To reimburse or not to reimburse? Calculating the cost-effectiveness of multiple indications of Pembrolizumab in The Netherlands

Student: Floor Verbeek

Supervisor: Prof. Dr. Uyl – de Groot & Dr. van Gils

Student number: 582117

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Erasmus University Rotterdam

Abstract

Background

In light of the increased focus on conscious spending in healthcare given the expanding expenditures within the Dutch healthcare sector, The Lock was invented to critically assess the clinical value and financial picture of new and expensive healthcare interventions prior to reimbursement. Pembrolizumab was one of the first new tumor-agnostic immunotherapies on the market to be placed in The Lock. Even though it received a negative reimbursement recommendation based on its unfavorable cost-effectiveness and the clandestine nature of possible price discounts, it was included in the basic care package in 2017. Ever since, many additional indications of pembrolizumab have emerged and have been applied in Dutch clinical practice. However, none of these new indications have been investigated in terms of value for money and financial sustainability. This study aims to shed a light on the current stance of the general cost-effectiveness landscape of pembrolizumab to estimate the impact of overlooking the budgetary impact following the automatic reimbursement of additional indications of tumor-agnostic immunotherapies in the Netherlands.

Methods

First, a full cost-effectiveness analysis was performed for the indication of pembrolizumab in the first-line treatment of metastasized NSCLC with a PD-L1 expression of ≥ 50%. Then, cost and utility inputs, and results of sensitivity analysis of this first cost-effectiveness analysis were used to generally assess the overall cost-effectiveness of pembrolizumab for seven additional of its current indications. To adhere to clinical practice as accurately as possible, survival estimations for OS and PFS were changed, and costs associated with the treatment of pembrolizumab and standard of care were changed according to each respective OS and PFS. Throughout all indications, utilities, costs associated with adverse events and end-of-life were left identical to the first cost-effectiveness analysis. All cost-effectiveness analyses included utility values representative for the Dutch patient population and cost inputs of real-world peer reviewed studies performed in the Netherlands.

Results

The investigated indications of pembrolizumab showed base-case ICERs ranging from €126,474 to €2,600,719, some even taking on negative values amounting to - €1,282,553 (all three first-line treatments of NSCLC). Generally, PSA results show a 0 – 9% probability of reimbursement given a willingness-to-pay threshold of €80,000, with a maximum of 30% (first-line treatment of melanoma). Taken together, this implies that all performed cost-effectiveness analyses would receive a negative reimbursement decision from Zorginstituut Nederland given a willingness-to-pay threshold of €80,000 for cancer treatments as commonly applied in the Netherlands, albeit in the absence of any price discounts of pembrolizumab which were not taken into account in this study. As reported in one sensitivity

analysis surrounding first-line monotherapy of advanced NSCLC, only in the case of a 50% price reduction of pembrolizumab would the ICER show a favorable cost-effectiveness below €80,000. Furthermore, there does not seem to be a correlation between the magnitude of the ICER and the line of treatment, the context of treatment or the cancer histology.

Implications

In the face of current and upcoming immunotherapies entering the market, this study finds that various indications of the same immunotherapy can yield substantially different cost-effectiveness outcomes, even though some indications might pertain to the same cancer histology. In that light, overlooking cost-effectiveness as an important of a complete pharmaceutical evaluation of additional indications of tumor-agnostic immunotherapies such as pembrolizumab while continuing to include new indications the basic care package could lead to the clinical application of cost-ineffective healthcare. Complicated by a lack of transparency with regards to financial agreements between the Ministry of Health and the drug manufacturer, assuming that all new indications of a given immunotherapy are cost-effective because a single initial assessed indication displayed cost-effectiveness could result in a misallocation of the Dutch inpatient healthcare budget, possibly crowding out of other cost-effective healthcare interventions, and potentially endangering the financial sustainability, accessibility, quality and affordability of healthcare in The Netherlands.

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Introduction

Background

Advances in oncology research of the past decade have marked a paradigm shift in cancer treatment. Traditionally, anti-cancer compounds are manufactured based on one specific property of a given tissue or organ of origin on which the tumor would be dependent [1]. Alongside surgical interventions to excise tumor bulk, chemotherapy and radiotherapy are still the main treatment options to tackle this particular molecular tumor characteristic [2]. However, cancer drug resistance, which describes the cancer's ability to become tolerant to and circumvent anti-cancer therapy, still substantially hinders the effectiveness of current cancer treatment and exhausts the possible treatment options available today [3].

Recently, targeted therapy in the form of immunotherapy has been proposed as an up-and-coming solution to resolve the threat of drug resistance [3]. The premise of immunotherapy builds on enabling the host's own immune system to mount an adequate immune response against cancer cells, either by stimulation of effector immune cells of the host or by neutralization of immunosuppressor mechanisms caused by the tumor [4]. Importantly, a key advantage of immunotherapy is its ability to transcend treatment of one specific cancer histology, tissue or organ [1]. Given its effect on the tumor micro-environment, a feature ascribed to almost all cancer types, these so-called 'tumor-agnostic' therapies allow targeted treatment of oncogenic drivers across a distinct but heterogeneous population of cancer patients, regardless of tumor site [1].

KEYNOTE-trials

One of the immunotherapies to make it into clinical practice is pembrolizumab. Also known under its brand name Keytruda, pembrolizumab is an antibody targeting programmed cell death protein 1 (PD-1) on immune effector cells, through which it prevents their neutralization by programmed cell death-ligand 1 (PD-L1) on tumor cells [4], [5]. As of 2015, the compound received its initial market authorization by the European Market Authorization (EMA) for adult patients with advanced melanoma [6]. In 2017, as the first ever oncology drug, pembrolizumab was granted a tumor agnostic status by the Food and Drug Administration for treatment of patients with advanced microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors in the second line of therapy in 2017 [7].

