immune checkpoint inhibitors has been the most important change in the NSCLC treatment paradigm (Melosky, 2018).

These targeted agents and immune checkpoint inhibitors have come with improved outcomes, but also increased costs (Sleijfer & Verweij, 2009; Verma et al., 2018). Lung cancer has a substantial economic burden on society with total costs of lung cancer in the Netherlands are estimated to be over 457 million euros in the year 2017. The majority of these costs are spent on hospital care (87%) (Plasmans, Ramjiawan, Vonk et al., 2019). Total mean

hospital costs, including chemotherapy, monitoring and follow-up care, are estimated to be €33.143 per patient with NSCLC in the Netherlands (van der Linden et al., 2016).

1.2 The Checkmate 9LA trial: chemo-immunotherapy as first-line treatment

Immunotherapy plus chemotherapy has been approved regardless of PD-L1 expression levels in both patients with squamous (SQ) and non-squamous (NSQ) histology (Paz-Ares et al., 2021). Promising objective response rate was observed in the Checkmate 012 trial in which patients without targetable EGFR or ALK aberrations received nivolumab plus standard of care chemotherapy (Rocco et al., 2019). Furthermore, data from the Checkmate 227 trial showed the clinical benefit across PD-L1 expression levels and tumor histology's of nivolumab plus ipilimumab in patients with NSCLC. In both trials the immunotherapy performed well when compared to chemotherapy alone in terms of PFS (Rocco et al., 2019). It was postulated that a short course of chemotherapy added on to nivolumab and ipilimumab might improve early survival and preserve the long-term benefit from nivolumab and ipilimumab. Therefore, the Checkmate 9LA trial randomized patients with metastatic NSCLC to nivolumab and ipilimumab plus two cycles of platinum-doublet chemotherapy (which will be referred to as NIC), versus four cycles of platinum-doublet chemotherapy (which will be referred to as PDC). The results of the Checkmate 9LA trial showed improved OS compared with PDC, with a median OS of 14.1 months versus 10.7 months, respectively. The one-year OS was 63% for the NIC arm and 47% for the PDC arm (Paz-Ares et al., 2021). The treatment was registered by the European Medicines Agency (EMA) in September 2020 (EMA, 2020). While clinical results are favorable, this new treatment is expected to increase treatment costs for NSCLC patients.

1.3 Relevance of cost-effectiveness

The increasing cost of innovative cancer drugs imposes a heavy economic burden on the society and healthcare system. Furthermore, the Dutch Ministry of Health has a limited budget to finance healthcare and a vast number of potential spending options. Thus, within these boundaries choices must be made as to how this limited budget is spent. In response to rising healthcare costs, payers increasingly consider the cost-effectiveness of novel treatments in reimbursement decisions. Cost-effectiveness analysis enables the decision maker to consider systematically the most efficient health, when costs matter. It compares the incremental costs with the incremental effects of the treatments and thus provides insight

into which option gives the most value for money. And today, costs frequently matter (Weinstein, Wittenberg et al., 2014). As the number of therapies available to treat aNSCLC increases, cost-effectiveness analysis will play an important role in reimbursement decisions in this area. It is thus highly relevant to investigate the cost-effectiveness of first-line application of NIC for aNSCLC patients to support decision making. The results of this study could help to further facilitate the reimbursement discussion that is expected to take place with expensive treatments like this.

1.4 Research question

The aim of this study is to evaluate whether NIC compared to PDC is cost-effective for aNSCLC patients without known driver mutations. This will be investigated by using the latest clinical 2-year-survival data published in October 2021 (Reck et al., 2021). Cost-effectiveness is calculated for the Dutch healthcare setting by means of a cost-utility analysis. Furthermore, this study attempts to provide reference for policy decisions. Therefore, the main research question is:

What is the cost-effectiveness of nivolumab plus ipilimumab and two cycles of platinum-doublet chemotherapy (SQ: carboplatin plus paclitaxel; NSQ: carboplatin plus pemetrexed or cisplatin plus pemetrexed) compared to four cycles of platinum-doublet chemotherapy alone ((SQ: carboplatin plus paclitaxel; NSQ: carboplatin plus pemetrexed or cisplatin plus pemetrexed) for first-line treatment of advanced NSCLC in the Netherlands?

Sub questions:

- What are the health effects of NIC and current standard of care treatment (four cycles of PDC)?
- What are the costs of NIC and current standard of care treatment (four cycles of PDC)?
- What is the incremental cost-effectiveness ratio (ICER)?
- To what extent is the ICER uncertain when changing input parameters?
- What is the budget impact?
- What are the conclusions for decision making using the willingness-to-pay threshold?

The remainder of this thesis will be structured as follows. Chapter 2 elaborates on the background of chemo-immunotherapy combination treatment and the framework for economic evaluations. Chapter 3 describes the methodology to conduct the cost-utility analysis in a Dutch healthcare setting. Chapter 4 presents the results of the cost-effectiveness analysis and the budget impact analysis. Finally, chapter 5 includes an overall conclusion, the points for discussion, limitations of the research, and implications for Dutch policy makers.

2. Background

2.1 Epidemiology

The disease stages of lung cancer ranges from stage I to IV, with stage IV corresponding to metastatic lung cancer. Patients with metastatic disease are no longer eligible for treatment with curative intention. The 5-year survival rate is on average 62% in stage I, 44% in stage II, 19% in stage III and only 3% in stage IV (Kanker.nl, 2021; IKNL, 2021). However, in recent years, several treatment options have become available, therefore the 5-year survival rate is expected to increase (Garon, Hellmann, Rizvi et al., 2019; Rocco, Gravara, Battiloro & Gridelli, 2019; Chen et al., 2020). According to the IKNL, in 2020 there were 36.764 patients in the Netherlands who have or have had lung cancer (20-year prevalence). In addition, 13.500 new people in the Netherlands are diagnosed with lung cancer every year, of which approximately 10,000 people are diagnosed with NSCLC (IKNL, 2021). There are slightly more men than women (55% versus 45%) in the Netherlands with lung cancer. When diagnosed with NSCLC, 16% of patients are in stage I, 9% in stage II, 25% in stage III, and 50% in stage IV (Kanker.nl, 2021).

2.2 Burden of disease

Half of the NSCLC patients already have metastatic disease at the time of diagnosis and are no longer eligible for curative treatment. Furthermore, aNSCLC strongly influences life expectancy. The Dutch National Health Care Institute (ZIN) uses categories with burden of diseases and reference values of costs per QALY, given that burden of disease (ZIN, 2018b). The burden of disease is determined on the basis of the loss of quality of life and influence on life expectancy. To determine the disease burden of aNSCLC, the approach taken in the pharmacoeconomic report of nivolumab for NSCLC and the pharmacoeconomic report of pembrolizumab for NSCLC is used (ZIN, 2015; ZIN, 2016a). For aNSCLC the estimated burden of disease will likely be between 0,7 and 0,9, which classifies as the highest burden of disease and therefore justifies a WTP threshold of €80.000 per QALY gained (ZIN, 2018b).

2.3 Chemo-immunotherapy combination treatment

To date, chemotherapy and immunotherapy as stand-alone therapies play an important role in the treatment of NSCLC. Immunotherapy is recommended both for non-squamous and

squamous histology immune checkpoint inhibitors naïve patients. Immune checkpoint inhibitors can block the inhibitory pathways that are important in the immune system's ability to control cancer growth, restoring and sustaining antitumor (Lim, Hong & Kim, 2020). Combination trials assessing combination of immune checkpoint inhibitors with chemotherapy, targeted therapy are ongoing (Kaufman, 2015; Melosky, 2018; Lim, Hong & Kim, 2020; Chen et al., 2020). The four agents nivolumab, pembrolizumab, ipilimumab and atezolizumab have been investigated for efficacy in clinical trials involving NSCLC patients (Borghaei et al., 2015; Reck, Rodriquez-Abrue, Robinson et al., 2016; Hellmann et al., 2019; Herbst et al., 2020). Most trials assessed the efficacy in the second-line setting and showed improvement in OS with the immune checkpoint inhibitor monotherapy compared with standard chemotherapy in previously treated and untreated patients with NSCLC. Currently, the anti-PD-1 agent pembrolizumab is approved for use as first- and second-line therapy in patients whose tumors express high levels of PD-L1 (50% or greater) (Reck et al., 2016). Access to first-line pembrolizumab is limited to patients with high expression of PD-L1. For other patients, several immune checkpoint inhibitors are available in the second-line. Nivolumab (anti-PD-1) and atezolizumab (anti-PD-L1) are both indicated as monotherapy for use as second-line therapies regardless of PD-L1 expression (Lim, Hong & Kim, 2020). For first-line therapy for patients with low expression of PD-L1, immunotherapy in combination with chemotherapy is recommended (Chen et al., 2020). Immunotherapy-based regimen alone or in combination with chemotherapy is now the preferred option (Xia, Liu & Wang, 2019).

A new first-line chemo-immunotherapy combination treatment for aNSCLC was registered by the EMA (EMA, 2020). This concerns the registration of nivolumab plus ipilimumab with two cycles of platinum-based chemotherapy for first-line treatment of aNSCLC whose tumors do not harbor a sensitizing EGFR mutation or ALK translocation (Paz-Ares et al., 2021). The CTLA-4 inhibitor ipilimumab provides anti-tumor T cell responses which keeps the immune system in check and the PD-1 inhibitor nivolumab enhances an existing T cell response which prevents the immune system from attacking cancer cells. This results in a restored anti-tumor T cell function (Altena, 2019). Both agents therefore have different mechanisms of action, which work synergistically. This has been confirmed in the treatment of patients with renal cell carcinoma and melanoma, where the combination of nivolumab plus ipilimumab showed clinical activity (BMS, 2019). During the European Society for Medical Oncology Congress in

2019, comparable results were shown in patients with NSCLC (Altena, 2019). However, there remains a need for disease control during the first few weeks of immunotherapy to enhance clinical benefit (Paz-Ares et al., 2021).

2.4 Economic evaluations

Healthcare spending for NSCLC has increased with the growing number of new expensive treatments (van der Linden et al., 2016). The effect of choosing one course of action over another will not only have effects on health, but also on healthcare resources. Therefore, it is necessary to take consideration of costs and benefits in making healthcare decisions in so called economic evaluations. Economic evaluations are carried out to compare the cost-effectiveness of alternative healthcare interventions and inform decision making about which healthcare interventions to fund from available resources (Briggs, Claxton & Sculpher, 2006). Because of increasing pressure on the healthcare budget with new innovative expensive treatments and the fact that healthcare resources are finite, the focus has shifted on assessing both clinical- and cost-effectiveness. These health economic models that estimate cost-effectiveness of new strategies are commonly used to support decision making. Resulting cost-effectiveness estimates can inform hospital-, industry- and governmental policy makers on costs of NSCLC and impact of new treatment technologies.

Standardization of methodology for economic evaluations is needed to ensure high-quality evaluations and obtain outcomes that can be compared between healthcare interventions. For this purpose, pharmacoeconomic guidelines have been developed (Hakkaart-van Roijen et al., 2015). According to the Dutch guidelines of ZIN, economic evaluations require several methodological choices, for example with respect to which costs should be included and how to calculate costs and discounting. The different aspects that must be addressed in economic evaluation according to the Dutch guidelines are further explained below.

2.4.1 Cost-effectiveness analysis and outcomes

There are different types of cost analysis: cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), and cost-utility analysis (CUA). In CBA a monetary valuation of the different effects of the healthcare intervention is undertaken using prices that are revealed in markets. This can also be achieved by inquiring about the willingness to pay for different outcomes. In

CEA costs are related to a single, common effect that may differ in magnitude between the alternative treatments. The effects can be expressed in common natural units, such as life-years gained or improvement in functional status. The limitation of this analysis is the difficulty to compare alternative healthcare interventions with effects expressed in different natural units. Studies of CUA are essentially a variant of cost-effectiveness. The only difference is that they use for the effects a generic measure of health gain. This offers the potential to compare healthcare interventions in different areas of healthcare and to assess the opportunity cost (on the healthcare budget) (Drummond et al., 2005).

CUA focus on the incremental cost of a new healthcare intervention compared to the incremental health improvement from the new healthcare intervention, where the health improvement is measured in quality-adjusted life year (QALY). QALY is a weighted aggregate of health utilities over time. The outcome of CUA is typically expressed in terms of the cost per healthy life-year gained, or cost per QALY gained (Drummond et al., 2005). The advantage of the QALY as a measure of health outcome, is that it can simultaneously capture the effects of life expectancy and health-related quality of life by combining these into a single measure (Briggs, Claxton & Sculpher, 2006). The use of a generic measure of outcome such as the QALY enables comparison across healthcare interventions and disease areas. The result of such a comparison is stated in terms of an incremental cost-effectiveness ratios (ICER) expressed as the incremental cost to gain an extra QALY. This approach incorporates both increases in survival time and changes in quality of life into one measure. The cost-effectiveness is assessed by comparing the ICER estimate with a threshold value which decision makers are willing to pay for an additional unit of effect. This threshold is referred as a willingness-to-pay threshold. The Dutch National Health Care Institute currently applies a threshold of €80.000 per QALY for high severe diseases (ZIN, 2018b).

2.4.2 Perspective

The perspective is the point of view adopted in an economic evaluation. It can have an important influence in how an intervention is assessed, because of deciding which types of costs and benefits are to be included. A healthcare intervention that looks unattractive from one perspective may look better when other perspectives are considered. Possible perspectives include those of society, the health service, the Ministry of Health, other

government ministries, the government in general, the patient, and the employer (Drummond et al., 2005). Typical viewpoints are those of the health service, since economic evaluations are used to assess the relative efficiency of alternative healthcare interventions, or the society, since the healthcare intervention impacts the welfare of the whole society and not just on the individuals directly involved. A healthcare perspective in an economic evaluation will only include direct and indirect health costs. This encompasses treatment costs such as medicine costs, administration and monitoring, other health service resource use costs associated with managing the disease (e.g. hospital admissions, general practitioner visits), and costs of managing adverse events caused by treatment. In a societal perspective point of view indirect costs outside of healthcare such as travelling costs, informal care costs, and costs or benefits that may occur in other sectors (e.g. productivity losses), are also considered (Drummond et al., 2005).

2.4.3 Time horizon

The time horizon used for an economic evaluation is the duration over which health effects and costs are calculated. The time horizon should be sufficiently long to reflect all the key differences in costs and effects between the healthcare interventions being compared (Briggs, Claxton & Sculpher, 2006; Drummond et al., 2005). The choice of time horizon can depend on the nature of the disease and intervention. Longer time horizons are applicable to chronic conditions associated with constant medical management. A shorter time horizon may be appropriate for some acute conditions, for which long-term consequences are less important. The appropriate time horizon for healthcare interventions with a potential mortality effect will often need to be the patient's lifetime to capture all the differences in costs and effects (Briggs, Claxton & Sculpher, 2006). Clinical studies will not follow all patients up until they die. Thus, the use of a lifetime horizon involves extrapolating of the survival curves. The use of modelling to extrapolate beyond the follow-up period in the clinical study involves predicting what the survival curves will look like beyond what has been observed (Drummond et al., 2005). Establishing a robust estimate of OS for patients treated with immunotherapy is of increased importance to capture the pattern of delayed treatment effects and, for a subset of patients, the plateau of long-term survival (Gibson et al., 2017; Bullement et al., 2020). Longitudinal time-to-event data are primarily extrapolated by assuming a parametric distribution (Hoyle & Henley, 2011; Guyot et al., 2012). Extrapolation is achievable by

estimating the parameters of this distribution on the basis of the observed data from the Kaplan-Meier curve. Commonly used parametric distributions are exponential, Weibull, log-normal, log-logistic, generalized gamma and Gompertz (Gibson et al., 2017).

2.4.4 Discounting

Comparison of healthcare interventions are usually made in the present, but the timing of costs and consequences that do not occur entirely in the present must be considered. Different healthcare interventions may have different time profiles of costs and consequences. In many circumstances the health benefits will occur in future periods. For example, the life-years and QALYs gained from an intervention that reduces mortality will occur in future periods. Similarly, interventions will not just impose costs and offer cost savings in the current period but in future periods as well. Discounting of health benefits is based on the concept of time preference, meaning that society prefers to benefit sooner rather than later (Severens & Milne, 2004). Therefore, when projecting costs and benefits into the future, those costs and effects need to be discounted to reflect the fact that the amounts spent or saved in the future should not weigh as heavily in decisions as those spent or saved today. Discounting allows to set equivalents for outcomes that play out at different times (Hunink, Weinstein, Wittenberg et al., 2014). This ensures that the time preferences of the society affected by the decision are taken into account.

2.4.5 Decision modelling

Elements to decision analysis are the use of probabilities to reflect the likelihood of changes in health and the expected values of the costs or outcomes. When using decision models to estimate the costs and health effects of interventions, a range of alternative approaches can be used, such as decision trees and Markov models (both cohort models), and partitioned survival models (theoretical cohort model). Health technology assessment in lung cancer are typically based on Markov models or partitioned survival models (McEwan et al., 2016).

The decision tree represents individuals' possible prognoses in terms of branches by a series of pathways (Drummond et al., 2005). The decision nodes in the tree indicate a decision point between alternative options. The branches represent the possible events patients may experience at that point in the tree. The likelihood of the event is represented in terms of

branch probabilities and the combination of the different branches determines a series of pathways for patients. The expected cost for the interventions can be calculated by weighting each pathway cost by its respective probability, and then summing across all the pathways (Drummond et al., 2005).