All evidence of the clinical effectiveness of pembrolizumab is captured by trial data from the KEYNOTE-studies executed and funded by Merck Pharmaceuticals [5]. These open-label, phase III randomized controlled trials register the overall survival and progression-free survival of pembrolizumab against the current standard of care of a wide range of cancer histologies in patients from all over the world. In the Netherlands, data from these trials lie at the basis of approval decisions surrounding the clinical value, implementation and reimbursement of pembrolizumab [8]–[10]. Evaluated by the Commissie ter Beoordeling van Oncologische Middelen (Oncology Appraisal Committee;

cieBOM) and the Wetenschappelijke Adviesraad – commissie geneesmiddelen (Scientific Advisory Board; WAR-CG), the first registered indication of pembrolizumab was weighed against the official Dutch guidelines at the time to assess scientific evidence of its clinical value [8], [11], [12]. This evaluation allowed them to issue recommendations on the implementation of pembrolizumab in Dutch clinical practice together with the Zorginstituut Nederland (ZIN), the main Dutch governmental body appointed by the government that looks to uphold and encourage accessibility and quality within the Dutch healthcare system [8], [13]. At the time of this writing, thirteen indications of pembrolizumab were approved as of March 2021 according to the Farmacotherapeutisch Kompas, the official Dutch drug registry by ZIN (Table 0.1) [14]. Ever since, the list of approved indications had expanded with five new indications, and it is expected that another 10 extensions of indication will follow within the foreseeable future (Table S.1-S.2) [15].

Indications of pembrolizumab as of March 2021	
Tumor Type	**Full Indication**
Colorectal Cancer (CRC)	First line monotherapy of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) CRC
Hodgkin Lymphoma (cHL)	Monotherapy of recurrent or refractory cHL after previous failure of an autologous stem cell transplant, including pediatric patients ≥ 3 years of age
Head & Neck Squamous Cell Carcinoma (HNSCC)	Monotherapy of recurrent or metastasized HNSCC with PD-L1 expression (TPS ≥ 50%) with disease progression on or after platinum-containing chemotherapy
	Monotherapy as first line treatment of metastasized or unresectable recurrent HNSCC with PD-L1 expression (CPS ≥ 1), combined with 5-fluoro-uracil and platinum-containing chemotherapy
Melanoma	Monotherapy of unresectable or advanced melanoma
	Adjuvant treatment of stage III melanoma with involvement of lymph nodes following complete resection of melanoma and lymph nodes
Renal Cell Carcinoma (RCC)	Combination therapy as first line treatment of advanced RCC with axitinib
Non-Small Cell Lung Cancer (NSCLC)	Monotherapy as first line treatment of metastasized NSCLC with PD-L1 expression (TPS ≥ 50%) with no EGFR- or ALK-positive genomic mutations
	Monotherapy of locally advanced or metastasized NSCLC with PD-L1 expression (TPS ≥ 1%) and disease progression on or after previous chemotherapy. Patients with EGFR- or ALK-positive genomic mutations should have disease progression after receiving approved therapy for these mutations prior to pembrolizumab
	Combination therapy as first line treatment of metastasized NSCLC with no EGFR- or ALK-positive genomic mutations, with Pemetrexed and platinum-containing chemotherapy
	Combination therapy as first line treatment of metastasized NSCLC, with carboplatin and either paclitaxel or (nab-)paclitaxel

Urothelial Carcinoma (UC)	Monotherapy of locally advanced or metastasized UC with disease progression during or following platinum-containing chemotherapy
	Monotherapy of locally advanced or metastasized UC with PD-L1 expression (CPS ≥ 10) not eligible for cisplatin-containing chemotherapy

Table 0.1: Approved indications of pembrolizumab as of March 2021, according to the Farmacotherapeutisch Kompas. Abbreviations: PD-L1, programmed death-ligand 1; TPS, tumor proportion score; CPS, combined positive score; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

Financial sustainability

Even though the drug has only made its way into Dutch clinical practice a couple of years ago, treatment with pembrolizumab is already estimated to be good for €200 million Euros annually in the Netherlands, approximately 1% of all total costs associated with inpatient pharmaceuticals [16], [17]. Since the drug aims to treat genetic aberrations with currently exhausted treatment options, indicating its therapeutic and societal relevance to a substantial fraction of several cancers, it will add even more costs to the total expenses associated with this new agnostic therapeutic avenue [7]. So, while this innovative and pan-tumor immunotherapy might be clinically promising, this information implies that its current and future impact on the Dutch inpatient healthcare budget is not to be underestimated, and raises questions as to its financial sustainability [18].

In the Netherlands, new drug registrations with proof of added clinical value as assessed by the cieBOM and WAR-CG undergo an extensive cost-effectiveness analysis commissioned by the Dutch Ministerie van Volksgezondheid, Welzijn en Sport (Ministry of Health; VWS) prior to official reimbursement decisions [19], [20]. Usually, these analyses yield an incremental cost-effectiveness ratio (ICER) which can be tested against a willingness-to-pay-value (WTP-value) to determine whether the new drug optimizes health effects with the available resources [21]. For oncology drugs, this WTP-value generally amounts to €80,000 [21], [22]. However, after the evaluation of the first indication and concomitant financial agreements between the VWS and the drug manufacturer, possible additional indication often do not warrant new cost-effectiveness analyses, resulting in no new ICERs nor conclusive evidence of whether the increased costs of that indication weigh up against the expected additional benefits. Therefore, while the initial indication of tumor-agnostic therapies seems to be cost-effective, it remains unclear whether the entire range of indications, thus including extensions of indication, offer enough value for money.

Problem Analysis

Ever since its first approval, pembrolizumab has steadily established its place in clinical practice of cancer treatment in the Netherlands (Table 0.1 and S.1) [14], [15]. However, in the light of extension of these therapeutical indications

and its expanding tumor agnostic status, it remains unclear whether these new indications of treatment offer any value for money. Therefore, the main research question is:

What is the cost-effectiveness of pembrolizumab in the Netherlands?

In order to address this research question, first, the cost-effectiveness of pembrolizumab for the treatment of non-small cell lung cancer (NSCLC) will be extensively investigated. Subsequently, the outcome of that analysis will be the main framework to assess cost-effectiveness of some of the other indications as listed in Table 0.1. To that end, the goal is to explore potential implications for other existing and future indications in terms of risks to accept another treatment indication when not appropriately assessing its cost-effectiveness.

To answer the main research question, this work will focus on the following sub-questions:

1. What is the current evidence of cost-effectiveness of pembrolizumab in the Netherlands?
2. For which current and future indications of pembrolizumab has a cost-effectiveness analysis not yet been performed in the Netherlands?
3. What is the cost-effectiveness of pembrolizumab for the treatment of first-line NSCLC in the Netherlands?
4. What does the cost-effectiveness of current and future indications of pembrolizumab roughly look like?
5. What does the cost-effectiveness analysis of a single NSCLC indication of pembrolizumab imply for the value for money of other current and future indications of pembrolizumab?
6. What lessons can be learned from the pembrolizumab case with regards to future tumor-agnostic therapies?