Markov models are structured around mutually exclusive health states over a series of discrete time periods (cycles) (Drummond et al., 2005). The length of these cycles depend on the disease and interventions. A consideration in assessing the appropriate length of the cycle is to limit the probability that a patient can experience more than one event in the time of the cycle. Transition probabilities are used to determine the speed with which patients move between the health states in the model. This requires estimates of the individual transition probabilities. These transitions can occur either at the beginning or at the end of each cycle. A half-cycle correction is used to remedy the bias of over- or underestimation resulting from assuming patients move at the beginning or end of the cycle (Naimark, Kabboul & Krahn, 2013). Costs and effects in the Markov model are a mean value per state per cycle. Application of a state transition model such as the Markov model raises implementation challenges. The individual transitions are not typically reported in clinical trials publications. This is not problematic in cases where there is access to individual patient data. Nevertheless, it is often the case that modelers do not have this access and estimating the required transition probabilities becomes more challenging (Woods et al., 2020).

Partitioned survival models are also characterized by a series of health states with associated state values. Nevertheless, partitioned survival models do not use transitions between states to determine the proportion of patients in each health state at each point (Woods et al., 2020). Instead the number of patients occupying health states is predicted using the area under the curve of parametric survival distributions for OS and PFS. The partitioned survival model has been extensively used in the National Institute for Health and Care Excellence (NICE) Technology Appraisal Programme and is now the most commonly used approach for NICE appraisals of interventions for advanced or metastatic cancers. (Woods et al., 2020; Woods et al., 2017). The health states commonly applied in economic evaluations of treatments for advanced or metastatic cancer includes progression-free, progressed and dead. Where progression implies a worsening of spreading of the cancer. The OS curve describes time from

model entry to death and is used to directly determine the proportion of patients alive and dead over time. The PFS curve describes time from model entry to exiting the progression-free state via progression or death. Individuals in the progressed health state are derived as the difference between the OS and the PFS curve at each point. This represents the proportion of patients who are alive, but not progression free. Partitioned survival models therefore directly use standard survival analysis of clinical time-to-event endpoints to derive state membership. This approach can be applied to models if patients only move progressively through health states. There is no backward transition from progressed to progression-free allowed.

2.4.6 Sensitivity analysis

The approach for dealing with uncertainty is called sensitivity analysis. In a sensitivity analysis various parameters in the model are varied in order to assess how this impacts the results (. The most common form of sensitivity analysis is a one-way deterministic sensitivity analysis (DSA). In a DSA each parameter is varied one at a time in order to investigate the impact on the results (Briggs, Claxton & Sculpher, 2006). However, DSA cannot handle the combined variability in several parameters. Second, a probabilistic sensitivity analysis (PSA) is used in economic evaluations. PSA involves sampling parameters from their respective distributions (Briggs, Claxton & Sculpher, 2006). This is repeated many times resulting in a distribution of outputs that can be graphed on a cost-effectiveness plane (CE-plane). In addition, an output of the PSA is the proportion of results that fall favourably (cost-effective) in relation to a given cost-effectiveness threshold, which is presented using a cost-effectiveness acceptability curve (CEAC).

3. Methods

3.1 Patient population

The economic evaluation considers adults with untreated stage IV NSCLC without known EGFR mutation or ALK translocation. This is consistent with the study population of CheckMate 9LA. The economic evaluation was performed for the Dutch healthcare setting in accordance with current guidelines (ZIN, 2016b).

3.2 Intervention and comparator

Nivolumab plus ipilimumab plus 2 cycles of platinum doublet chemotherapy is registered for first-line treatment of stage IV NSCLC in adults without known EGFR mutation or ALK translocation (NIC arm). The comparator in this economic evaluation is platinum doublet chemotherapy for 4 cycles (PDC arm). Drug administration schedules in the CUA were consistent with the CheckMate 9LA trial. Nivolumab was administered at a dose of 360 mg intravenously every 3 weeks and ipilimumab at a dose of 1mg/kg intravenously every 6 weeks. Histology-based platinum doublet chemotherapy was administered intravenously every 3 weeks for two cycles in the NIC arm and every 3 weeks for four cycles in the PDC arm. The chemotherapy regimens for both treatment arms consisted of carboplatin plus paclitaxel for patients with squamous histology, and carboplatin or cisplatin plus pemetrexed for patients with non-squamous histology. In patients with squamous histology, carboplatin was administered at a dose of the area under the concentration-time curve (AUC) 6, and paclitaxel was administered at a dose of 200 mg/m^2. In patient with non-squamous histology, carboplatin was administered at a dose of AUC 6, cisplatin was administered at a dose of 75 mg/m^2 and pemetrexed was administered at a dose of 500 mg/m^2. After cycle 4 in the PDC arm, maintenance pemetrexed (500 mg/m^2) was allowed in patients with non-squamous histology until disease progression or unacceptable toxicity. The base case model followed the Checkmate 9LA trial protocol, in which patients received treatment with NIC until disease progression, development of unacceptable toxic effects, or 2 years of treatment time, whichever occurred first. Patients who were receiving only chemotherapy in the base case model also received treatment until disease progression, development of unacceptable toxic effects, or 3 months (4 chemotherapy cycles) of treatment time, whichever occurred first.

3.3 Subsequent therapy

After disease progression, 31% of patients in the NIC arm and 40% of patients in the PDC arm received subsequent systematic therapy (Paz-Ares et al., 2021). Other patients received best supportive care. Subsequent systematic therapy consists of nivolumab, ipilimumab, pembrolizumab, atezolizumab or platinum-doublet chemotherapy. The types of subsequent therapy differed between the groups, with the most common subsequent therapy being chemotherapy in the NIC arm (29%) and immunotherapy in the PDC arm (30%). See Appendix A3 for further details on subsequent therapy schemes. Nivolumab, ipilimumab and platinum-doublet chemotherapy were administered at the same dose as in the first-line setting. Pembrolizumab was administered at a dose of 200 mg and atezolizumab was administered at a dose of 1200 mg. Given the advanced nature of the disease and the lack of data on multiple lines of therapy beyond second-line treatment, only one line of subsequent treatment is modelled. The proportion of patients receiving subsequent treatment with chemotherapy is assumed to be in the same proportions as the chemotherapy options in first-line treatment. The percentage of patients on each subsequent treatment is based on the CheckMate 9LA study. Since no data is available on the average time on subsequent treatment and the low survival rate for aNSCLC patients, it was assumed that all patients received subsequent treatment or best supportive care until death.

3.3 Model structure

The cost-effectiveness of NIC was compared to PDC by means of a CUA from a Dutch societal perspective and in accordance with the Dutch recommendations for economic evaluations in healthcare (ZIN, 2016b; Hakkaart-van Roijen et al., 2015). A partitioned survival model was utilized to simulate costs, quality of life, adverse effects, progression, and survival among aNSCLC patients receiving NIC or PDC as first-line treatment. The model was developed in Microsoft Excel®. Model inputs are based on results reported in the Checkmate 9LA trial. In the model aNSCLC patients could progress through 3 three mutually exclusive health states reflecting different characteristics of the disease: progression-free (PFS), progressed disease (PD) and death. Figure 1 shows the three-health state model structure. These health states correspond to the primary and secondary endpoints in the CheckMate 9LA trial. This model structure is also consistent with the approaches adopted in previous published economic

evaluations and appraisals within NSCLC. The initial health state of all patients was assumed to be PFS and received first-line treatment with either NIC or PDC. The number of patients in each health state of each cycle was determined by the PFS rates and OS rates which were obtained from the Kaplan-Meier curves (PFS and OS curves) in the Checkmate 9LA trial. The proportion of patients in the PD health state is calculated as the difference between OS and PFS. During each treatment cycle patients either remained in their assigned health state or transition to another health state. Once disease progression occurred, it was assumed that the patients entered the PD state and received subsequent therapy or best supportive care until death. A restriction is that patients cannot transition to an improved health state. The proportion of patient in each health state is calculated using the following equations:

$$PF = P(PFS) \quad (1)$$

$$Death = 1 - P(OS) \quad (2)$$

$$PD = P(OS) - P(PFS) \quad (3)$$

Costs and health-related utilities are allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALY per cycle. A cycle length of 21 days was used for the model, which is consistent with the length of the treatment period of nivolumab and is an appropriate length given the rate at which lung cancer develops. A lifetime time horizon was used, in line with the Dutch Guidelines, accounting for all relevant costs and effects associated with the intervention (ZIN, 2016b). Half-cycle correction was applied to both costs and effects. Effects are expressed in life years (LY) gained and in QALY gained. Outcomes are presented as ICERs, i.e. incremental costs per LY gained and incremental costs per QALY gained. The ICER was compared to the societal willingness-to-pay (WTP) threshold. Additionally, the incremental net-monetary benefits (NMB) was calculated as the total number of health effects, in this case QALY, multiplied by the willingness to pay (WTP) for a QALY minus the total costs: INMB = (E_1-E_2)*WTP-(C_1-C_2). Costs were discounted at an annual rate of 4% and effects at 1,5%, according to Dutch guidelines for economic evaluations (ZIN, 2016b).

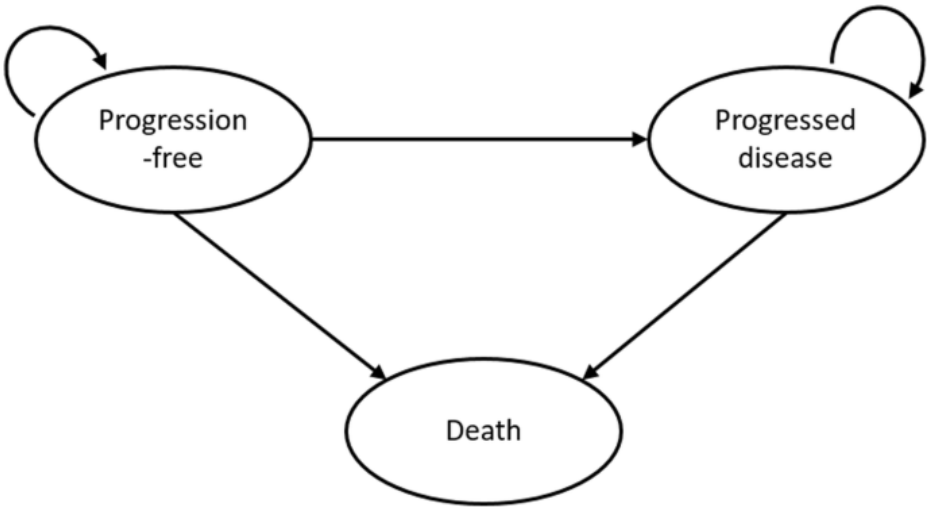

Figure 1: The structure of the three-health state partitioned survival model

3.4 Extrapolation of survival curves

The Kaplan-Meier curves of PFS and OS for aNSCLC patients treated with NIC or PDC from the CheckMate 9LA trial were explored. However, as the time horizon of the model is lifetime, whereas the Kaplan-Meier curves are truncated at 24 months, where a substantial number of patients are still alive, it was necessary to extrapolate the Kaplan-Meier curves using a parametric survival curve. Since there was no access to the individual patient data (IPD) of the CheckMate 9LA trial, methods that use the published survival curves and summary statistics to recreate the survival data are essential. Two methods that are available to reconstruct survival data in the absence of IPD are explored, specifically the method of Hoyle and Henley (2011) and the method of Guyot et al. (2012). Since the method of Guyot et al. supports the use of more extensive packages in R (Rstudio, 2020), which enables fitting more parametric distributions, the method of Guyot was used to recreate the IPD (Guyot et al., 2012). First, the Kaplan-Meier curves from the CheckMate 9LA trial were uploaded in WebPlotDigitizer to extract the data points from the Kaplan-Meier curves (Rohatgi, 2021). Using these coordinates and information on numbers at risk, pseudo-patient-level data were created following the algorithm of Guyot (2012). With the use of statistical program R (Rstudio, 2020) the Kaplan-Meier curves were extrapolated beyond the follow-up duration of the clinical trial by fitting the parametric survival functions to the recreated IPD. Specifically, six parametric distributions were considered including exponential, Weibull, log-normal, log-logistic, generalized gamma and Gompertz. To evaluate the goodness-of-fit of each parametric distribution, the fit for OS

and PFS was assessed for all parametric distributions using the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and visual inspection based on clinical plausibility. Lower AIC and BIC values indicate better fit of the selected model. The log-logistic model was chosen as the best fit model for the OS curve for both arms and the generalized gamma model for the PFS curve for both arms. Log-logistic distribution for OS yielded the lowest AIC and BIC (except for OS of chemotherapy arm the second-lowest AIC). This was also considered most appropriate from a clinical perspective, because the log-logistic curve best reflects the characteristics of the plateau phase at the end. The plateau phase is defined as the phase during which constant treatment response is achieved and the curve may flatten out. For PFS, generalized gamma distribution yielded the lowest AIC and BIC and best reflect the initial course of the Kaplan-Meier curves, whereas other distributions overestimate PFS in the beginning of the curve. The PFS and OS Kaplan-Meier graphs generated by using the constructed data and the predicted curves by adopting the selected parametric survival models, AIC and BIC values are presented in supplementary Appendix A1.

3.5 Utility weights

Health utility values reflect the health-related quality of life (HRQoL) in each health state and are measured on a scale of 0 to 1, with 1 corresponding to perfect health and 0 corresponding to death. Utility values are key drivers in CUA because estimates of QALYs are obtained by multiplying health state utility values for each health state by the time spent in that health state. Estimates of cost per QALY are sensitive to the choice of health state utility values (Paracha, Abdulla & MacGilchrist, 2018). It is therefore important to identify health state utility values that have been derived using methods acceptable to Health Technology Assessment (HTA) authorities. ZIN prefer utilities to be estimated using a generic preference-based instrument, with health states described by patients through use of a questionnaire, and with the health state valued using a country-specific tariff that reflects societal preferences (ZIN, 2016b). Health utility values for NSCLC patients have been reported for several populations and different disease stages. Utility values were derived from the study from Chouaid et al. (2013), which measured HRQoL using the EQ-5D questionnaire. Utility values applied in the model were the same for the NIC arm and PDC arm. The progression-free health state had an estimated health utility value of 0,71. After progression of first-line treatment, the health utility value was estimated at 0,67 (see Table 1).

Table 1: Health state utilities applied in the model

Health state	Utility value	Source
Progression free	0,71	(Chouaid et al., 2013)
Progressed disease	0,67	

Experiencing adverse effects was considered a decrement in health utility (disutility). Disutility scores of grades 3 and 4 treatment related severe adverse events are included in the analysis. It was assumed that grade 1 and 2 adverse events are of such mild nature, that the quality of life burden of these adverse events is implicitly included in base-case utilities. Occurrence of grade 3 and 4 adverse events were extracted from the Checkmate 9LA trial and were only included when at least 1,5% of the patients experiences a certain adverse event in one of the treatments arms. The disutility estimates were derived from published literature and applied in the model to adjust for quality of life losses associated with adverse events. The adverse events were assumed to all occur in the first cycle of that specific treatment, since the adverse events commonly appear within the first weeks after starting these treatments (Remon, Mezquita, Corral et al., 2018). Decrements are applied based on the incidence of adverse events per treatment and corresponding utility decrement. The total disutility value for NIC was -0,02 and for PDC -0,03. All health disutility values applied in the model are summarized in Table 2 along with their respective literature sources.

Table 2: Adverse events disutilities applied in the model

	NIC arm	**PDC arm**		
Adverse event	Incidence	Incidence	Disutility value	Source
Aneamia	6%	14%	-0,125	(ZIN, 2018a)
Diarrhea	4%	1%	-0,0468	(Nafees et al., 2008)
Neutropenia	4%	7%	-0,08973	
Febrile neutropenia	2,5%	2%	-0,09002	

3.6 Cost inputs

Following the Dutch guideline, costs were considered from a societal perspective (Hakkaart-van Roijen et al., 2015). This implies that all costs related to the disease had to be considered.

All costs are reported in 2020 euros and were adjusted for inflation to 2020 euros using the Consumer Price Index (CPI) (CBS, 2022). The input cost parameters are gathered from published literature. The aim is to collect Dutch specific parameters. When unavailable, international data is used instead. Assumptions are formulated when necessary. The types of costs considered in the economic model included drug acquisition and administration costs related to the intervention and comparator, subsequent treatments, disease management, costs related to terminal care, costs related to grade 3 and 4 adverse events, travel costs, informal care costs, and costs related to productivity losses. See Appendix A4 for an overview of all cost inputs with corresponding standard errors and distributions.