Chapter 1 will focus on the current knowledge of the cost-effectiveness of all indications of pembrolizumab in the Netherlands and will identify the scope of the evidence gap. Chapter 2 and 3 will describe an attempt at closing this evidence gap by assessing the cost-effectiveness of pembrolizumab in the Dutch setting, including an extensive account of the applied methods and obtained results. Finally, Chapter 4 will be used to critically reflect upon the outcomes of the cost-effectiveness analyses and their place in the current and future landscape of implementation and reimbursement of tumor-agnostic therapies in the Netherlands.

Chapter 1: Current evidence of the cost-effectiveness of pembrolizumab in the Netherlands

This chapter focuses on the existing knowledge of cost-effectiveness that pembrolizumab has demonstrated thus far. In favor of understanding the exact path that pembrolizumab has trod in its course to reimbursement of its first indication in the Netherlands, and to fathom the implications this might hold for the reimbursement of the subsequent indications, it is imperative to appreciate the current Dutch healthcare system and the process of how reimbursement of a new and expensive (oncologic) healthcare intervention comes to be. With this information in mind, the path of pembrolizumab, its strengths and its flaws, can be evaluated to identify possible evidence gaps.

Road to reimbursement

As one of the countries acclaimed for the success and prosperity of its healthcare system, the Netherlands upholds three universal values which constitute the backbone of its healthcare organization: quality, accessibility and affordability [23]. To benefit these goals, every insured Dutch citizen has access to a basic care package as part of an extensive insurance solidarity program, which includes a large spectrum of healthcare use, such as care received in the hospital, care related to mental health, visits to the general practitioner's, pharmaceutical services and even the use of medical devices [24]**.** Dictated by law, the contents of this package are determined by the Ministerie van Volksgezondheid, Welzijn en Sport (Ministery of Health; VWS) and may only contain pharmaceuticals or healthcare technologies that meet the requirements of the 'established medical science and medical practice' [25]. In other words, only effective healthcare interventions that attain the level of the current position of clinical practice deserve consideration with respect to their admittance to the basic care package.

In the Netherlands, all inpatient healthcare interventions, including anti-cancer compounds, follow the same path in their pursuit to reimbursement. Any inclusion of medical care in the basic care package occurs through a so-called open system [8], [24]. This system implies that, as long as the particular healthcare intervention is found to be effective by the preconditions mentioned above, they can be introduced in the basic care package and receive reimbursement without interference of the VWS. As a result, the exact content of the basic care package are usually decided upon at the level of health insurers and healthcare providers [24].

The Lock

However, in exceptional circumstances, the VWS maintains the right to intervene in this open system of reimbursement [8]. This applies specifically to healthcare interventions that are at risk to the quality, accessibility and affordability of the basic care package of the Dutch population as a collective, such as new and expensive anti-

cancer compounds. In that case, the VWS can place these healthcare interventions in The Lock to restrain costs incurred by inpatient healthcare and avoid nationwide budgetary constraints. The Lock refers to a fictional place that allows the VWS to temporarily block or at least suspend inclusion of these healthcare interventions in the basic care package in order to assess the financial and societal impact of its inclusion in the package in the meantime. Usually, this period also permits the VWS to critically reflect upon financial arrangements to be put in place or to establish guidelines concerning the appropriate practical use of the healthcare intervention in question. Implemented in 2015, this Lock-procedure is most often carried out due to high financial risks associated with particular new healthcare interventions that would otherwise be added to the basic care package without any assessment in this open system of inpatient reimbursement [24].

Created by the VWS as a tool to monitor new inpatient healthcare interventions that will likely enter the market within two years, the Horizonscan Geneesmiddelen (HG) lists all possible inpatient pharmaceuticals for one or multiple disease indications that could pose a challenge to the Dutch national healthcare budget [8], [15]. Based on this biannually updated HG, these indications can be placed in The Lock if they meet one or more of the following criteria [8]:

- The total annual budget impact of the pharmaceutical of one indication or multiple indications amounts to €40 million or more. This implies that all indications will be placed in The Lock.
- The total annual expected expenses of the pharmaceutical for the treatment of a single indication are €50,000 or more, and the total annual budget impact of that indication totals €10 million or more. In that case, the single indication of the pharmaceutical will be placed in The Lock.

As of 2019, a total of 14 different anti-cancer compounds were placed in The Lock, including pembrolizumab in 2016 [20].

Zorginstituut Nederland

Once placed in The Lock, additional investigations should demonstrate whether or not the healthcare intervention in question will ultimately receive a positive reimbursement recommendation and will thereafter be covered by the basic care package. Playing a pivotal role in this risk assessment process to safeguard the three aforementioned universal values, the Dutch National Health Care Institute (Zorginstituut Nederland; ZIN) is the main independent body appointed by the government that advises the VWS on decisions surrounding possible reimbursement of inpatient healthcare interventions placed in The Lock [8]. In their so-called ‘pakketadvies’ ((basic care) package advice), they conduct extensive research into the value of the inpatient health intervention based on the pharmaceutical dossier submitted by its market authorization holder [13]. This process is shaped by a preliminary selection phase, an assessment phase, and a final appraisal, during which various stakeholders will be consulted. A summarized overview of this entire process is shown in Figure 1.1.

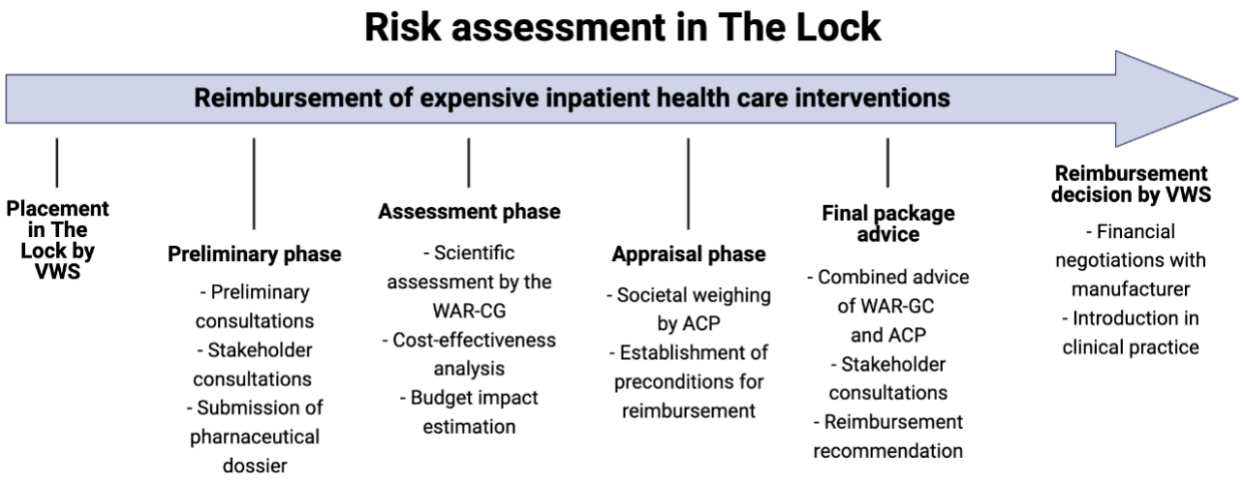

Figure 1.1: Overview of the risk assessment performed by the ZIN in case of placement in The Lock. Abbreviations: ZIN, Zorginstituut Nederland; VWS, Ministerie van Volksgezondheid, Welzijn en Sport; WAR-GC, Wetenschappelijke Adviesraad – commissie geneesmiddelen; ACP, Adviescommissie Pakket.

Preliminary phase

During the first phase, market authorization holders can request a preliminary consultation prior to submitting their definitive pharmaceutical dossier to the ZIN in order to flatten out any emerging unclarities or flaws, or to inquire formal scientific advice form the ZIN for the same reason [8]. Then, the ZIN often organizes several consultations with stakeholders to address any remaining substantive questions about the healthcare intervention, or to consult stakeholders in search of additional relevant information to complement the evidence of the pharmaceutical dossier [8], [24]. Stakeholders include but are not limited to health insurers, patient associations, care providers or professional groups. The preliminary phase is concluded with a formal submission of the pharmaceutical dossier by the market authorization holders to the ZIN.

Assessment phase

In the second phase, the scientific content of the submitted dossier is carefully evaluated by the ZIN. More specifically, this scientific valuation consists of a pharmacotherapeutic assessment, a budget impact analysis and a pharmaco-economic report, including a cost-effectiveness analysis or calculation of the disease burden if necessary [8].

In the pharmacotherapeutic assessment, the healthcare intervention is weighed against the current stance of clinical practice by the Wetenschappelijke Adviesraad – commissie geneesmiddelen (Scientific Advisory Board; WAR-CG), a scientific committee made up of (bio-)medical academics, clinicians, pharmacists, or other members with a health economic background [10]. Frequently, gathered scientific evidence consists of clinical trials executed or funded by the manufacturer [24]. In case of added clinical value compared to the current standard treatment, a budget impact

analysis and cost-effectiveness analysis are requested to be performed by the ZIN [8], [13], [21]. In case of equal clinical value, a budget impact analysis alone will suffice. In case of no proven clinical value, the healthcare intervention is deemed to display insufficient efficacy to warrant reimbursement and will therefore always result in a negative advice from the WAR-CG and subsequently the ZIN.

The budget impact and the cost-effectiveness analyses paint the financial picture following the possible inclusion of the new healthcare interventions in the basic care package. In the budget impact analysis, all estimated costs associated with the use of the new healthcare intervention of the first three years after its reimbursement are calculated. All patients that fit the description of the proposed indication(s) for which the ZIN initially received a reimbursement application are taken into account [8], [13]. Furthermore, the cost-effectiveness analysis grants the ZIN more insight into the relationship between the costs and the effects of the healthcare intervention as compared to the current standard of care. Usually, the cost-effectiveness is offset against a reference value, which depends on the results of the calculation of the burden of disease. During the evaluation of this analysis, the ZIN exercises a societal perspective, implying that all relevant societal costs and effects should be considered [13], [26].

Collectively, the results of these analyses lay the foundation of an interpretation or weighing of the complete case at hand by the Wetenschappelijke Adviesraad – commissie geneesmiddelen (WAR-CG). In order to ensure that all significant scientific evidence was taken into account and weighed correctly, the findings of the WAR-CG are shared with the market authorization holder, the relevant professional groups and patient associations, and health insurers [8], [10]. If confirmed, a second evaluation takes place, and its conclusion is further drawn up in the appraisal phase.

Appraisal phase

In this final phase, all evidence assembled in the assessment phase is weighed from a societal perspective based on four criteria, including necessity, efficacy, cost-effectiveness and feasibility [9], [24]. Logically, any inpatient healthcare intervention requires a medical necessity to warrant reimbursement. In addition, this criterium considers the necessity of publicly insuring the new healthcare intervention from a societal point of view. As mentioned earlier, the criterium of efficacy relates to the evidence-based medicine argument on which any new healthcare intervention should be based in order to be eligible for reimbursement through the open system. Thirdly, evaluating the cost-effectiveness of a healthcare intervention involves offsetting all its associated costs to all its associated gains to determine whether the healthcare intervention in question offers enough value for money. Lastly, the criterium of feasibility largely covers any issues surrounding the implementation of a healthcare intervention in clinical practice.

One of the main players in this phase is the Adviescommissie Pakket (ACP), an advisory committee consulted by the ZIN consisting of several experts appointed by the VWS [9], [24]. Like the WAR-CG, they also issue a recommendation on whether the new healthcare intervention offers enough value for money upon reimbursement, but their focus is

concentrated more so on the societal implications from the perspective of the Dutch population altogether. For example, examined aspects include the availability of other healthcare interventions, patient vulnerability, the type of intervention (e.g. curative versus palliative) [9], [24]. In this stage, any preconditions to reimbursement of the healthcare intervention are discussed as well, such as financial agreements or guidelines concerning its appropriate use in clinical practice.