3.6.1 Medical costs

Treatment

For all treatments, list prices retrieved from the official site of ZIN for information on medicine prices are used and the calculations of drug costs per patient were made on the basis of the costs per administration (ZIN/medicijnkosten.nl). Calculations are based on the use of the entire vial, so including spillage. Fixed doses are recommended for nivolumab, pembrolizumab and atezolizumab. For ipilimumab there are recommended doses depending on body weight. To facilitate the calculation of the costs per administration of ipilimumab, patient characteristics (weight, percentage male/female) are applied based on the CheckMate 9LA trial. In this study, the mean body weight was 72.33 kg (i.e. 75.43 kg in males and 65.06 kg in females), body surface area of 1,84 m^2 and a creatine clearance of 70 mL/min to calculate the required dosage and related costs of various chemotherapy treatments per administration (Paz-Ares et al., 2021). In cases where the treating physicians were allowed to choose between different chemotherapy treatment regimens, the distribution of patients between the different chemotherapy treatment regimens was taken into account for the calculation of the total drug costs per course of chemotherapy. See Table 3 for the drug costs per cycle per treatment. For readability, all input values and detailed sources for medication-related costs are displayed all together in Appendix A2 (CPI) and A3 (treatment schemes, drug prices).

Table 3: Drug costs per cycle applied in the model

Drug	Price per cycle	Source
Nivolumab	€3.973,22	
Ipilimumab	€3.562,65	
PDC: carboplatin + paclitaxel	€1.386,32	
PDC: carboplatin + pemetrexed	€2.599,32	(ZIN/medicijnkosten.nl)
PDC: cisplatin + pemetrexed	€2.433,87	
Pembrolizumab	€5.721,12	
Atezolizumab	€4.032,99	

Administration of nivolumab, ipilimumab and PDC is intravenous and requires to be taken place in the hospital. As a result, there are costs associated with administering the medication. Drug administration costs were estimated based on the ZIN package advice report for nivolumab rate for parenteral chemotherapy/immunotherapy in an outpatient setting (ZIN, 2015). It follows from this report that the cost of €369 per patient per administration must be taken into account. It is assumed that combination administrations require only once the administration cost.

Resource use

There is limited published literature that explores in detail the resource use associated with patients with NSCLC previously untreated. Consequently, the main source of resource utilization per health state used in this model is based on a published observational study conducted in the Netherlands (Van der Linden et al., 2016). In this study, healthcare utilization and direct costs for NSCLC were measured associated with the treatment of first-line and second-line patients with squamous cell and non-squamous cell histology. Healthcare use related to disease management included hospitalization, laboratory tests (including pathology, microbiology, hematology, chemistry, immunology), medical imaging services and procedures, outpatient visits, telephone consultations, visits to the emergency room and intensive care unit, and radiotherapy. Mean costs per phase of NSCLC management were analyzed by splitting the relevant cost items into the initial treatment phase and second/later treatment phase. In the model, the same set of procedures as in the Dutch study by Van der Linden et al. (2016) are assumed for treating aNSCLC. Mean costs per category are used and adjusted to account for the 21 days cycles used in the model, since the average frequencies

per patient of the procedures are not reported. Patients incur disease management costs for as long as they remain on treatment. The unit costs of health care resource use are consistent over cycle lengths, however the frequency of resource consumption per cycle varies depending on the health state. Table 4 presents health state related resource use costs.

Table 4: List of health states and associated resource use applied in the model

Resource	Unit costs Progression Free	Unit costs Progressed	Unit	Source
Inpatient hospital days	€9.698,54	€7.243,83	Per annum	(Van der Linden et al., 2016)
Intensive care unit days	€363,34	€292,23	Per annum	
Outpatient visits	€3.561,50	€3.824,00	Per annum	
Medical imaging services and procedures	€5.152,99	€3.006,34	Per annum	
Pathology (cytology, histology)	€285,76	€68,40	Per annum	
Day with laboratory testing (excluding pathology and genetic biomarker tests)	€1.619,90	€1.411,46	Per annum	
Genetic biomarker tests	€391,72	-	Per annum	
Day-care	€747,50	€886,06	Per annum	
Consultations by telephone	€43,53	€52,86	Per annum	
Radiotherapy	€2.942,68	€3.895,51	Per annum	
Best supportive care	-	€1.277,53	Per cycle	(NZA, 2021)

An one-off cost was applied to patients at the moment they entered the death state to reflect the cost of terminal care, see Table 5. The calculation of these cost is based on a report published by the National Health Care Institute (ZIN, 2017a). It is assumed that 38% of patients are hospitalized for an average duration of 10,1 days. Unit costs includes diagnostics and treatment. These costs were assumed to be the same for all treatments.

Table 5: Terminal care costs used in the model

Resource	Resource use	Unit costs	Source
Hospital admissions	38%		(ZIN, 2017a)
	10,1 days	€1175,22	
Total cost		€4510,49	

Adverse events

The costs of grade 3 and 4 adverse events are applied as an one-off in the first cycle of the model, since the adverse events commonly appear within the first weeks after starting these treatments (Remon et al., 2018). Costs of adverse events comprised the total costs of the treatment of an adverse event per patient and were multiplied by the proportion of patients experiencing adverse events from the clinical trial to obtain the per-patient cost of managing adverse events. It is assumed that both the treatment cost per adverse event and disutility per adverse event accounts for the duration of the adverse event. Table 6 summarizes the costs of adverse events as used in the model.

Table 6: Treatment-related adverse events in the model

Adverse event	NIC rate	PDC rate	Unit costs	Source
Anaemia	6%	14%	€2.006,29	(ZIN, 2015)
Diarrhea	4%	1%	€2.423,83	
Neutropenia	4%	7%	€1.443,19	
Febrile neutropenia	2,5%	2%	€3.116,55	

3.6.2 Non-medical costs

Informal care

Adopting a societal perspective also entails including costs of informal care. The value of time on informal care is an important aspect of patient and family costs. The price for informal care is determined to be €14 per hour (Hakkaart-van Roijen et al., 2015). Based on previously published reports from ZIN package advice on osimertinib for NSCLC patients and nivolumab for NSCLC patients, informal care is calculated as an average of 8 hours per week in PF health state and 12 hours per week in PD health state (ZIN, 2015; ZIN, 2018a). It is assumed that patients treated with NIC had on average a better quality of life, so the number of hours of informal care in the NIC arm is 2 hours lower than in the PDC arm. The costs of informal care are calculated by multiplying the number of hours of care by the cost price per hour. Table 7 shows the amounts used in the model.

Table 7: Informal care use and costs applied in the model

Health state	Resource use per treatment cycle (hours)		Cost per treatment cycle		Source
	NIC	**PDC**	**NIC**	**PDC**	(ZIN, 2015; ZIN, 2018a;
Progression Free	18	24	€269,10	€358,80	Hakkaart-van Roijen et
Progressed	30	36	€448,50	€538,20	al., 2015)

Travel

Travel costs were based on a price per kilometer plus parking costs. According to the Dutch guidelines, an average distance to a hospital of 7 km can be assumed (Hakkaart-van Roijen et al., 2015). A distance of 14 kilometer was used for traveling from a patient's home to the hospital and back to estimate patient's travel costs. Travelling by car and public transport is valued at a kilometer price of €0,20, and average parking costs are €3,20. Travel costs per cycle includes costs of 1,57 return travel to some outpatient visits and 0,32 return travel to a hospital including parking costs. It was assumed that during a treatment scheme, the administration moments of drugs is performed simultaneously with the diagnostics and monitoring during outpatient and/or inpatient visits. Travel costs were applied for both first-line NIC or PDC treatment and subsequent therapy.

Table 8: Travel costs applied in the model

Travel	Unit costs	Source
Average travel costs	€8,36	(Hakkaart-van Roijen et al., 2015)

Productivity costs

Patient's productivity costs were estimated by using the friction cost method. According to the Dutch costing manual, wage per hour is €37,10 and a friction period of 15,8 weeks is assumed (Hakkaart-van Roijen et al., 2015; CBS, 2020). The length of the friction period is calculated based on the average duration to fill up a vacancy and increased by 4 weeks. These 4 weeks are an estimate of the period that employers are supposed to use before a decision is made to post a vacancy for temporary or permanent replacement of the employee with sick leave. Based on data from CBS (2020) on filled and unfilled vacancies in 2020, the friction period has been calculated at 15,8 weeks, with the following equation:

$$Friction\ period = 365 / \left(\frac{Number\ of\ vacancies\ filled\ in\ a\ year}{Number\ of\ open\ vacancies\ at\ a\ given\ time\ in\ that\ year}\right) + 4\ weeks \quad (4)$$

Approximately 71% of the people in the relevant age category have a job of at least 20 hours per week, with an average number of 30 hours per week. The retirement age is 67 years and 2 months. Based on the ZIN package advice osimertinib for NSCLC, the following assumptions are made: 90% of people stop working at time of diagnosis lung cancer, in PFS patients will work 2 days a week, all patients stop working when disease progression occurs, and patients who have stopped working will not start again (ZIN, 2018a). All patients in PFS health state as well as all the patients quitting their jobs upon diagnosis receive the productivity loss cost as one-off costs in cycle 1. In subsequent cycles, only patients who progress receive the productivity loss costs for the two days they worked while being in PFS health state.

Table 9: Productivity costs applied in the model

Health state	Cost per friction period	Source
Progression Free	€10.579,27	(Hakkaart-van Roijen et al., 2015)
Progressed	€40,17	

3.7 Sensitivity analysis

Several scenario analyses were performed to test the robustness of the assumptions of the CUA model. In each scenario a key model parameter/assumption was varied with all other parameters fixed at base-case values. In the first scenario tested, different parametric distributions are used to estimate the survival probabilities in the model. Second, the average treatment time of 7,9 months for NIC was used as reported in the CheckMate 9LA trial. Third, no wastage for the drug agents was assumed. One-way and probabilistic sensitivity analysis were performed to assess the robustness of the base-case results.

Deterministic sensitivity analysis

One-way deterministic sensitivity analysis (DSA) was performed to determine which input parameters of the model were most sensitive. In the DSA the impact of varying single input parameters on the ICER while holding all other parameters constant was assessed. DSA was carried out for variation in input values for utilities for all health states, incidence of PDC and subsequent therapy, parameters that have close relationship with the costs of NIC and PDC, incidence and costs of AE, input values for travel and productivity costs. See Appendix A6 for an overview of the top 10 parameters and the minimum and maximum values for the DSA. DSA was performed on the parameters by setting the lower and upper boundaries for each parameter. The estimated range was assumed to be 20% of the baseline value. Results of the DSA are presented in a tornado diagram.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) is used as a technique to quantify the level of confidence in the output, as a result to uncertainty in the inputs. To capture uncertainty in parameters, each parameter was specified as a random variable. In the PSA, a Monte Carlo simulation of 1000 iterations was performed with parameter values drawn from pre-specified distributions for all parameters in the model before each run. Gamma distribution was set for cost parameters, beta distributions was set for parameters such as utilities and probabilities, and Dirichlet distributions was set for categorial (multinomial data) input parameters such as incidence of different treatments. Standard errors were obtained from literature if possible. For remaining parameters for which no data were available related to statistical uncertainty of the parameter, 10% of the mean were taken as standard errors. In each simulation samples were randomly drawn from the distributions of all parameters, and each time the ICER was recalculated. For the parameters of the parametric survival functions random variables were generated using the Cholesky decomposition of the covariance matrices, by multiplying a vector (randomly drawn between 0 and 1) with the Cholesky decomposition matrix and added on the baseline estimates value for the parameter. The results of the PSA were presented in a cost-effectiveness plane (CE-plane) and cost-effectiveness acceptability curve (CEAC). The CE-plane is displayed graphically in a scatter plot with incremental costs on the y-axis and the incremental effects on the x-axis. The CEAC graph indicates the likelihood of NIC being cost-effective at different WTP levels.

Expected value of perfect information analysis

Value of information analysis provides information on the consequences of adopting the wrong treatment strategy (Oostenbrink et al., 2008). Because of uncertainty around the input parameters in the model and the ICER, taking the wrong decision because of imperfect information comes with a cost in terms of health benefit and resources forgone. The price that a decision maker is willing to pay to have perfect information, so removing all uncertainty, is expressed as the expected value of perfect information (EVPI). The optimal decision is the intervention that generates the maximum expected net-monetary benefit (NMB). The expected value of a decision taken with perfect information is found by the average of the maximum NMB. First, the maximum NMB was calculated for each iteration from the simulation. Then, the mean over these maximum NMB was taken. For an individual patient the EVPI is calculated as the difference between the expected value of the decision made with perfect information about the uncertain parameters, and the decision in the current situation of existing evidence:

$$EVPI = mean(\max(NMB)) - \max\,(mean(NMB)) \qquad (5)$$

The EVPI can also be calculated for the entire disease population affected by the decision (PEVPI). The EVPI was converted into a population EVPI as follows:

$$\text{PEVPI} = EVPI * \sum_{t=1,2,\dots,T} \frac{I_t}{(1+r)^t} \qquad (6)$$

The EVPI associated with future patients is discounted at a rate (r) of 4% for costs to provide the total EVPI for the population of current and future patients. I_t is the number of patients affected by the decision in year i=1,2,…T and was set to 2.514 based on estimations for the Dutch aNSCLC patients subjected to first-line treatment in 2020 (see chapter 4.5 Budget impact for more details). In this case, the effective lifetime of the technology (T) was set to 3, 5, and 10 years, since it is uncertain how the pallet of treatment options will evolve in the upcoming years.

4. Results

4.1 Base-case results

Output of the partitioned survival model matched the results of the CheckMate 9LA trial adequately, as shown in Table 10. This resulted in a median PFS and median OS for the present model (and the original CheckMate 9LA data) in the PDC arm of 5,2 (5,3) months and 11,7 (11,0) months, respectively. Corresponding results for the NIC arm were 6,6 (6,7) months and 16,6 (15,8) months, respectively.

Table 10: Median progression-free and overall survival in the model and original data

		Model (months)	CheckMate 9LA data (months)
PFS (median)	PDC	5,2	5,3
	NIC	6,6	6,7
OS (median)	PDC	11,7	11,0
	NIC	16,6	15,8

Table 11 shows the base-case results of the CUA. In the partitioned survival model conducted, nearly all patients (99,7%) entered the death state within 14 years. The life-years estimates were 2,52 and 1,76, respectively for NIC and PDC. Therefore, the overall length of survival for patients receiving NIC is 30 months, including a treatment survival benefit of 9 months. NIC accrued 1,74 QALY per patient at a total cost of €225.715, while PDC accrued 1,19 QALY per patient at a cost of €123.729. NIC leads to better health outcome in QALY as patients remain disease-free for a longer period. Compared to the PDC arm , NIC resulted in a QALY gain of 0,55 and 0,76 LY, and the accompanying cost increase of €101.986. This yielded an ICER of €185.579 per QALY gained and €133.968 per LY gained.

Table 11: Model outcomes

	NIC	PDC	Increments
Costs			
Costs in PFS	€171.387	€48.874	
Costs in PD	€54.328	€74.854	
Total costs	€225.715	€123.729	€101.986
Effects			
LY	2,52	1,76	0,76
QALY in PFS	1,17	0,56	
QALY in PD	0,61	0,67	
QALY lost due to AE	-0,02	-0,03	
Total effects in QALY	1,74	1,19	0,55
ICER (€/QALY)	185.579		
ICER (€/LY)	133.968		

Total average per-patient costs by cost category are displayed in Table 12. For a detailed version of the disaggregated results for PF and PD see Appendix A5. The ICER is most driven by drug-related costs, through more expensive drug costs of nivolumab and ipilimumab per cycle and longer treatment duration, and in much smaller extent through higher drug administration costs because NIC is more intensive in terms of drug administration moments. Furthermore, costs related to the management of the disease represent a big increment. This is mainly explained by the more expensive healthcare resource costs in the progression-free state and that patients in the NIC arm remain longer progression-free. Another contributor to the increased costs is informal care costs. Both travel costs and productivity losses have a minor impact on the total incremental costs.

Table 12: Average per-patient costs by category

	NIC	PDC	Increment
Drug-related costs (acquisition and administration)	€129.376	€48.081	€81.295
Healthcare resource use and management of adverse events	€54.917	€37.857	€17.061
Informal care costs	€13.530	€10.598	€2.932
Travel costs	€339	€240	€98
Productivity losses	€10.591	€10.592	€-1

4.2 Scenario analysis

Considering a Dutch threshold of €80.000/QALY, NIC appears not to be cost-effective at an ICER of €185.579/QALY. Several scenario analysis were conducted to show the effect on the outcomes of different situations. The results of the scenario analysis are presented in Table 13 as well as Figure 2 (see Appendix A7 for all scenarios). None of the scenarios renders an ICER below the WTP threshold of €80.000 per QALY gained. Based on visual inspection, the log-normal distribution for OS can be regarded as a plausible alternative for the log-logistic distribution. Since the log-normal distribution additionally scored second for AIC and BIC, a scenario analysis using the log-normal distribution for OS was performed to estimate the survival probabilities which were then included in the model. This resulted into a somewhat lower ICER. Furthermore, the log-normal distribution and Gompertz distribution for PFS were used in scenarios since log-normal scored second for AIC and BIC and the Gompertz distribution was observed to be a good alternative for the PFS curve (especially for the long tail in the PFS curve for NIC). This mainly resulted in higher incremental costs and higher ICER for the log-normal distribution, and lower incremental costs and lower ICER for the Gompertz distribution. Overall, when using alternative parametric distributions for OS and PFS, there is little effect on the ICER. In another scenario, it was assumed vials for drugs could be shared between patients to prevent wastage. Vial sharing decreased the ICER to €160.649. Limiting the treatment duration of NIC to a maximum of 7,9 months (the average treatment duration in the trial) appears to have a major influence on the ICER, which reduces by approximately 52% to €96.458. For nivolumab and ipilimumab in the base-case model, a price reduction of 60% is required in order to bring the ICER below the threshold value of €80.000/QALY, and to be regarded as cost-effective. In the scenario where treatment duration of NIC is limited to 7,9 months, a price reduction of 19% is required in order to bring the ICER below the threshold value of €80.000/QALY.