Final decisions and the package advice

In short, the final reimbursement recommendation by the ZIN is based on the advice of the WAR-CG, the ACP, and feedback of the consulted stakeholders mentioned previously. This allows the ZIN to accurately and reliably formulate its recommendation to the VWS, which ultimately decides on reimbursement and is in charge of any financial negotiations with the manufacturer of the healthcare intervention [8]. Only after the assessment of the ZIN, the establishment of possible financial arrangements, and the assurance regarding its appropriate practical use can a healthcare intervention previously placed in The Lock be eligible for inclusion in the basic care package.

Cost-effectiveness

As part of the assessment phase of the inpatient evaluation process, one of the main criteria on which an inpatient healthcare intervention in The Lock is weighed**,** is its cost-effectiveness. Often met with controversy in the media, the cost-effectiveness of a healthcare intervention attempts to determine whether the clinical effects of a certain new intervention outweigh its estimated costs with respect to the existing standard of care of the intervention in question [21]. This analysis enables the VWS to favor interventions that benefit the current insurance solidarity program in order to spend the healthcare budget wisely for society as a whole [13], [21].

Guided by the submitted pharmaco-economical dossier of the market authorization holder, the ZIN conducts an extensive cost-effectiveness analysis of each healthcare intervention that was found to demonstrate added clinical value to the current treatment option [8], [21]. Generally, clinical effects of this cost-effectiveness analysis are expressed in quality-adjusted life years or QALYs, referring to one year of life in perfect health. In the Netherlands, costs are expressed in Euros. Connecting both effects and costs yields an incremental cost-effectiveness ratio (ICER), which indicates the amount of Euros the health intervention demands for each QALY it produces. When comparing all incurred costs and effects of the new healthcare intervention and the existing one, there are several conclusions to be drawn with respect to their place in clinical practice:

- The new healthcare intervention yields less clinical effects and incurs more costs than the existing one;
- The new healthcare intervention yields more clinical effects, but also incurs less costs than the existing one;
- The new healthcare intervention yields less clinical effects, but also incurs less costs than the existing one;
- The new healthcare intervention yields more clinical effects, but also incurs more costs than the existing one.

Rationally, the first two scenarios will most likely result in a clear-cut recommendation by the ZIN, that is to say a negative recommendation for the first statement due to lack of societal value, and a positive recommendation for the second statement given its lack of societal disadvantage. However, the third and fourth scenario ask for a more careful consideration in terms of their potential value to society. Essentially, it raises the question how much society is willing to pay for additional health benefits, or is willing to save for fewer health benefits, associated with a certain healthcare intervention. This suggests the existence of a reference value, a so-called 'willingness-to-pay' value (WTP-value), that represents the amount of costs one particular society considers acceptable to spend on a single QALY.

In an attempt to estimate this reference value for the Dutch population, the Raad voor Volkgsgezondheid en Samenleving (Council of Public Health and Health Care) describes a WTP-structure that based on the burden of disease [27]. Recently, research has shown that the Dutch society is prepared to pay more for diseases causing a greater disease burden, ranging from €10,000/QALY for treatment of high blood pressure, to €80,000/QALY for treatment of advanced cancer [22], [27]. In practice, these values are found to be substantiated within the Dutch cost-effectiveness debate [21].

Importantly, while considered a valuable addition to the pharmaceutical dossier in its totality, cost-effectiveness alone is never the sole criterium on which the ZIN could issue a negative recommendation in its package advice [21]. As explained previously, many factors simultaneously lie at the basis of the advice concerning reimbursement of a healthcare intervention made by the ZIN [8], [13]. The role of the cost-effectiveness analysis is a mere supportive one, and even equipped the VWS with the possibility to enter negotiations of financial arrangements of the new healthcare interventions with their manufacturer with additional bargaining power.

The path of pembrolizumab

Given that the present state-of-the-art science allows for the discovery of very sophisticated and expensive techniques to combat cancer, most recently developed anti-cancer compounds follow the pathway as described above, including pembrolizumab [20]. After its registration for the second-line therapy of locally advanced or metastasized NSCLC, initial estimations found that total treatment costs per patient would amount to approximately €50,000, with a total annual treatment cost of €200 million [16]. Meeting both financial conditions to be placed in The Lock, the VWS issued its exclusion from the basic care package and enquired further investigations by the ZIN in 2016 [16].

Commissie BOM

In an effort to obtain a nationwide consensus regarding the clinical application of newly registered oncology drugs in particular, the Commissie ter Beoordeling van Oncologische Middelen (Oncology Appraisal Committee; cieBOM)

was installed by the Nederlandse Vereniging voor Medische Oncologie (Dutch Association of Medical Oncology) [11], [12]. Consisting of experts in the field of (clinical) oncology and health technology assessment, the cieBOM evaluates anti-cancer compounds and advises the ZIN based on additional oncology-focused criteria beyond the scope of the general scientific advice disclosed by the WAR-GC. These so-called PASKWIL-criteria describe the efficacy (often expressed in overall survival or progression-free survival), adverse events, quality of life, the treatment impact, the treatment costs, and the level of evidence of anti-cancer compounds (Table 1.0) [11].

To obtain a positive recommendation, several requirements need to be met (Table 1.0) [28], [29]. In terms of overall survival and progression-free survival, the PASKWIL-criteria demand a hazard ratio of at least 0.70, or an extension of at least three months as compared to the prevailing standard treatment. Moreover, the new anti-cancer compound needs to display at least a 5% reduction in lethal adverse events, and a 25% decrease in severe adverse events. All information necessary to grade these criteria stem from official peer-reviewed KEYNOTE-trials in the case of pembrolizumab [5].

PASKWIL-criterium		Requirement versus SoC if applicable
Efficacy	Overall survival	(1) Hazard ratio ≤ 0,70, or (2) ≥ 3 months
	Progression-free survival	
Adverse events	Amount of lethal adverse events	Reduction of 5%
	Amount of severe adverse events	Reduction of 25%
	Amount of chronic adverse events	
	Occurrence of adverse events issuing a dose reduction or treatment withdrawal	
Quality of life	Validated measuring instruments	
Treatment impact	Acceptable treatment burden	
Treatment costs	Monthly treatment costs as compared to the SoC	
Level of evidence	Phase of the clinical trial	

Table 1.0: Breakdown of the PASKWIL-criteria applied by the cieBOM and their clinical requirements of newly registered anti-cancer compounds. Derived and altered from [28]. Abbreviations: SoC, standard of care.

Results from the pharmaceutical dossier of 2016

All pharmaceutical, pharma-economical and scientific assessment of pembrolizumab was extracted from the KEYNOTE-010 clinical trial accompanying the indication of second-line treatment in locally advanced or metastasized NSCLC in which treatment with pembrolizumab was offset against treatment with docetaxel [17], [30].

Clinical benefit

In the KEYNOTE-010 study, the difference in median overall survival following treatment with the pembrolizumab versus docetaxel amounted to 1.9 months with a hazard ratio of 0.71. Based on this evidence, treatment with pembrolizumab would not meet the PASKWIL-criteria. However, in a subgroup analysis of the same paper, patients with a PD-L1-score of 50% or more treated with pembrolizumab demonstrated an improved median overall survival of 6.7 months with a hazard ratio of 0.54, which does satisfy the PASKWIL-criteria. Additionally, all conditions regarding the incidence of adverse events reached the prescribed differences compared to the standard of care. Taken together, even though the survival benefit of patients with a PD-L1 expression lower than 50% did not technically suffice, the reduction in the number of adverse effects was substantial enough to consider pembrolizumab conforming to the 'established medical science and medical practice' according to cieBOM and the ZIN [17], [31]. Subsequently, pembrolizumab was ascribed added clinical benefit for the indication of patients suffering from locally advanced or metastasized NSCLC harboring a PD-L1 expression of more than one percent.

Cost-effectiveness and budget impact

In view of a burden of disease associated with cancer ranging between 0.7 and 0.9 according to the ZIN, the established WTP-values for the Dutch population imply that treatment with pembrolizumab should not exceed €80,000/QALY in order to receive a positive reimbursement recommendation from the ZIN with respect to its cost-effectiveness [17], [21], [27]. Still, the cost-effectiveness analysis reported a health gain of 1.35 QALYs per patient for a total of approximately €90,000 for treatment with pembrolizumab, and 0.61 QALYs per patient for a total of approximately €70,000 after treatment with docetaxel [17]. Drivers of these cost inputs were identified to be the drug costs of pembrolizumab as well as the overall survival extrapolation estimates. In short, the ZIN published an ICER of approximately €113,000/QALY as compared to treatment with docetaxel, rendering treatment with pembrolizumab cost-ineffective against the given WTP-value.

Finally, the budget impact analysis reveals that annually about 1,200 to 2,300 patients suffering from locally advanced or metastasized NSCLC with PD-L1 expression would be eligible for treatment with pembrolizumab upon its inclusion in the basic care package [17]. Calculations from the ZIN estimate that these patients would incur a treatment cost of approximately €12 million to €22 million in additional costs compared to the current treatment with docetaxel. This suggests that for this indication only, treatment costs of pembrolizumab would make up about 1% of the annual inpatient drug expenditures of the Netherlands [20]. Following these findings in combination with the obtained ICER, the ZIN issued a negative recommendation regarding the consideration of its inclusion in the basic care package, going so far as to warn the VWS about the consequential strain on the healthcare budget and the subsequent health loss for the Dutch society as a whole.

In an effort to benefit its unfavorable cost-effectiveness and budget impact, the ZIN strongly advocated for several preconditions regarding the use of pembrolizumab in Dutch clinical practice [17]. First of all, they recommended VWS to negotiate a price reduction of pembrolizumab of about 30% with the manufacturer. As one of the cost drivers, a discount of this extent could cut costs of treatment with pembrolizumab sufficiently to become cost-effective at the existing WTP-value. In addition, it was proposed to centralize the treatment and research centers of pembrolizumab to ensure appropriate clinical use in the desirable patient population. The exact details of this preconditions were left to be developed and carried out by the respective professional groups.

In spite of the evidence of the pharmaceutical dossier and the negative recommendation by the ZIN, pembrolizumab left The Lock in 2017 to be included in the basic care package [20]. While the exact details that led to its reimbursement remain unknown, it has been reported that the VWS managed to secure a price discount of 17.5%, in addition to having agreed on another price reduction of pembrolizumab together with the manufacturer [32]. Nevertheless, the current price of the drug or the amount of discount that was provided by the manufacturer in total continues to be confidential information only accessible to these two parties. To this date, it is unknown whether the use of pembrolizumab in the current daily clinical practice is cost-effective.

Current evidence

In the meantime, the number of indications for which pembrolizumab became available have continued to grow, including the extension of treatment of pembrolizumab to the first line of cancer therapy (Table 0.1, Table S.1). As of today, an estimated 1,800 to 2,500 patients with a PD-L1 expression are eligible to receive treatment with pembrolizumab, yielding a total drug cost of €104 million to €140 million, or 4-6% of the annual Dutch inpatient drug expenditures in 2019 [17], [20]. Compared to the budget impact analysis of 2016, these new calculations propose an even bigger risk to the inpatient healthcare budget in the Netherlands.

Still, evidence relating to the financial ramifications of treatment with pembrolizumab has not changed since its only cost-effectiveness analysis and budget impact calculation in 2016. The increase of indications in recent years and the consecutive larger share of pembrolizumab in the oncology drug market could have laid the foundation of a bigger discount on its price, but this is unclear given the nontransparent aspect of the agreement established between the VWS and the manufacturer. Additionally, more evidence points out another course of events [17], [20]. At the time, it was evident that many new indications of pembrolizumab would follow the first NSCLC indication in light of the amount of ongoing or newly instituted KEYNOTE-trials, and the rise of anti-PD-1 compounds in research and in the media. Therefore, the general belief is that, instead of having to be at the negotiating table with the manufacturer for every new future indication of pembrolizumab, the VWS anticipated one single financial arrangement based on the available information of the KEYNOTE-010 study to be applied to the initial second-line NSCLC indication as well as all subsequent indications of pembrolizumab to follow.

Evidence gap

In practice, this implies that all new indications of pembrolizumab after the initial second-line NSCLC indication only needed to demonstrate added clinical value according to the PASKWIL-criteria to receive a positive recommendation of the cieBOM and to be granted inclusion in the basic care package. Since financial arrangements regarding the price of pembrolizumab for all new indications were already in place, the VWS did not have to request the ZIN to establish new cost-effectiveness studies or budget impacts. In essence, this has led to the establishment of the same open system which the VWS was trying to avoid: all new indications of pembrolizumab need only pass a clinical evaluation, whereafter they are immediately eligible for reimbursement. As a consequence, the financial aspect of each new indication of pembrolizumab has been completely neglected ever since its placement in The Lock back in 2016.