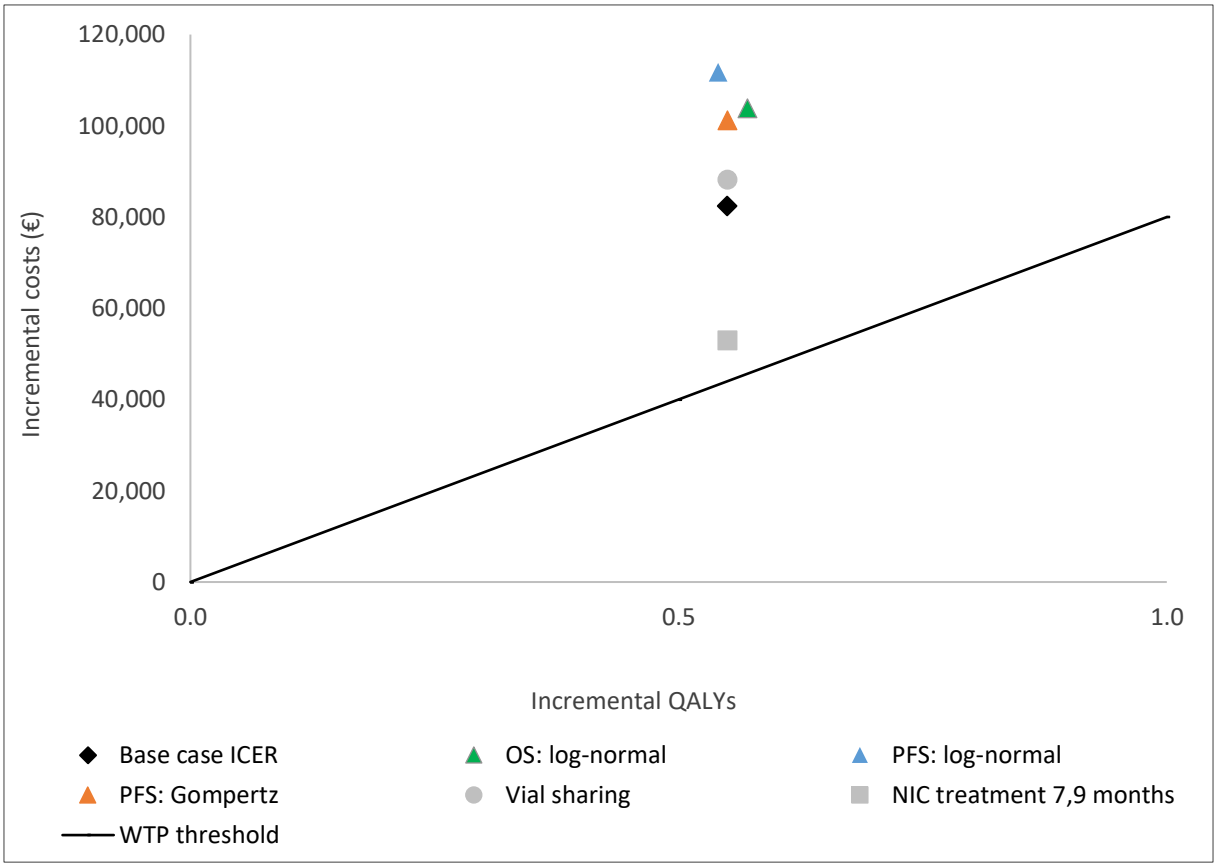

Figure 2: Scenario analysis

Table 13: Scenario analysis

	Incremental costs	Incremental LY's	Incremental QALYs	ICER
Base case	€101.986	0,76	0,55	€185.579
Log-normal function for OS	€103.896	0,80	0,57	€181.138
Log-normal function for PFS	€111.782	0,76	0,54	€208.478
Gompertz function for PFS	€101.211	0,76	0,55	€182.686
No wastage: vial sharing	€88.286	0,76	0,55	€160.649
NIC treatment for 7,9 months	€53.009	0,76	0,55	€96.458
Price reduction of 60% of NIC being cost-effective	€43.607	0,76	0,55	€79.348

4.3 Sensitivity analysis

4.3.1 Deterministic sensitivity analysis

The results of the top 10 parameters of the DSA are shown in a tornado diagram (Figure 3 and Appendix A6 for more details). DSA showed that the utility value of the progression-free health state seemed to be the most influential driver. Changing this utility value highly impacts the incremental QALY, because the QALYs accrued pre-progression in the NIC arm will increase (or decrease) to a larger extent than the QALYs accrued in pre-progression in the PDC arm, since patients in the NIC arm stay longer in progression-free health state. Similarly the utility value in progressive disease had an impact on the ICER, but to much smaller extent. Prices of ipilimumab and nivolumab both had substantial effect on the ICER. Most likely due to the high prices of these drugs and the assumption of no vial sharing. In the scenario analysis it is observed that vial sharing had substantial impact on the ICER. Proportions of subsequent treatment or subsequent best supportive care, cost of inpatients days and price of pembrolizumab, all had a negligible effect on the ICER.

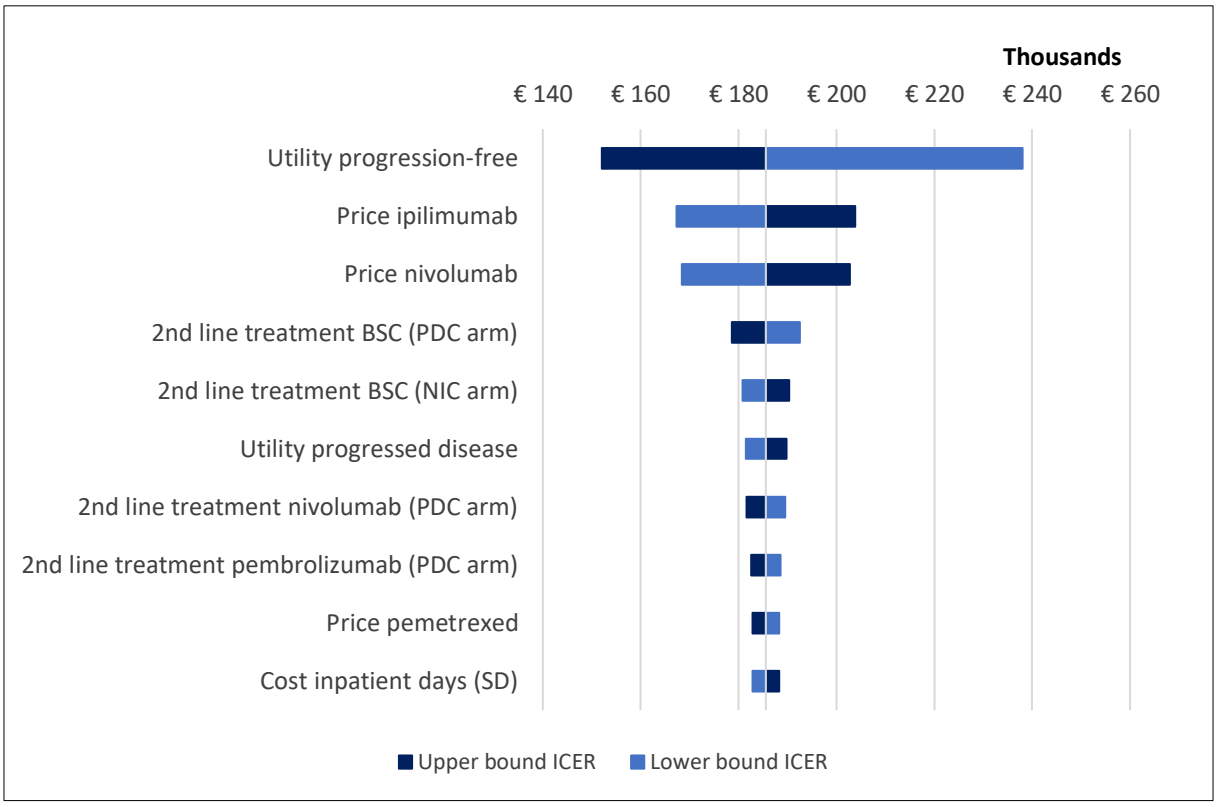

Figure 3: Tornado diagram with the top 10 most influential parameters for the ICER

Legend: BSC = best supportive care; NIC = nivolumab, ipilimumab and chemotherapy; PDC = platinum-doublet chemotherapy, SD = stable disease.

4.3.2 Probabilistic sensitivity analysis

The PSA yielded a probabilistic ICER of €194.903. The incremental cost-effectiveness plane (Figure 4) that resulted from the PSA shows that 100% of the 1000 PSA iterations were in the upper right quadrant, indicating that more QALYs are gained at additional costs for NIC compared to PDC. Whether these cases are cost-effective depends on the WTP for a QALY. The CEAC indicated that at a WTP of €80.000/QALY, the probability of NIC being cost-effective is 0%. This increases to 36% at a WTP threshold of €185.000/QALY, which is around the base case ICER. When the WTP threshold becomes higher than €196.000/QALY the probability of NIC being cost-effective (52%) is higher than the probability of PDC being cost-effective (48%).

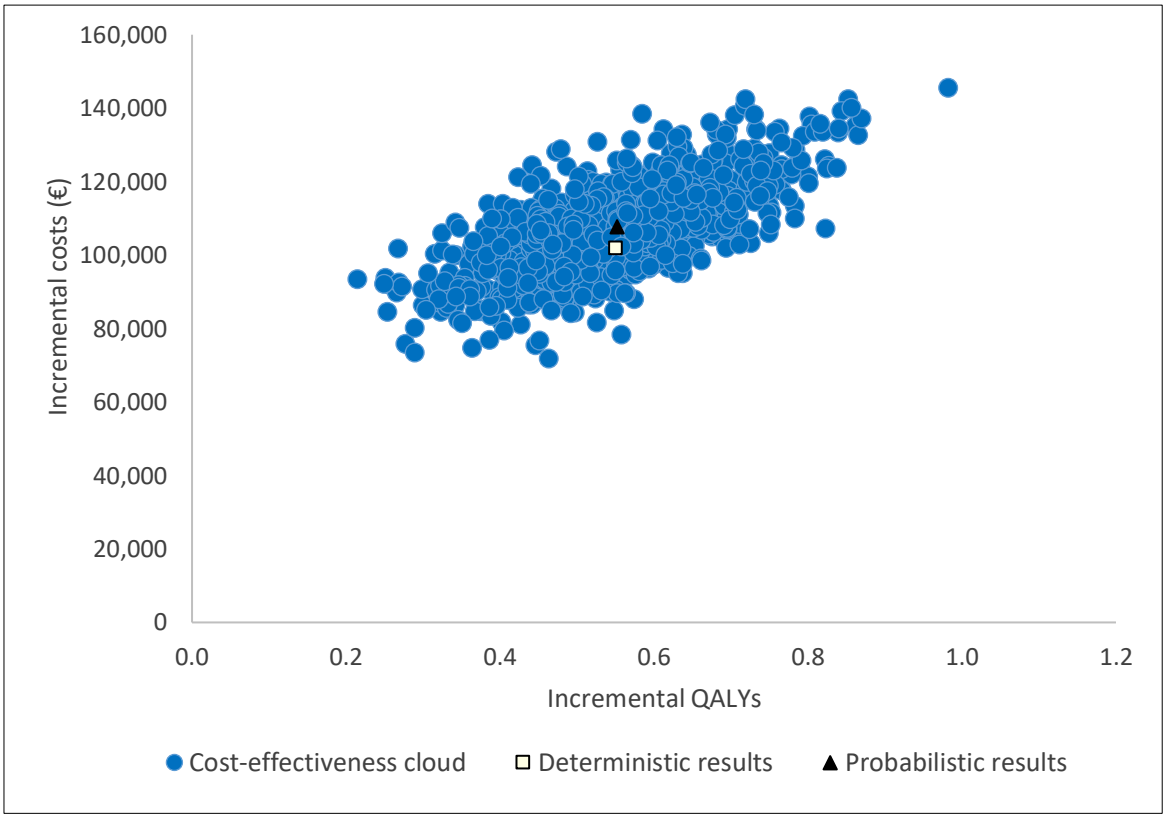

Figure 4: Cost-effectiveness plane for NIC versus PDC

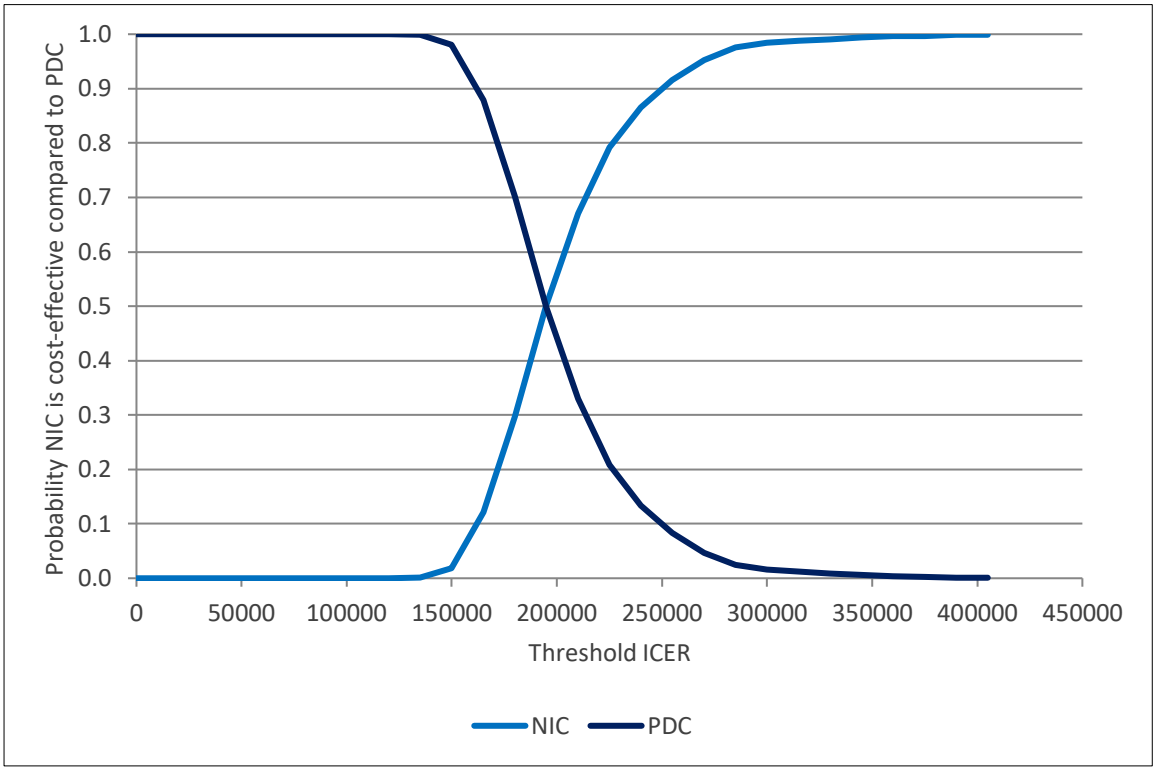

Figure 5: Cost-effectiveness acceptability curve (CEAC)

At a WTP threshold of €80.000/QALY, the cost-effectiveness of NIC versus PDC is unfavourable. The EVPI at the WTP threshold of €80.000/QALY is €0 for the entire patient population. This is because the probability of NIC being cost-effective is 0% at this threshold. At a WTP threshold of €150.000/QALY NIC starts to become cost-effective in some of the iterations, and the population EVPI increased at that point (see Figure 7). The population-based EVPI at the WTP threshold of €200.000/QALY, which is around the base-case ICER, is €77.352.868 for an effective lifetime of 10 years, €42.456.620 for an effective lifetime of 5 years, and €26.465.788 for an effective lifetime of 3 years. These amounts reflect the risk associated with the reimbursement of NIC, based on the uncertainties in the model. It should be mentioned that this risk estimate is conditional on the current ICER, and therefore current price.

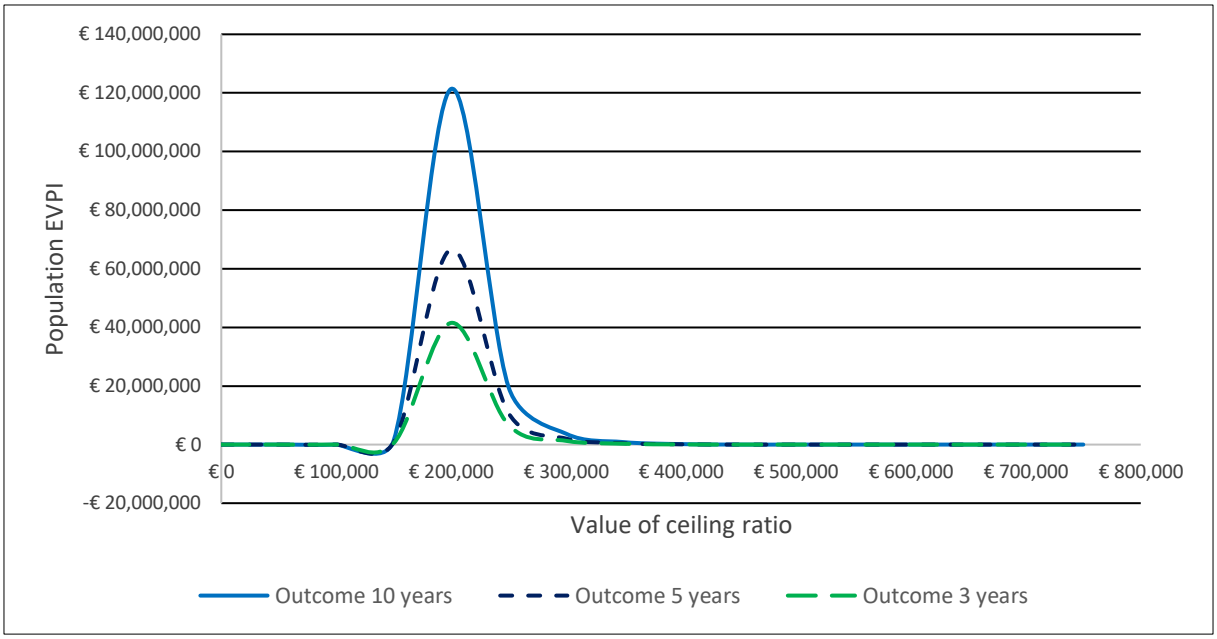

Figure 6: Population-based EVPI

4.5 Budget impact analysis

A budget impact analysis was conducted to estimate the total annual financial consequences of the reimbursement of NIC for the treatment of aNSCLC patients within the Dutch healthcare setting. The budget impact analysis considered the costs associated with the drug acquisition, using the average outcome per patient from the CUA model. The average drug costs per patient was multiplied by the annual number of aNSCLC patients in the Netherlands eligible for first-line treatment with NIC. The Netherlands Cancer Registry estimated a total of 9.429 patients with NSCLC in 2020 (NKR, 2020). The incidence of metastatic disease at time of diagnosis is 52% (=4.903 patients). In addition, 40-50% (it is assumed 45%) of patients develop metastatic disease over time (=2.037 patients) (NVALT, 2020). In total, the incidence of stage IV NCLSC is therefore equal to 4.903 + 2.037 = 7.210 patients. In line with earlier budget impact analysis on atezolizumab in 2017, pembrolizumab in 2016 and nivolumab in 2015, it is estimated that approximately 60% of patients will receive first-line treatment (ZIN, 2017b; ZIN, 2016; ZIN, 2015). The remaining patients participate in clinical trials or forgo treatment. As a result, 4.326 patients are expected to be eligible for first-line treatment.

Only patients without EGFR mutation or ALK translocation are eligible for first-line treatment with NIC. It is estimated that 5% of patients have an ALK translocation and 12% of patients have an EGFR mutation (ZIN, 2017b). Therefore, 735 patients are not eligible for treatment

with NIC. Of the 3.591 (=4.326 – 735) patients 30% are expected to have a PD-L1 expression ≥50% and are eligible for the first-line treatment with monotherapy pembrolizumab (NVALT,2020; ZIN, 2016). It is expected that these patients will not be treated with first-line NIC, which means that these patients are not relevant for this budget impact analysis (ZIN, 2021a). Based on these assumptions a total of approximately 2.514 NSCLC patients per year in the Netherlands is calculated.

For the remaining patient group, competing treatment options exist. Patients are currently treated with pembrolizumab in combination with chemotherapy or atezolizumab in combination with chemotherapy. Patients with metastatic squamous histology are treated with pembrolizumab plus 4 cycles carboplatin-paclitaxel. Patients with metastatic non-squamous histology are treated with either pembrolizumab plus 4 cycles platinum-pemetrexed, or atezolizumab plus 4-6 cycles carboplatin-paclitaxel-bevacizumab. Of the Dutch patients, 23% have squamous histology and 77% have non-squamous histology (IKNL, 2021). In this budget impact analysis it is assumed that the market will split equally between the treatment options, as might be expected on the basis of equal therapeutic value. This implies that NIC will have 50% market share in squamous histology and 33% market share in non-squamous histology, resulting in an overall market share of 37%. The results of the budget impact analysis are presented in Table 14. Only drug costs are included based on the average outcome per patient over the whole treatment duration of 2 years in the partitioned survival model (see Appendix A3). Possible extra costs or savings at the expense of the broader health budget are ignored. The outcome of the budget impact analysis was presented as the total budget impact per year over the maximum treatment duration of 2 years. It is important to mention that costs of substitution treatments are not included and for nivolumab there is already a financial arrangement concluded for all current and future indications, as a result that the actual price is lower than the list price used. The exact effect of this on the budget impact analysis is unclear, because these arrangements are confidential. It is, however, publicly available from the Dutch Health Care Institute what the total reduction is through negotiations with the pharmaceutical industry. In 2020 the Dutch Health Care Institute managed to get an average reduction of 42% on intramural medicines. This is not treatment specific, but could be a good indication, therefore the budget impact is also calculated taken into consideration the price reduction of 42% for nivolumab (ZIN, 2021b). Table 14 shows the

budget impact results and Table 15 shows the budget impact results taking into consideration the price reduction of 42% for nivolumab.

Table 14: Budget impact analysis of NIC

Year	Market penetration	Number of patients	Total costs per year per patient	Total costs per year NIC
1[a]	-	-	-	-
1[b]	37%	930	€55.490	€51.605.235
1		**930**	**€55.490**	**€51.605.235**
2[a]	37%	930	€55.490	€51.605.235
2[b]	37%	930	€55.490	€51.605.235
2		**1.860**	**€110.979**	**€103.210.470**

[a]: Shows patients who complete treatment that year; [b]: Shows patients who start treatment in that year.

Table 15: Budget impact analysis of NIC with 42% price reduction

Year	Market penetration	Number of patients	Total costs per year per patient	Total costs per year NIC
1[a]	-	-	-	-
1[b]	37%	930	€42.172	€39.219.960
1		**930**	**€42.172**	**€39.219.960**
2[a]	37%	930	€42.172	€39.219.960
2[b]	37%	930	€42.172	€39.219.960
2		**1.860**	**€84.344**	**€78.439.920**

[a]: Shows patients who complete treatment that year; [b]: Shows patients who start treatment in that year.

5. Discussion

5.1 Key findings

The present study assessed the cost-effectiveness of NIC versus PDC for first-line treatment of metastatic squamous and non-squamous NSCLC patients. Based on the CheckMate 9LA clinical trial, the economic analysis was performed for the Dutch healthcare setting in accordance with current guidelines (Hakkaart-van Roijen et al., 2015). The value of NIC resulted from the additional LY and QALY gained among these patients. Over a 14-year time horizon, the base-case simulation showed for NIC (versus PDC) a moderate increase in OS of 4,9 months and PFS of 1,4 months, and a gain of 0,55 QALYs. This survival advantage is associated with an average additional lifetime cost of €101.986, resulting in deterministic ICERs of €185.579 per QALY gained and €133.968 per LY gained. Considering a WTP threshold of €80.000/QALY, first-line treatment with NIC versus PDC for aNSCLC is with 100% certainty not cost-effective at a deterministic ICER of €185.579 per QALY gained. The additional costs associated with NIC are mainly the acquisition costs of nivolumab and ipilimumab. Furthermore, the ICER was sensitive to utilities before and after progression. When the costs of nivolumab and ipilimumab together was reduced by 60% or more, NIC treatment would become cost-effective at a threshold of €80.000/QALY. If the disease burden of aNSCLC is estimated to be lower by policymakers or if a lower proposed threshold value is taken as starting point, then the price reduction should be higher. In a scenario in which patients received nivolumab and ipilimumab until the average treatment duration of 7,9 months, the ICER decreased to €96.458 per QALY gained. To reduce the chance of taking the wrong decision to not reimburse NIC for first-line treatment, a maximum amount of €66.617.008 should be invested in further research, assuming an effective lifetime of 5 years with a WTP threshold of €200.000/QALY. Based on the budget impact analysis, introducing NIC would be associated with estimated drug costs of €103.210.470 after year 2, assuming 37% market penetration.

To the best of my knowledge, this is the first study in the Netherlands that compared the cost-effectiveness of first-line NIC treatment for aNSCLC patients. Three US-based studies have recently addressed the same topic from a healthcare perspective. Yang et al. (2021) developed

a Markov model and compared three first-line treatments, specifically nivolumab plus ipilimumab (N+I), NIC and PDC. They calculated an ICER of $239.072 for N+I compared to PDC and $838.198 for N+I compared to NIC. The results from Yang et al. indicated that adding chemotherapy over N+I is not cost-effective, and should be discouraged. Yang et al. did not report the ICER of NIC compared to PDC, but using the incremental costs and incremental QALY reported in the study, the ICER of NIC versus PDC was $369.186 per QALY gained. The higher costs and even more unfavorable cost-effectiveness may be mainly explained by a higher purchasing cost of nivolumab and ipilimumab. Another explanation is that Yang et al. did not include the costs of pemetrexed maintenance therapy after 4 cycles in the PDC arm, leading to lower cost estimates in the PDC arm and consequently a higher ICER. Furthermore, DSA showed that the ICER was most sensitive to costs of nivolumab and ipilimumab, and utilities, consistent with the findings of this thesis.

A study by Peng et al. (2021) also developed a Markov model to evaluate the cost-effectiveness of NIC in comparison with PDC. The results showed an additional 0,80 QALYs and 1,22 LYs, and the accompanying incremental cost of $161.993. They calculated an ICER of $202.275 per QALY gained. At the maximum WTP threshold of $150.000/QALY, NIC for the treatment of aNSCLC was not cost-effective with 82% certainty. DSA showed that the ICER was most sensitive to the hazard ratio of OS, costs of nivolumab and ipilimumab, and utilities. The baseline utility values used related to PFS and PD states were 0,84 and 0,47, respectively, which show a bigger difference than the utility values used in this thesis. As a consequence the ICER of Peng et al. may be underestimated, compared to the results of this thesis. Furthermore, Peng et al. conducted several subgroup analysis and concluded that the subgroup with Eastern Cooperative Oncology Group (ECOG) performance score of 0, which indicates that the patient's level of functioning is fully active in terms of their ability to care for themselves, had the probability of NIC being cost-effective of 80,33%. Secondly, the subgroup with central nervous system metastases had considerably higher probability of NIC being cost-effective with 95,45%. Another US-based study by Polyzoi et al. (2021) evaluated the cost-effectiveness with a partitioned survival model and found a mean ICER of $132.960/QALY. This study only presented limited results. Polyzoi et al. extrapolated the survival curves from the CheckMate 9La trial with data from the more mature CheckMate 227 trial involving nivolumab plus ipilimumab as first-line therapy. In CheckMate 9LA the follow-

up was too short to reflect the emerging plateau seen in CheckMate 227. Using the conditional survival estimates from CheckMate 227 may accurately capture the long-term overall survival trend. Because the 4-year outcomes of CheckMate 227 came available while writing this thesis and there remains uncertainty in the potential plateau that could emerge in Checkmate 9LA, the extrapolation was done using parametric distributions which is an acceptable method in HTA. Nonetheless, it is crucial to continue to assess longer term outcomes for patients in CheckMate 9LA to fully characterize response benefits and the potential plateau of the survival curve. A sustained OS plateau could improve the cost-effectiveness of NIC. Finally, a Canadian cost-effectiveness analysis from a healthcare perspective, calculated an ICER of $99.008 per QALY gained for NIC compared to PDC and concluded that NIC offers a cost-effective option for first-line treatment of aNSCLC (Young et al., 2021). They also developed a partitioned survival model and extrapolated data from CheckMate 227, which corresponds to the study of Polyzoi et al. (2021). Unfortunately, the study only presented limited results, which make it difficult to compare results with this thesis. All studies report drug acquisition cost and utilities as the key drivers of the higher cost for NIC. This is consistent with the findings of this study. Furthermore, in all above US-based and Canada-based economic evaluations only direct medical costs are included, such as drug costs, administration costs and management of adverse events costs. Non-medical costs such as transportation costs, informal care costs and costs due to productivity losses are not considered, in contrast to this thesis from a societal perspective. However, from the DSA the ICER is not very sensitive to transportation costs and costs due to productivity losses.

ZIN did perform a budget impact analysis and estimated costs associated with the use of NIC at €72.412.890 (ZIN, 2021a). This is somewhat lower than the budget impact calculated in this study, mainly because ZIN assumed market penetration in the first year at 12%, second year 23% and third year 35%. Taking into consideration the substitution of treatment in the budget impact, ZIN calculated a budget impact of €4,7 to €11 million (depending on market penetration 15-35%) in the third year after reimbursement. In this study no data was available on the budget impact of standard of care immunotherapy-based treatments pembrolizumab monotherapy, pembrolizumab in combination with chemotherapy, and atezolizumab in combination with chemotherapy. Therefore, total cost including substitution of treatments could not be calculated.

5.2 Limitations

The results and conclusions are dependent on the validity of the assumptions made in the model. However, various alternative assumptions were assessed through sensitivity analysis, which showed the robustness of the results. Nevertheless, certain limitations must be recognized.

First, the clinical effectiveness of NIC relative to other currently available treatments is limited to a direct comparison between NIC and PDC in the CheckMate 9LA trial, which suggest NIC is associated with improved OS and PFS. However, immunotherapy-based treatments such as pembrolizumab monotherapy, pembrolizumab in combination with chemotherapy, or atezolizumab in combination with chemotherapy, is currently standard of care in the Netherlands for the treatment of patients with aNSCLC with no EGFR or ALK genomic tumour aberrations. Therefore, PDC is not the most relevant treatment comparator. As there is currently no direct trial evidence that compares NIC to these immunotherapy-based treatments, the relative effectiveness and accompanying incremental costs of NIC remains unknown.

Second, the number of adverse events may be underestimated due to exclusion of lower frequency adverse events. Immunotherapy-related adverse events are rare, and the cost of treatment in such cases is high. Therefore, more cases of immunotherapy-related adverse events would be favourable to more accurate evaluation of adverse events cost for patients treated with NIC. In this thesis only incidence of grade 3 and 4 adverse events were used to estimate costs and disutility due to adverse events. The incidence of grade 3 or 4 adverse events was higher in the NIC group (46,9%) compared to the PDC group (37,8%), and neutropenia and anaemia were the most common grade 3 or 4 adverse events included in the model in both treatment groups. However, the incidence of neutropenia and anaemia was lower with NIC compared to the PDC group. This resulted in higher adverse events costs in the PDC group compared to the NIC group, while it was expected that the NIC group had higher adverse events costs due to more incidence of adverse events. Another limitation is that this study ignores the adverse events that are associated with the additional line of treatment. In addition, the application of adverse events costs and disutility in the first model cycle is potentially a conservative assumption, because the potential recurrence of adverse events as

well as the timing of occurrence was not accounted for. Adverse events that are incurred after one year on treatment would be discounted in terms of costs and QALYs. Furthermore, the first cycle has the maximum number of patients on treatment who are at risk of experiencing adverse events. Therefore, applying the cost and disutility of adverse events in the first cycle will overestimate the impact of adverse events.

A third limitation is that to project OS and PFS over a patient's lifetime horizon, survival benefits beyond the follow-up time of the CheckMate 9LA trial were inferred by fitting the parametric distributions based on the reported Kaplan Meier curves. Since mean survival times are sensitive to assumptions around what occurs after the trial follow-up, there remains uncertainty in the long-term survival predictions. The survival data shows a small tail on the PFS and OS curve in CheckMate 9LA with 2-year follow-up, as likewise evident in the trend toward flattening of tails of the Kaplan Meier curves in CheckMate 227 (nivolumab plus ipilimumab as first-line therapy in NSCLC patients) with 4-year follow-up data (Paz-Ares et al., 2022). Therefore, the benefits in the NIC group will maybe become more significant when compared to those with PDC with a long-term follow-up. This analysis likely underestimates the long-term survival benefits of NIC, because the parametric distributions may not account fully for the potential for a durable long-term survival. However, the ICER is not sensitive for alternative parametric distributions.

Another limitation is that assumptions are made about clinical practice. It is assumed that patients received the same follow-up care for management of the disease in stable disease state and progressed disease state. More accurate healthcare resource use costs could be obtained if frequencies for the different procedures specified for Dutch patients were found. Treatment costs could be overestimated somewhat as they are not adjusted for dose reductions for PDC; dose reductions for nivolumab and ipilimumab was not permitted. There is ongoing research to whether small-dose treatment with immunotherapy drugs is as effective as normal-dose treatments (Yoo et al., 2018; Renner, Burotto & Rojas, 2019; Louedec et al., 2020). Small-dose treatment is an important area for investigation, as it comes at a much reduced cost. Therefore, adjustment for dose reductions may have an impact on the cost-effectiveness results. In one of the scenario analysis in which vials can be shared between patients, the ICER was considerably lower. However, it is unclear whether it is feasible in

practice to share vials between patients. Nevertheless, it is more precise when drug wastage is taken into consideration.

In addition, it is assumed that patients receive second-line treatment until death. Though it may be reasonable that these patients discontinue treatment at a given time and were treated with best supportive care. However, no data was available to make such distinctions. Besides that, in reality patients may also receive third-line treatments, that are not included in the current model. However, in the absence of clear guidance on duration of second-line therapy and the small survival rate for this patient group, these assumptions were considered as a valid strategy.