While the VWS's intention behind the single financial arrangement struck in 2017 was undoubtedly to accelerate the clinical availability of pembrolizumab to Dutch cancer patients, it should be recognized that the important role of the cost-effectiveness analysis during the weighing of reimbursement criteria of this expensive oncology drug has been foregone in the process. In doing so, no further evidence of whether the increased costs of each new indication of pembrolizumab weigh up against the additional clinical benefits in the Dutch population currently exists, possibly threatening misplacement of the national healthcare budget and crowding-out of other healthcare interventions that are cost-effective. As a result, the Dutch society as a collective could be subjected to a health loss. Driven by the clandestine nature of the current financial position of pembrolizumab, this absence of conclusive evidence places a question mark over its value for money and its financial sustainability as a whole.

Taken together, this study will focus on the lack of information surrounding the current stance of the general cost-effectivity landscape of pembrolizumab. By performing several cost-effectiveness analyses of a selection of indications that were introduced in Dutch clinical practice in the years following pembrolizumab's inclusion in the basic care package, this work aims to establish the financial and societal impact of overlooking cost-effectiveness as essential part of a complete pharmaceutical evaluation. Hopefully, the results of these analyses will be able to contribute to the critical assessment of the current and past state of affairs concerning the reimbursement decision and concomitant financial arrangement of pembrolizumab. In addition, they could set a precedent for a complete and integral approach to define cost-effectiveness for newly registered (agnostic) cancer therapies in the Netherlands.

Chapter 2: Cost-effectiveness of pembrolizumab as first-line treatment of NSCLC in the Netherlands

Principal indication

The main framework for the cost-effectiveness of all indications of pembrolizumab will be based on the cost-effectiveness model of the KEYNOTE-024 study [33], [34]. This study assessed the effectiveness of first-line monotherapy with pembrolizumab versus standard of care (SoC) consisting of platinum-based chemotherapy in patients suffering from metastasized NSCLC with a PD-L1 expression ≥ 50% without EGFR- or ALK-positive genomic mutations.

Model properties

Due to the limited follow-up in the KEYNOTE-024 trial, an economic model was used to project all costs and effects associated with the treatment of either pembrolizumab or SoC and simulate the natural course of disease. Given the use of parametric survival distributions to estimate transition probabilities, a partitioned survival model was most suitable. More specifically, a model with three mutually exclusive health states was developed: progression-free (PF), progressive disease (PD) and death. All patients were assumed to enter the model in the PF state. In subsequent cycles, patients could remain in the PF state or transition to the PD state or death state. Patients in the PD state could remain in the PD state or transition to the death state. Patients in the PD state could not return to the PF state, just as patients in the death state could not transition back to the PF or PD states. Each cycle lasted 21 days. All transitions occurred halfway through each cycle. A visual representation of the Markov model and all possible health state transitions can be found in Figure 2.1.

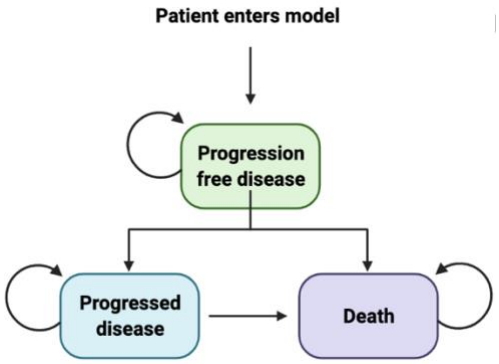

Figure 2.1: Visual breakdown of the Markov model used in all cost-effectiveness models of this study.

As requested by VWS, a lifetime horizon of 20 years was used to accommodate patients' lifetime and to encompass all possible differences in costs and effects between the intervention and the comparator [26]. This time horizon is consistent with survival data published by Integraal Kankercentrum Nederland, the official Dutch cancer registry [35]. After applying this time horizon to the model, more than 99% of patients had died. The primary outcomes of the model were quality-adjusted life years (QALYs), life years (LYs), total costs per treatment option and ICERs. The model was run in Microsoft® Excel 2020 (version 16.43) (Microsoft Corporation, Redmond, WA, USA).

Efficacy inputs

Clinical data parameters OS and PFS were estimated from Kaplan-Meier (KM) curves reported in the KEYNOTE-024 trial (Table 2.1) [33], [34]. In particular, OS data was obtained from the extended data described in their follow-up paper of 2019 [34]. Since patients in the SoC group were allowed to switch to pembrolizumab upon disease progression, OS data was adjusted to correct for the possibility of attributing the survival benefits from the second line pembrolizumab to the first line SoC. OS of patients in the SoC group was statistically adjusted using the simplified two-stage, rank-preserving structural failure time, and inverse probability of censoring weighting as described in [36]–[40]. To adhere to Dutch treatment guidelines as closely as possible, this OS data was used as the input in the Markov model (Table 2.1).

	Median adjusted OS (95% CI)	Hazard ratio (95% CI) and p-value	Median PFS (95% CI)	Hazard ratio (95% CI) and p-value
Pembrolizumab (months)	30.0 (± 18.3)	0.63 (0.47 to 0.86) p = 0.002	10.3 (6.7 to not reached)	0.50 (0.37 to 0.68) p < 0.001
Standard of Care (months)	14.2 (9.8 to 19.0)		6.0 (4.2 to 6.2)	

Table 2.1: Clinical effectiveness parameters as described in the KEYNOTE-024 trial [34]. Abbreviations: OS, overall survival; PFS, progression-free survival; CI, confidence interval.

To fit accurate parametric survival curves to this data, individual patient data was extracted from the KM-curves and the number of patients at risk in the KEYNOTE-024 trial using the Hoyle and Henley method [41]. Four different types of parametric survival curves were obtained to extrapolate trial data according to the time horizon: an exponential distribution, a Weibull distribution, a lognormal distribution, and a loglogistic distribution. Their visual fits and statistical properties can be found in Table 2.2, 2.3 and Figure 2.2. The highlighted numbers indicate the smallest Aikake Information Criterion (AIC) or Bayesian Information Criterion (BIC) value(s) of a given set of fitted parametric distributions, as they represent the parametric distributions which minimize the loss of information [42], [43]. Multiple AIC values are highlighted if the difference between the AIC values of a given set of fitted parametric distributions is smaller than two, indicating no virtual discrepancy between those values [42].