5.3 Future research

In further research, it is recommended to use real-world data of second- and third-line treatment strategy after first-line treatment failure, when it is available. For this purpose, possibly a sequential model/disease model needs to be constructed simulating disease and treatment pathways. Furthermore, it may be worthwhile to update the cost-effectiveness analysis of first-line NIC with immunotherapy-based treatments as comparator once clinical data is available. Finally, subgroup analysis in squamous and non-squamous patients may be valuable to further research, since chemotherapy costs for non-squamous patients is considerably higher due to the high price of pemetrexed.

5.4 Reimbursement recommendations

The clinical effectiveness of NIC for patients with aNSCLC is promising, as it could improve PFS and OS. Despite this clinical relevance, the results of this study showed that the addition of NIC as first-line treatment for aNSCLC patients could not be regarded cost-effective compared to PDC. Total budget impact would amount €103.210.470 after year 2. Based on the results of this study, it is not recommended to include NIC in the Dutch health care package. Price negotiations can influence the reimbursement decision. A price reduction of 60% is required in order to bring the ICER below the threshold value of €80.000/QALY, and to be regarded as cost-effective. However, for nivolumab there already is a financial arrangement concluded for all current and future indications valid until January 2024, so it is unclear how high the discount will have to be (ZIN, 2021a). A discount on the price of nivolumab and ipilimumab is

not the only option to achieve cost-effectiveness. Limiting the number of doses of nivolumab and ipilimumab would also lead to a significant decrease in the ICER. In the scenario analysis, a scenario is assumed in which patients stop treatment after 7,9 months. It could also be proposed that patients who are still progression-free after 7,9 months receive the drug free of charge. Such risk-sharing agreements between pharmaceutical companies and payers aim to ensure better budgetary control and access to medicines despite uncertainty surrounding the clinical benefit (Gonçalves et al., 2018; Adamski et al., 2010). However, the drawbacks of risk-sharing agreements is that they are costly in terms of implementation and monitoring of the agreement, the follow-up of patients is costly and complex, difficulty in defining easily measurable performance indicators, and a lack of resources in data collection (Gonçalves et al., 2018). Hopefully the uncertainties will decrease over time as more long-term data becomes available from which a better estimate of the OS and an optimal treatment duration can be derived.

References

Adamski, J., Godman, B., Ofierska-Sujkowska, G. et al. (2010). Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. BMC Health Serv Res 10, 153 (2010).

Alexander, M., Kim, S.Y. & Cheng, H. (2020). Update 2020: Management of non-small cell lung cancer. *Nature Public Health Emergency Collection*. (11): 1-11. doi: 10.1007/s00408-020-00407-5

Altena, W. (2019). Duale immuntherapie met nivolumab en ipilimumab mogelijk nieuwe eerstelijnstheraptie bij gevorderd NSCLC. *ESMO 2019.* Available from: *https://www.ntvo.nl/zorgprofessional/duale-immuuntherapie-met-nivolumab-en-ipilimumab-is-een-mogelijke-nieuwe-eerstelijnsbehandeling-bij-patienten-met-gevorderd-niet-kleincellig-longcarcinoom/*

Borghaei, H., Paz-Ares, L., Horn, L., Spigel, D.R. et al. (2015). Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 373:1627-1639

Briggs, A., Claxton, K. & Sculpher, M. (2006). Decision modelling for health economic evaluation. *Oxford University Press 2006.*

Bristol Meyers Squibb (BMS). (2019). Five-Year Outcomes for Opdivo (nivolumab) in Combination with Yervoy (ipilimumab) Demonstrate Durable Long-Term Survival Benefits in Patients with Advanced Melanoma. Available from: https://news.bms.com/press-release/corporatefinancial-news/five-year-outcomes-opdivo-nivolumab-combination-yervoy-ipilimu.

Bullement, A., Willis, A., Amin, A., Schlichting,M., Hatswell, A.J., Bharmal, M. (2020). Evaluation of survival extrapolation in immuno-oncology using multiple pre-planned data cuts: learnings to aid in model selection. *BMC Medical Research Methodology*. 20: 103.

Cancer.net (2021). Lung cancer – Non Small cell: Types of treatment. Available from: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/types-treatment

Centraal Bureau Statisitiek (CBS). (2020). Vacatures. Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/80857ned/table?ts=1649861683644

Centraal Bureau Statisitiek (CBS). (2022). Consumer prices. Data portal. Available from: https://opendata.cbs.nl/#/CBS/en/dataset/83131ENG/table

Centraal Bureau Statistiek (CBS). (2021). Arbeidsdeelname; kerncijfers 2021. Available from: https://www.cbs.nl/nl-nl/cijfers/detail/82309NED

Chan, B.A., Hughes, B.G.M.. (2015). Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. Transl Lung Cancer Res. 2015 Feb; 4(1): 36–54.

Chen, R., Manochakian, R., James, L. et al. (2020). Emerging therapeutic agents for advanced non-small cell lung cancer. *J Hematol Oncol* 13, 58.

Drummond, M.F., Sculpher, M.J., Torrance, G.W., O'Brien, B.J. & Stoddard, G.L. (2005). Methods for the economic evaluation of health care programmes. *Oxford University Press 2005.*

Dutch National Health Care Institute (ZIN) / www.medicijnkosten.nl.

Dutch National Health Care Institute (ZIN). (2015). Pakketadvies nivolumab (Opdivo ®) bij gevorderde (plaveiselcel) niet-kleincellige longkanker.

Dutch National Health Care Institute (ZIN). (2016)(a). Pakketadvies pembrolizumab (Keytruda ®) bij de behandeling van niet-kleincelling longkanker.

Dutch National Health Care Institute (ZIN). (2016)(b). Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. Available from:

https://www.zorginstituutnederland.nl/over-ons/werkwijzen-en-procedures/adviseren-over-en-verduidelijken-van-het-basispakket-aan-zorg/beoordeling-van-geneesmiddelen/richtlijnen-voor-economische-evaluatie

Dutch National Health Care Institute (ZIN). (2017)(a). Verbetersignalement Zorg in de laatste levensfase bij mensen met long- of darmkanker. *Zinnige zorg ICD-10:18; ICD-10:C34.*

Dutch National Health Care Institute (ZIN). (2017)(b). Pakketadvies atezolizmab (Tecentriq®) bij lokaal gevorderde of gemetastaseerde niet-kleincellige lonkgkanker (NSCLC) na eerdere behandeling met chemotherapie

Dutch National Health Care Institute (ZIN). (2018)(a). Pakketadvies sluisgeneesmiddel osimertinib (Tagrisso ®) bij de behandeling van volwassen patiënten met lokaal gevorderde of gemetastaseerde niet-kleincellige longkanker met activerende EGFR-mutaties.

Dutch National Health Care Institute (ZIN). (2018)(b). Ziektelast in de praktijk; de theorie en praktijk van het berekenen van ziektelast bij pakketbeoordelingen.

Dutch National Health Care Institute (ZIN). (2021a). Pakketadvies ipilimumab (Yervoy ®) in combinatie met nivolumab (Opdivo ®) bij de behandeling van niet-kleincellige longkanker.

Dutch National Health Care Institute (ZIN). (2021b). Voortgangsbrief financiële arrangementen geneesmiddelen 2021. Tweede Kamer. Vergaderjaar 2021-2022, 29 4777, nr. 691. Retrieved from: https://open.overheid.nl/repository/ronl-47f81255-147b-4cea-8251-46d161e75465/1/pdf/kamerbrief-over-voortgangsbrief-financiele-arrangementen-geneesmiddelen-2021.pdf

Ettinger, D.S. et al. (2012). Non-small cell lung cancer Clinical practice guidelines in oncology. *National Comprehensive Cancer Network.* 10(10).
doi:**:** https://doi.org/10.6004/jnccn.2012.0130

European Medicines Agency (EMA). (2020). European Public Assessment Report (EPAR) ipilimumab (Yervoy®) & nivolumab (Opdivo®).

Federatie Medisch Specialisten (FMS). (2020). Niet-kleincellig longcarcinoom. *Richtlijnendatabase.* Retrieved from: *https://richtlijnendatabase.nl/richtlijn/niet_kleincellig_longcarcinoom/startpagina_-_niet-kleincelling_longcarcinoom.html*

Garon, B.E., Hellmann, M.D., Rizvi, N.A. et al. (2019). Five-Year Overall Survival for Patients with Advanced Non-small-cell Lung Cancer Treated with Pembrolizumab: Results from the Phase I KEYNOTE-001 Study," *Journal of Clinical Oncology*. Volume 37(28): 2518-2527

Gibson, E., Koblbauer, I., Begum, N., Dranitsaris, G., Liew,D., McEwan, P., et al. (2017). Modelling the survival outcomes of Immuno-oncology drugs in economic evaluations: a systematic approach to data analysis and extrapolation. PharmacoEconomics. 2017;35(12):1257–70.

Gonçalves, F.R., Santos, S., Silva, C., Sousa, G. (2018). Risk-sharing agreements, present and future. Ecancermedicalscience, 12:823.

Gridelli, C. et al. (2015). Non-small-cell lung cancer. *Nature Reviews Disease Primers.* 1 (15009). doi:10.1038/nrdp.2015.9

Guyot, P., Ades, A.E., Ouwens, M.J.N.M, Welton, N.J. (2012). Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-meier survival curves. BMC Med Res Methodol. 12(9).

Hakkaart-van Roijen, L., Van der Linden, N., Bouwmans, C., Kanters, T. & Tan, S. (2015). Costing manual: Methodology of costing research and reference prices for economic evaluations in healthcare [in Dutch: Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg].

Hellmann, M.D., Paz-Ares, L.M.D., Caro, R.B., Zurawski, B. et al. (2019). Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. N Engl J Med. 381:2020-2031

Herbst, R.S., Giaccone, G.M.D., Filippo de Marinis, F.M.D., Reinmuth, N.M.D. et al. (2020). Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. N Engl J Med. 38:1328-1339.

Hoyle, M.W. & Henley, W. (2011). Improved curve fits to summary survival data: application to economic evaluation of health technologies. *BMC Medical Research Methodology*. 11(139).

Hunink, M.G.M., Weinstein, M.C., Wittenberg, E. et al. (2014). Decision making in health and medicine. Integrating evidence and values. Cambridge Medicine.
Integraal Kankercentrum Nederland (IKNL). (2020). Non-small-cell lung cancer: Dutch guidelines.

Integraal kankercentrum Nederland (IKNL). (2021). Longkanker. Cijfers. Available from: https://iknl.nl/kankersoorten/longkanker/registratie/incidentie
Kanker.nl. (2021). Longkanker. Available from: https://www.kanker.nl/kankersoorten/longkanker/cijfers/overlevingscijfersniet-kleincellige-longkanker.

Kaufman, H.L. (2015). Precision Immunology: The promise of immunotherapy for the treatment of cancer. J Clin Oncol. 33: 1315-17.

Lim, S.M., Hong, M.H., Kim, H.R. (2020). Immunotherapy for non-small cell lung cancer: current landscape and future perspectives. Immune Netw. Volume 20(1).

Louedec, F., Leenhardt, F., Marin, C., Chatelut, E., Evrard, A., Ciccolini, J. (2020). Cancer immunotherapy dosing: a pharmacokinetic/pharmacodynamic perspective. *Vaccines (Basil).* 8(4): 632.

McEwan, P., Gordon, J., Penrod, J.R., Yuan,Y. (2016). Empirical assessment of the impact of model choice (Markov State Transition Versus Partitioned Survival) in modelling small-cell lung cancer. *Value in Health*. Volume 19 (7).

Melosky, B. (2018). Rapidly changing treatment algorithms for metastatic nonsquamous non-small-cell lung cancer. Curren Oncology, Vol 25, Supp 1.

Nafees, B., Stafford, M., Gavriel, S., Bhalla, S., Watkins, J. (2008). Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes*. 6:84.

Naimark, D.M.J., Kabboul, N.N. & Krahn, M.D. (2013). The half-cycle correction revisited: redemption of a kludge. *Med Decis Making.* 33(7): 961-70. doi: 10.1177/0272989X13501558

Nassar, N.J., Gorenberg, M., Agbarya, A. (2020). Review: First line immunotherapy for non-small cell lung cancer. Pharmaceuticals, 13, 373. www.mdpi.com/journal/pharmaceuticals

Nederlandse Kankerregistratie (NKR). (2020). Prevalentie | Luchtwegen / Long / Niet-kleincellig longcarcinoom. Available from: https://iknl.nl/nkr-cijfers?fs%7Cepidemiologie_id=526&fs%7Ctumor_id=1%2C202%2C204&fs%7Cregio_id=550&fs%7Cperiode_id=564%2C565%2C566%2C567%2C568%2C569%2C570%2C571%2C572%2C563%2C562%2C561&fs%7Cgeslacht_id=644&fs%7Cleeftijdsgroep_id=677&fs%7Cjaren_na_diagnose_id=687&fs%7Ceenheid_id=703&cs%7Ctype=line&cs%7CxAxis=periode_id&cs%7Cseries=tumor_id&ts%7CrowDimensions=periode_id&ts%7CcolumnDimensions=tumor_id&lang%7Clanguage=nl

Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (NVALT). (2020). Richtlijn niet-kleincellig longcarcinoom – Eerstelijnsbehandeling met immunotherapie bij NSCLC.

Nederlandse Zorgautoriteit (NZA). (2021). DBC tarif application.

Oostenbrink, J.B., Maiwenn, J., Oppe, M., Rutten-van Mölken, M. (2008). Expected value of perfect information: An empirical example of reducing decision uncertainty by conducting additional research. *Value in health.* Volume 11, number 7.

Paracha, N., Abdulla, A. & MacGilchrist, K.S. (2018). Systematic review of health state utility values in metastatic non-small cell lung cancer with a focus on previously treated patients. *Health and Quality of Life Outcomes* 16, 179.

Paz-Ares, L. et al. (2021). First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomized, open-label, phase 3 trial. *Lancet Oncol*ogy. 22(2): 198-211. doi: https://doi.org/10.1016/S1470-2045(20)30641-0

Paz-Ares, L.G., Ramalingam, S.S., Ciuleanu, et al. (2022). First-line nivolumab plus ipilimumab in advanced NSCLC: 4-year update outcomes from the randomized, open-label, phase 3 CheckMate 227 part 1 trial. *Journal of Thoracic Oncology*. Volume 17, issue 2, p 289-308.

Peng, Y. et al. (2021). Cost-effectiveness of nivolumab plus ipilimumab combined with two cycles of chemotherapy as first-line treatment in advanced non-small cell lung cancer. *Advances in Therapy.* 38, 3962-3972.

Plasmans, M.H.D., Ramjiawan, V.R., Vonk, R.A.A., Hulshof, T. (2019). Longkanker: zorguitgaven longkanker naar sector. RIVM. Available from: http://www.nationaalkompas.nl

Pompen, M., Gok, M., Novák, A., van Wuijtswinkel, R., Biesma, B., Schramel F,, et al. (2009). Direct costs associated with the disease management of patients with unresectable advanced non-small-cell lung cancer in The Netherlands. Lung Cancer. 2009;64(1):110-6.

Pylozoi, M. et al. (2021). A cost-effectiveness analysis of nivolumab plus ipilimumab plus two cycles of platinum doublet chemotherapy versus platinum doublet chemotherapy in the first-line treatment of stage IV or recurrent non-small cell lung cancer in the United States. *Economic evaluation in oncology studies Value in Health.* Volume 24: supplement 1.

Reck, M. et al. (2021). First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in advanced non-small-cell lung cancer: CheckMate 9LA 2-year update. *ESMO Open*

Reck, M., Rodríguez-Abreu, D., Robinson, A.G., et al. (2016). Pemrolizumab versus chemotherapy for PD-L1 positive non-small cell lung cancer. *N Engl J Med*. 375:1823–33.

Remon, J., Mezquita, L., Corral, J., Vilariño, N., Reguart, N. (2018). Immune-related adverse events with immune checkpoint-inhibitors in thoracic malignancies: focusing on non-small cell lung cancer patients. *Journal of Thoracic Disease*. Vol. 10, Supplement 13.

Renner, A., Burotto, M., Rojas, C. (2019). Immune checkpoint inhibitor dosing: Can we go lower without compromising clinical efficacy? *Journal of Global Oncology.* 5:1-5.

Rocco, D., Gravara, L.D., Battiloro, C. & Gridelli, C. (2019). The role of combination chemo-immunotherapy in advanced non-small cell lung cancer. *Expert Review of Anticancer Therapy. Volume 19 (7). p 561-568*

Rohatgi, A. (2021). WebPlotDigitizer (version 4.5) [Computer software]. Available from: https://automeris.io/WebPlotDigitizer/

RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/.

Severens, J.L. & Milne, R.J. (2004). Discounting health outcomes in economic evaluation: the ongoing debate. *Value in Health.* 7(4): 397-401. doi: https://doi.org/10.1111/j.1524-4733.2004.74002.x

Sleijfer, S., Verweij, J. (2009). The price of success: cost-effectiveness of molecularly targeted agents. *Clin Pharmacol Ther.; 85(2):136-8.*

van der Linden, N. et al. (2016). Costs of non-small cell lung cancer in the Netherlands. *Elsevier*. 91: 79-88. https://doi.org/10.1016/j.lungcan.2015.10.015

Verma, V., Sprave, T., Hague, W., Simone, C.B. et al. (2018). A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors. *Journal for ImmunoTherapy of Cancer.; volume 6, (128).*

WHO globoscan. (2020). The Global Cancer Observatory. The Netherlands fact sheet: Cancer.

Woods, B., Sideris, E., Palmer, S., Latimer, N., Soares, M. (2017). NICE DSU Technical Support Document 19. Partitioned Survival Analysis for Decision Modelling in Health Care: A Critical Review. NICE Decision Support Unit.

Woods, B.S., Sideris, E., Palmar, S., Latimer, N., Soares, M. (2020). Partitioned survival and state transition models for healthcare decision making in oncology: Where are we now? *Value in Health*. Volume 23(12).

Xia, L., Liu, Y., Wang, Y. (2019). PD-1/PD-L1 blockade therpay in advanced non-small-cell lung cancer: current status and future directions. Oncologist. Volume 24. Suppl. 1.

Yang, S.C., Kunst, N., Gross, C.P., Wang, J., Su, W.C., Wang, S.Y. (2021). Cost-effectiveness of nivolumab plus ipilimumab with and without chemotherapy for advanced non-small cell lung cancer. *Frontier In Oncology.*

Yoo, S.H., Keam, B., Kim, M. et al. (2018). Low-dose nivolumab can be effective in non-small cell lung cancer: alternative option for financial toxicity. *ESMO open*. 3, e000332.

Young, K.C. et al. (2021). A cost-effectiveness analysis of nivolumab plus ipilimumab plus two cycles of platinum doublet chemotherapy versus platinum doublet chemotherapy in the first-line treatment of stage IV or recurrent non-small cell lung cancer in Canada. *Economic evaluation in oncology studies Value in Health.* Volume 24: supplement 1.

Appendices

Appendix A1 Kaplan-Meier curves and parametric distributions

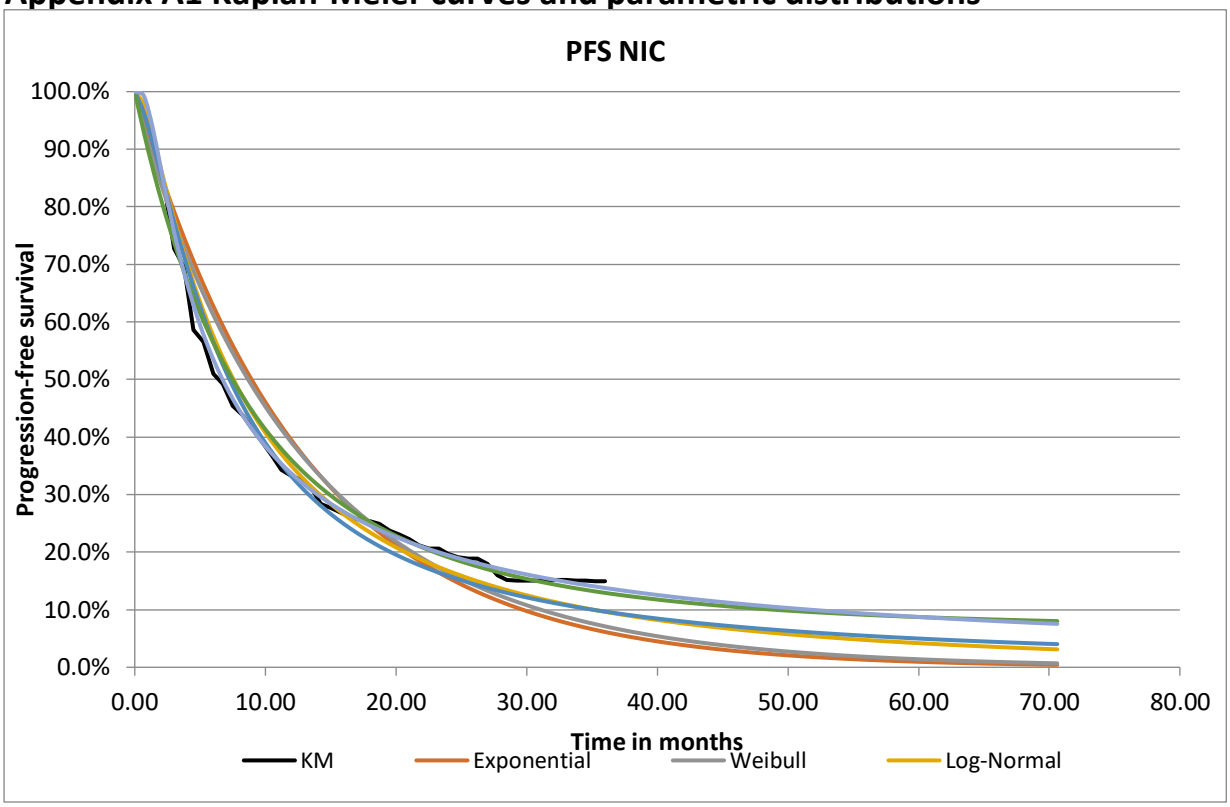

Figure 7: Kaplan-Meier curves and parametric distribution PFS NIC

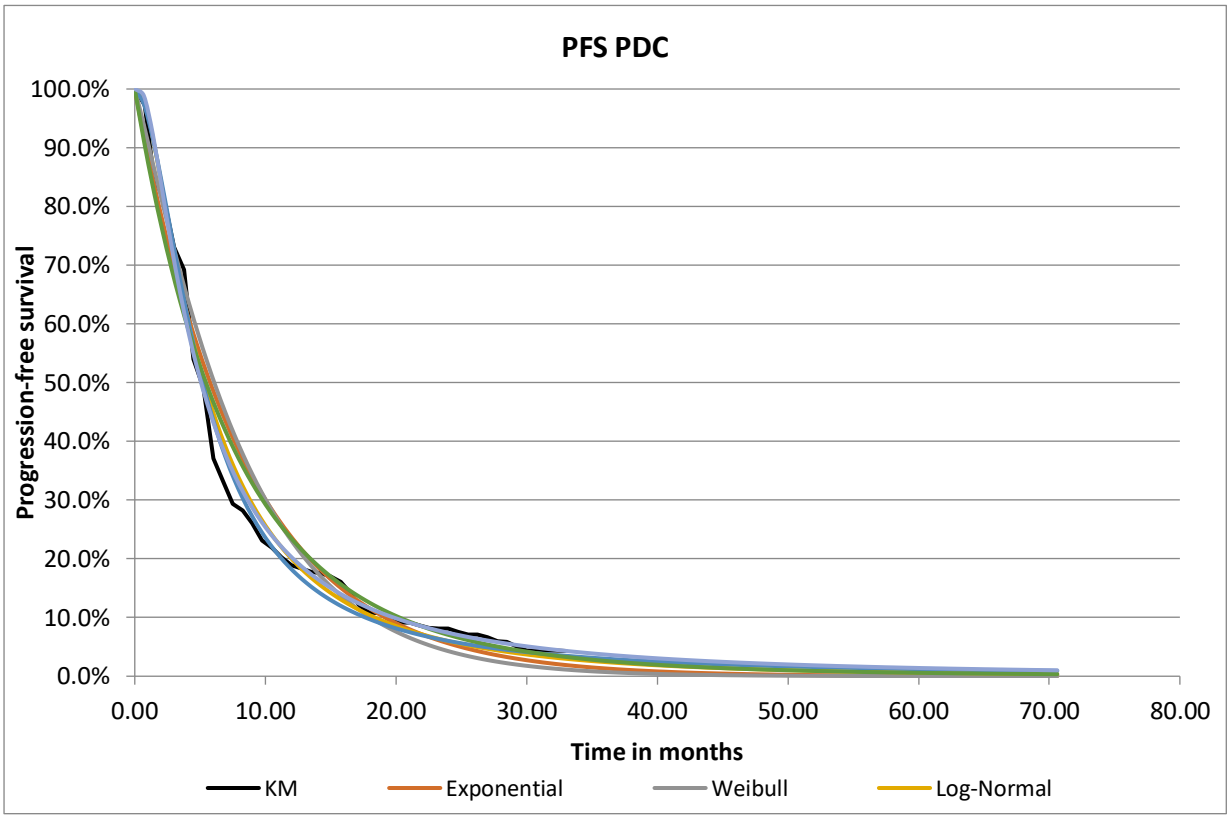

Figure 8: Kaplan-Meier curves and parametric distribution PFS PDC

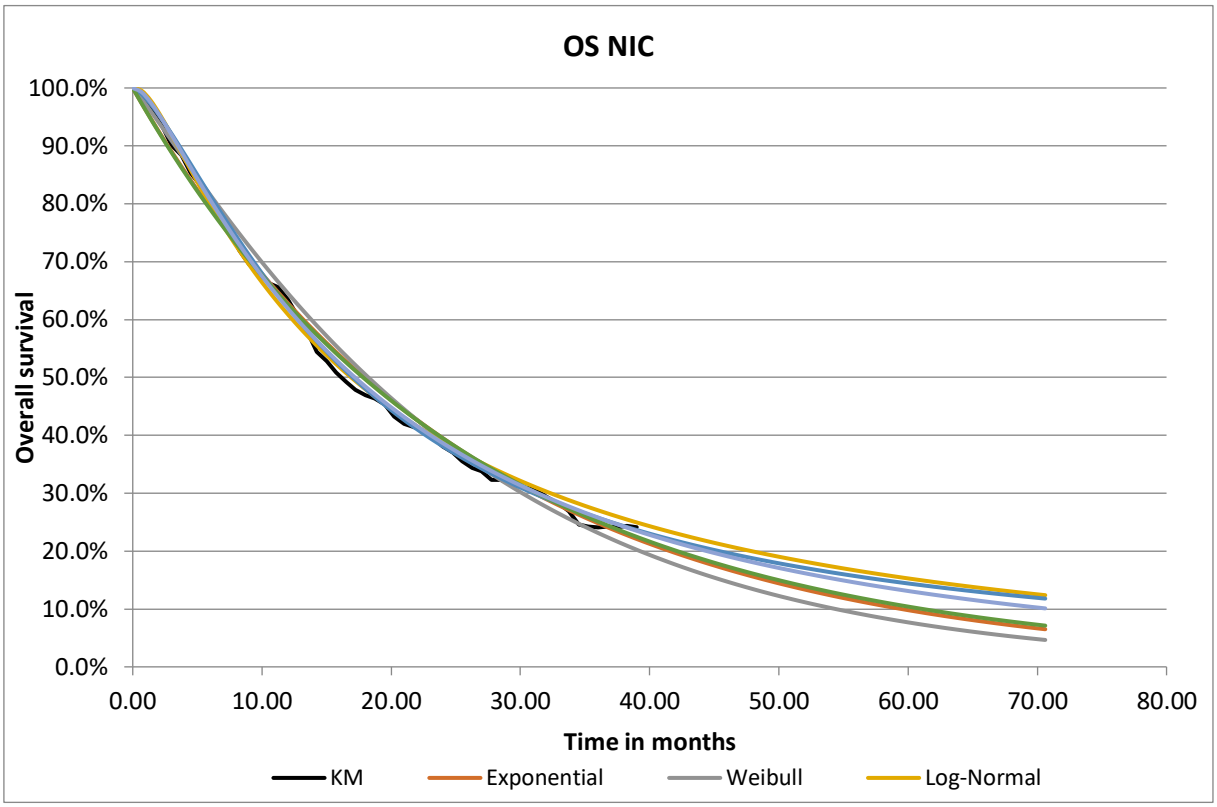

Figure 10: Kaplan-Meier curves and parametric distribution OS NIC

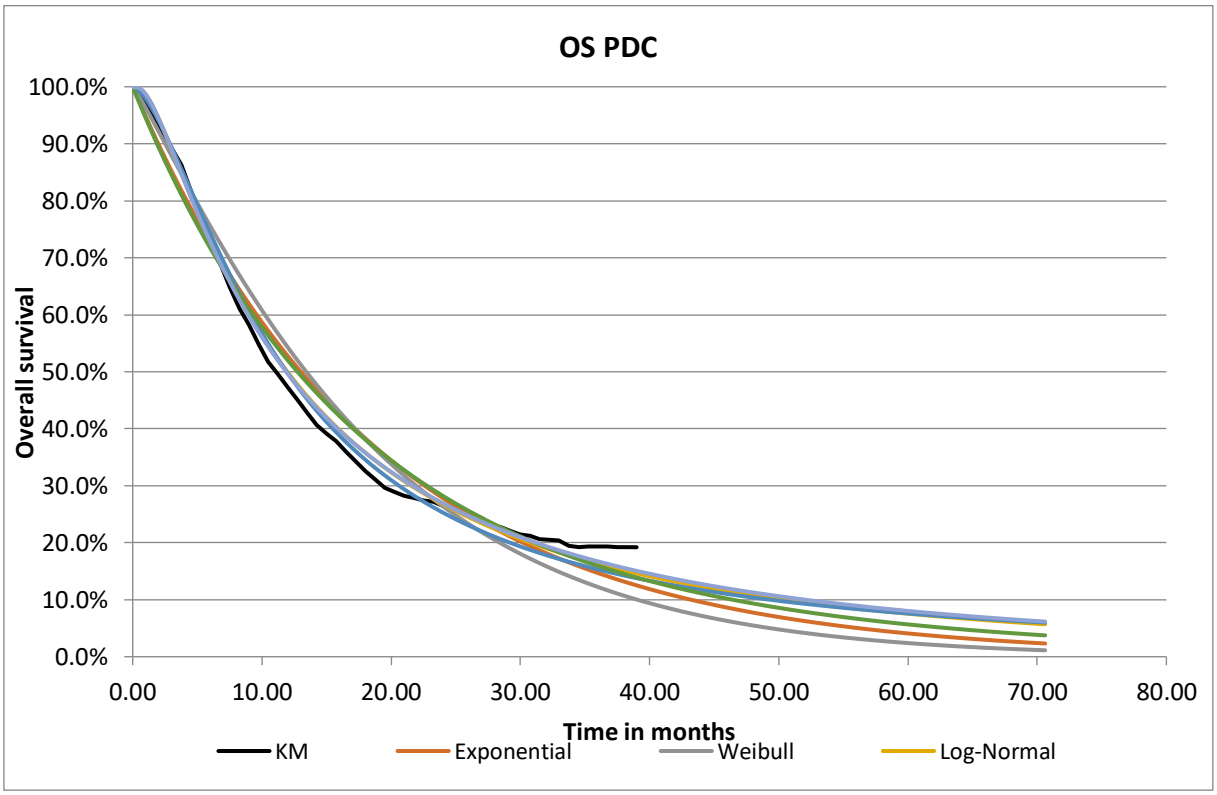

Figure 9: Kaplan-Meier curves and parametric distribution OS PDC

Table 16: AIC and BIC values PFS

Parametric distribution	PFS NIC		PFS PDC	
	AIC	BIC	AIC	BIC
Exponential	1965,3250	1969,214	1736,3780	1740,259
Weibull	1965,6710	1973,449	1733,5460	1741,307
Log normal	1910,1220	1917,900	1678,0330	1685,794
Log logistic	1921,0400	1928,817	1680,9340	1688,695
Gompertz	1945,7210	1953,499	1735,5520	1743,313
Generalized Gamma	1894,5160	1906,183	1676,2240	1687,865

Table 17: AIC and BIC values OS

Parametric distribution	PFS NIC		PFS PDC	
	AIC	BIC	AIC	BIC
Exponential	2059,7120	2063,600	1724,2790	1728,159
Weibull	2058,9790	2066,757	1721,8000	1729,562
Log normal	2050,6890	2058,466	1698,3190	1706,080
Log logistic	2049,1100	2056,888	1699,3400	1707,101
Gompertz	2061,6720	2069,450	1725,8380	1733,599
Generalized Gamma	2051,2850	2062,952	1700,2180	1711,860

Appendix A2 Consumer Price Index

Table 18: Consumer Price Index

Indexing parameter	Inflation CPI	Source
Index 2012	2,1	
Index 2013	1,3	
Index 2014	0,6	
Index 2015	0,5	(CBS, 2022)
Index 2016	0,3	
Index 2017	1,4	
Index 2018	1,6	
Index 2019	1,6	
Index 2020	1,2	

Appendix A3 Medication-related resource use and costs

Table 19: Proportion of patients treated with each PDC in both treatment arms

PDC treatment	Incidence	Source
Carboplatin plus paclitaxel	32%	(Paz-Ares et al., 2021)
Carboplatin plus pemetrexed	47%	
Cisplatin plus pemetrexed	21%	

Table 20: Medication treatment schemes first-line therapy NIC and PDC

	Nivolumab	Ipilimumab	Cisplatin	Carboplatin	Paclitaxel	Pemetrexed
Dosage per administration	360 mg	1 mg/kg	75 mg/m^2	AUC 6	200 mg/m^2	500 mg/m^2
Dose frequency (weeks)	3W	6W	3W	3W	3W	3W
Required amount per administration (mg)	360	72,33	138,3	685	368,8	922
Weighted average total cost per administration	€3.973,22	€7.125,30	€68,07	€233,52	€1.152,80	€2.365,80
Total medication costs per patient (NIC arm)						€110.979,37
Total medication costs per patient (PDC arm)						€17.658,25

Table 21: Subsequent therapy in the different treatment arms

Subsequent therapy	NIC arm	PDC arm	Source
Follow-up on BSC	69%	60%	(Paz-Ares et al., 2021)
Follow-up on subsequent therapy	31%	40%	
Type			
Nivolumab	1%	17%	
Ipilimumab	0%	1%	
Pembrolizumab	1%	9%	
Atezolizumab	1%	5%	
PDC: carboplatin plus paclitaxel	9%	7%	
PDC: carboplatin plus pemetrexed	14%	11%	
PDC: cisplatin plus pemetrexed	6%	5%	

Table 22: Medication (drug prices)

Drug	Relevant unit	Unit costs	Price per cycle	Source
Nivolumab	10 mg/ml flacon 4 ml	€441,48	€3.973,22	(ZIN/medicijnkosten.nl)
Ipilimumab	5 mg/ml flacon 10 ml	€3.562,65	€3.562,65	
Cisplatin	1 mg/ml flacon 50 ml	€22,69	€68,07	
Carboplatin	10 mg/ml flacon 5 ml	€16,68	€233,52	
)Paclitaxel	100 mg flacon	€288,20	€1.152,80	
Pemetrexed	500 mg flacon	€1.182,90	€2.365,80	
Pembrolizumab	25 mg/ml flacon 4 ml	€2.860,56	€5.721,12	
Atezolizumab	60 mg/ml flacon 20 ml	€4.032,99	€4.032,99	

Appendix A4: Input parameters for the model

Table 23: Input parameters for the model

Parameter name	Value	Standard error	Distribution	Source
Body surface area	1,84	0,18	gamma	(ZIN, 2021a)
Body weight	72,33	7,23	gamma	(ZIN, 2021a)
Utility progessed	0,67	0,01	beta	(Chouid et al., 2013)
Utility progession free	0,71	0,01	beta	(Chouid et al., 2013)
Disutility anaemia	-0,13	0,01	beta	(Nafees et al., 2008)
Disutility diarrhea	-0,05	0,02	beta	(Nafees et al., 2008)
Disutility febrile neutropenia	-0,09	0,02	beta	(Nafees et al., 2008)
Disutility neutropenia	-0,09	0,02	beta	(Nafees et al., 2008)
Incidence PDC: carboplatin paclitaxel	32%	-	dirichlet	(Paz-Ares et al., 2021)
Incidence PDC: carboplatin pemetrexed	47%	-	dirichlet	(Paz-Ares et al., 2021)
Incidence PDC: cisplatin pemetrexed	21%	-	dirichlet	(Paz-Ares et al., 2021)
Incidence maintenance pemetrexed	45%	0,05	beta	(Paz-Ares et al., 2021)
Incidence subsequent therapy nivolumab (NIC arm)	1,39%	-	dirichlet	(Paz-Ares et al., 2021)
Incidence subsequent therapy pembrolizumab_(NIC arm)	0,83%	-	dirichlet	(Paz-Ares et al., 2021)
Incidence subsequent therapy atezolizumab_(NIC arm)	1,11%	-	dirichlet	(Paz-Ares et al., 2021)
Incidence subsequent therapy PDC: carboplatin paclitaxel (NIC arm)	9,42%	-	dirichlet	(Paz-Ares et al., 2021)
Incidence subsequent therapy PDC: carboplatin pemetrexed (NIC arm)	13,57%	-	dirichlet	(Paz-Ares et al., 2021)

Incidence subsequent therapy PDC: cisplatin pemetrexed (NIC arm)	6,09%	-	dirichlet	(Paz-Ares et al., 2021)
Incidence BSC (NIC arm)	69,25%	-	dirichlet	(Paz-Ares et al., 2021)
Incidence subsequent therapy nivolumab (PDC arm)	15,64%	-	dirichlet	(Paz-Ares et al., 2021)
Incidence subsequent therapy pembrolizumab (PDC arm)	8,66%	-	dirichlet	(Paz-Ares et al., 2021)
Incidence subsequent therapy atezolizumab (PDC arm)	4,75%	-	dirichlet	(Paz-Ares et al., 2021)
Incidence subsequent therapy ipillimumab (PDC arm)	0,56%	-	dirichlet	(Paz-Ares et al., 2021)
Incidence subsequent therapy PDC: carboplatin paclitaxel (PDC arm)	7,26%	-	dirichlet	(Paz-Ares et al., 2021)
Incidence subsequent therapy PDC: carboplatin pemetrexed (PDC arm)	10,61%	-	dirichlet	(Paz-Ares et al., 2021)
Incidence subsequent therapy PDC: cisplatin pemetrexed (PDC arm)	4,75%	-	dirichlet	(Paz-Ares et al., 2021)
Incidence BSC (PDC arm)	59,78%	-	dirichlet	(Paz-Ares et al., 2021)
Price nivolumab	441,48	44,15	gamma	(ZIN/medicijnkosten.nl)
Price ipilimumab	3562,65	356,27	gamma	(ZIN/medicijnkosten.nl)
Price carboplatin	16,68	1,67	gamma	(ZIN/medicijnkosten.nl)
Price paclitaxel	288,20	28,82	gamma	(ZIN/medicijnkosten.nl)
Price pemetrexed	1182,90	118,29	gamma	(ZIN/medicijnkosten.nl)
Price cisplatin	22,69	2,27	gamma	(ZIN/medicijnkosten.nl)
Price pembrolizumab	2860,56	286,06	gamma	(ZIN/medicijnkosten.nl)
Price atezolizumab	4032,99	403,30	gamma	(ZIN/medicijnkosten.nl)
Costs administration IV	369,00	36,90	gamma	(ZIN, 2015)
Costs outpatient visits SD	2047,86	204,79	gamma	(van der Linden et al., 2016)
Costs day care SD	429,81	42,98	gamma	(van der Linden et al., 2016)

Costs phone consult SD	25,03	2,50	gamma	(van der Linden et al., 2016)
Cost inpatient days SD	5576,66	557,67	gamma	(van der Linden et al., 2016)
Costs intensive care SD	208,92	20,89	gamma	(van der Linden et al., 2016)
Costs laboratory testing SD	931,44	93,14	gamma	(van der Linden et al., 2016)
Costs genetic biomarker test SD	225,24	22,52	gamma	(van der Linden et al., 2016)
Costs pathology SD	164,31	16,43	gamma	(van der Linden et al., 2016)
Costs radiotherapy SD	1692,04	169,20	gamma	(van der Linden et al., 2016)
Costs medical imaging SD	2962,97	296,30	gamma	(van der Linden et al., 2016)
Costs outpatient visits PD	1338,40	133,84	gamma	(van der Linden et al., 2016)
Costs day care PD	310,12	31,01	gamma	(van der Linden et al., 2016)
Costs phone consult PD	18,50	1,85	gamma	(van der Linden et al., 2016)
Cost inpatient days PD	2535,34	253,53	gamma	(van der Linden et al., 2016)
Costs intensive care PD	102,28	10,23	gamma	(van der Linden et al., 2016)
Costs laboratory testing PD	494,01	49,40	gamma	(van der Linden et al., 2016)
Costs pathology PD	23,94	2,39	gamma	(van der Linden et al., 2016)
Costs radiotherapy PD	1363,43	136,34	gamma	(van der Linden et al., 2016)
Costs medical imaging PD	1052,22	105,22	gamma	(van der Linden et al., 2016)
Cost best supportive care	1277,53	127,75	gamma	(NZA, 2021)
End of life hospital costs	1175,22	117,52	gamma	(ZIN, 2017a)

Incidence hospital days terminal	38%	0,04	beta	(ZIN, 2017a)
Number of hospital days terminal	10,10	1,01	gamma	(ZIN, 2017a)
Incidence anaemia (NIC arm)	6%	0,01	beta	(Paz-Ares et al., 2021)
Incidence diarrhoa (NIC arm)	4%	0,00	beta	(Paz-Ares et al., 2021)
Incidence neutropenia (NIC arm)	7%	0,01	beta	(Paz-Ares et al., 2021)
Incidence febrile neutropenia (NIC arm)	4%	0,00	beta	(Paz-Ares et al., 2021)
Incidence anaemia (PDC arm)	14%	0,01	beta	(Paz-Ares et al., 2021)
Incidence diarrhea (PDC arm)	1%	0,00	beta	(Paz-Ares et al., 2021)
Incidence neutropenia (PDC arm)	9%	0,01	beta	(Paz-Ares et al., 2021)
Incidence febrile neutropenia (PDC arm)	3%	0,00	beta	(Paz-Ares et al., 2021)
Costs anaemia	2006,29	200,63	gamma	(ZIN, 2015)
Costs diarrhea	2423,83	242,38	gamma	(ZIN, 2015)
Costs neutropenia	1443,19	144,32	gamma	(ZIN, 2015)
Costs febrile neutropenia	3116,55	311,66	gamma	(ZIN, 2015)
Costs average productivity	37,10	3,71	gamma	(Hakkaart-van Roijen et al., 2015)
Costs unpaid employee	14,95	1,50	gamma	(Hakkaart-van Roijen et al., 2015)
Proportion people working	61%	0,06	beta	(CBS, 2021)
Proportion people working full-time	51%	-	Dirichlet	(CBS, 2021)
Proportion people working part-time	46%	-	Dirichlet	(CBS, 2021)
Hours per week informal care SD	8,00	0,80	gamma	(ZIN, 2015)
Hours per week informal care PD	12,00	1,20	Gamma	(ZIN, 2015)
Average distance hospital	7,00	0,70	gamma	(Hakkaart-van Roijen et al., 2015)

Cost Car	0,20	0,02	gamma	(Hakkaart-van Roijen et al., 2015)
Cost Parking	3,20	0,32	gamma	(Hakkaart-van Roijen et al., 2015)
Cost Public transit	0,20	0,02	gamma	(Hakkaart-van Roijen et al., 2015)
Cost taxi	2,83	0,28	gamma	(Hakkaart-van Roijen et al., 2015)
Number of outpatient visits	27,20	2,72	gamma	(Pompen et al., 2009)
Number of inpatient visits	5,50	0,55	gamma	(Pompen et al., 2009)

Appendix A5 Disaggregated model outcomes

Table 24: Disaggregated model outcomes

	NIC	PDC	Increment
PFS			
Drug acquisition	€ 110.979,37	€ 7.813,28	€ 103.166,08
Drug administration	€ 5.226,21	€ 1.324,56	€ 3.901,65
Healthcare resource use	€ 36.998,33	€ 18.284,75	€ 18.713,58
Adverse events	€ 352,97	€ 468,47	€ (115,50)
Productivity losses	€ 8.101,84	€ 8.101,84	€ -
Informal care	€ 6.956,58	€ 3.437,98	€ 3.518,61
Travel	€ 216,14	€ 106,82	€ 109,32
PD			
Best supportive care	€ 12.967,52	€ 12.191,35	€ 776,17
Drug acquisition	€ 11.417,59	€ 29.063,11	€ (17.645,51)
Drug administration	€ 1.752,90	€ 3.077,05	€ (1.324,15)
Healthcare resource use	€ 17.487,83	€ 19.047,27	€ (1.559,44)
Productivity losses	€ 11,85	€ 12,83	€ (0,98)
Informal care	€ 6.573,79	€ 7.159,99	€ (586,21)
Travel	€ 122,55	€ 133,47	€ (10,93)
End of life costs	€ 3.994,00	€ 4.169,41	€ (175,41)

Appendix A6: Deterministic one-way sensitivity analysis

Table 25: Deterministic one-way sensitivity analysis top 10 parameters

Rank ICER	Parameter	Base input	Low input	High input	Lower bound ICER	Upper bound ICER
1	Utility progression-free	0,71	0,57	0,85	€238.075,14	€152.051,46
2	Price Ipilimumab	3.562,65	2.850,12	4.275,18	€167.331,47	€203.826,74
3	Price Nivolumab	441,48	353,18	529,78	€168.416,51	€202.741,70
4	2nd line treatment BSC (PDC arm)	59,78%	47,82%	71,73%	€192.491,65	€178.666,56
5	2nd line treatment BSC (NIC arm)	69,25%	55,40%	83,10%	€180.859,85	€190.298,36
6	Utility progressed disease	0,67	0,54	0,80	€181.517,47	€189.826,66
7	2nd-line treatment nivolumab (PDC arm)	15,64%	12,51%	18,77%	€189.525,43	€181.632,77
8	2nd-line treatment pembrolizumab (PDC arm)	8,66%	6,93%	10,39%	€188.642,98	€182.515,23
9	Price pemetrexed	5.576,66	946,32	1.419,48	€188.309,49	€182.848,72
10	Costs inpatient days (SD)	5.576,66	4.461,33	6.691,99	€182.916,55	€188.241,65

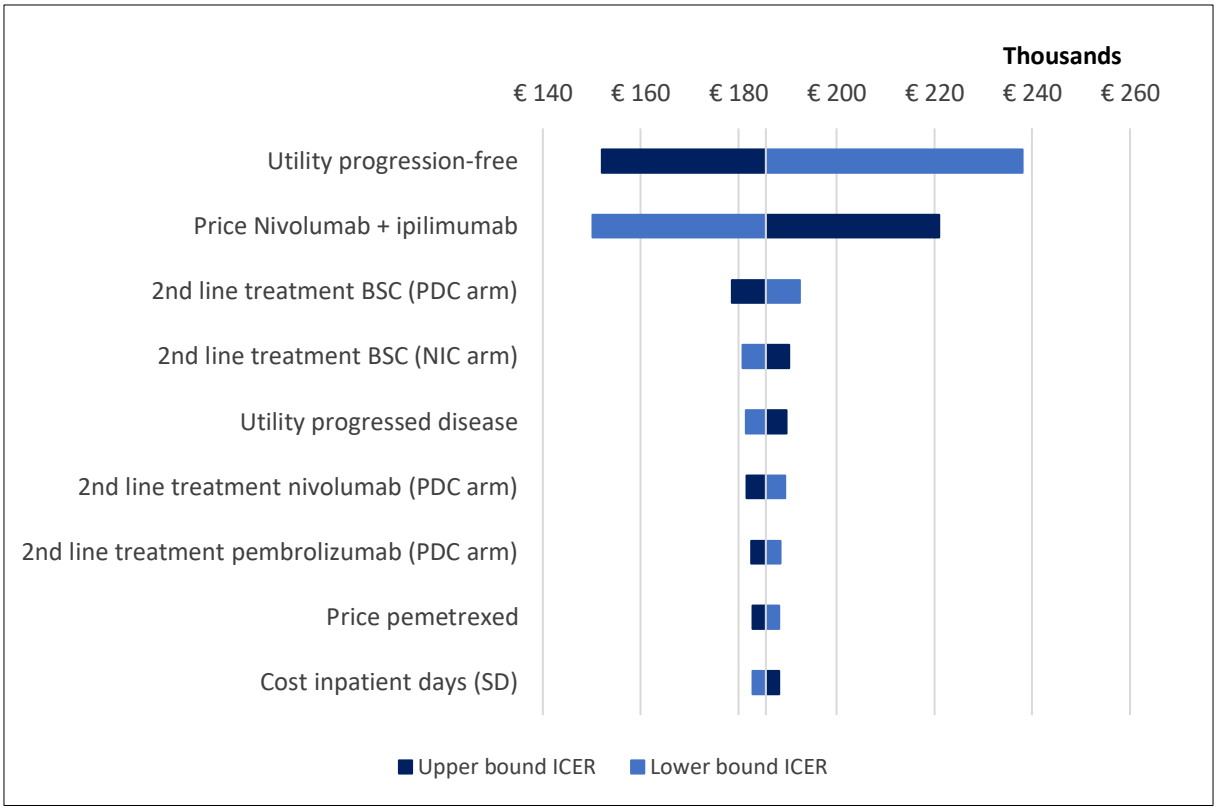

Figure 11: Tornado diagram with the top 10 most influential parameters for the ICER: with aggregate price of nivolumab and ipilimumab. Lower bound: €150.169; Upper bound: €220.989.

Appendix A7: Scenario analysis

Table 26: All scenario analysis performed

	Incremental costs	Incremental LY's	Incremental QALs	ICER
Base case	€101.986	0,76	0,55	€185.579
Parametric distribution:				
OS: Log-normal	€103.896	0,80	0,57	€181.138
OS: Exponential	€100.139	0,55	0,40	€248.985
OS: Weibull	€101.809	0,53	0,39	€263.307
OS: Gompertz	€95.864	0,51	0,37	€258.876
OS: Generalized Gamma	€93.646	0,57	0,42	€223.300
PFS: Log-normal	€111.782	0,76	0,54	€208.478
PFS: Exponential	€122.013	0,76	0,53	€230.105
PFS: Weibull	€119.703	0,76	0,53	€225.189
PFS: Gompertz	€101.211	0,76	0,55	€182.686
PFS: Log-logistic	€107.910	0,76	0,54	€200.888
Time horizon:				
Time horizon 5 years	€84.036	0,19	0,15	€549.708
Time horizon 7,5 years	€92.921	0,45	0,33	€283.425
Time horizon 10 years	€97.763	0,60	0,44	€223.633
No wastage: vial sharing	€88.286	0,76	0,55	€160.649
NIC treatment for 7,9 months	€53.009	0,76	0,55	€96.458
Price reduction of 60% of NIC being cost-effective	€43.607	0,76	0,55	€79.348