	OS pembrolizumab		OS Standard of Care		PFS pembrolizumab		PFS Standard of Care	
	AIC	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	*612.53*	*618.60*	605.11	611.14	651.26	657.33	774.61	780.64
Weibull	*612.74*	621.85	*575.48*	*584.53*	634.87	643.98	775.56	784.61
Lognormal	*611.80*	620.91	605.53	614.56	*621.15*	*630.26*	*761.69*	770.72
Loglogistic	*612.67*	*618.74*	593.92	599.94	626.76	632.83	*761.34*	*767.36*

Table 2.2: Aikake Information Criterion (AIC) and Bayesian Information Criterion (BIC) values of all four fitted parametric distributions of OS and PFS values of both pembrolizumab and SoC. Highlighted are the smallest AIC and BIC values of a given set of fitted parametric distributions for each treatment option.

	OS pembrolizumab		OS Standard of Care		PFS pembrolizumab		PFS Standard of Care	
	Intercept	**Scale**	**Intercept**	**Scale**	**Intercept**	**Scale**	**Intercept**	**Scale**
Exponential	3.5870	-	3.0180	-	2.7176	-	2.0136	-
Weibull	3.6743	0.1455	2.9224	-0.6004	2.6230	-0.5932	2.0915	-0.0764
Lognormal	3.7272	0.5218	2.6677	-0.0335	2.3762	-0.0067	1.5746	0.0477
Loglogistic	3.2447	-0.0425	2.7414	-0.7388	2.4598	-0.7496	1.5824	-0.4899

Table 2.3: Intercept and scale of all four fitted parametric distributions of OS and PFS values of both pembrolizumab and SoC.

Several criteria were taken into account when selecting a final parametric distribution for OS and PFS. Statistically, the lowest AIC and BIC value fits the given KM-curve best [42], [43]. Following this approach, the most suitable distribution for OS is a Weibull distribution. These findings are corroborated by the clinical plausibility of the curves. Given a crude death rate of approximately 8.5% in the Netherlands, an OS rate of about 10% after 20 years for the lognormal and the loglogistic distributions as seen in the OS graph of pembrolizumab seems unlikely (yellow and blue curve in Supplemental Figure S.1A) [44]. Strictly speaking, this evidence would leave the Weibull distribution as the superior option for OS as compared to the exponential distribution. However, the choice between the exponential or Weibull distribution can also be regarded as a strategic one. When comparing the two curves, the exponential distribution seems to take a more cautious path estimating survival for patients receiving pembrolizumab (orange and grey curves in Supplemental Figure S.1A). In addition, recent OS data in Dutch patients find that the real-world OS of first-line pembrolizumab patients is significantly shorter compared to the reported OS data in the KEYNOTE-024 clinical trial [45]. Therefore, it can be argued that the exponential distribution would be most suitable for this conservative base case scenario, whereas the course of the Weibull distribution might prove an excellent option to explore a more generous means of estimating survival following or after pembrolizumab treatment. This decision is in line with cost-effectiveness analyses of the KEYNOTE-024 trial in several other countries [46]–[48].

For PFS, a lognormal distribution or a loglogistic distribution would be most appropriate given their AIC and BIC values (Table 2.2). Clinically, data confirm that real-world PFS time for first-line pembrolizumab are comparable to the one reached in the KEYNOTE-024 trial [45]. In that light, a lognormal distribution was chosen as an estimator for PFS.

Clinical parameters

Patient characteristics were extracted from the KEYNOTE-024 trial [33], [34]. This phase III RCT recruited the following trial population: patients aged ≥ 18 years, diagnosed with metastatic NSCLC (stage IV) with an PD-L1 TPS ≥ 50% without EGFR- or ALK- positive mutations, which were naïve to any chemotherapy regimen for metastatic NSCLC disease. As the number of Dutch patients included in the KEYNOTE-024 study was insufficient to extrapolate to the Dutch population as a collective, the baseline disease characteristics of the intention-to-treat (ITT) population were considered as model inputs (Table 2.4). Nevertheless, similar baseline disease characteristics of Dutch metastatic NSCLC patients have been reported in various studies [49], [50].

Characteristic	Pembrolizumab Group (n = 154)	Standard of Care Group (n = 151)
Median Age (years)	64.5	66.0
Female sex (%)	40.3	37.1
ECOG performance status score (%)		
0	35.1	35.1
1	64.3	64.9
Histology (%)		
Squamous	18.8	17.9
Non-squamous	81.2	82.1

Table 2.4: Baseline characteristics of patients in the intention-to-treat population as published in the KEYNOTE-024 trial [33].

Treatment decisions were based the KEYNOTE-024 trial and were validated by official Dutch guidelines according to the Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (NVALT) to match the Dutch clinical practice [33], [51], [52]. Patients either received pembrolizumab at a dose of 2 mg/kg every 3 weeks until disease progression or a combination of five platinum-based chemotherapy regimens for 4-6 cycles. Patients with squamous NSCLC were eligible to receive gemcitabine (1250 mg/m^2) + cisplatin (75 mg/m^2) or gemcitabine + carboplatin (AUC 5-6). Patients with non-squamous NSCLC were eligible to receive pemetrexed (500 mg/m^2) + carboplatin, pemetrexed + cisplatin or paclitaxel (200 mg/m^2) + carboplatin. Upon disease progression, patients in the pembrolizumab group received the same regimen of platinum-based chemotherapy as first-line patient in the SoC arm, whereas patients in the SoC arm only received supportive pemetrexed therapy [53]. Observing data from the KEYNOTE-024 trial, the median PFS of the pembrolizumab arm amounted to 10.3 months, and was used to define time to disease progression in both stable and progressed disease states [34].

Cost inputs and resource use

All costs are expressed in 2021 Euro and discounted at 4% annually [26]. Costs made in previous years were indexed according to official inflation percentages as published by the CBS (Supplemental Table S.3) [54]. All standard deviations were assumed to be 20% of their main cost input parameter unless otherwise specified.

For direct medical costs of both SoC and pembrolizumab in the Netherlands, a one-off cost component describing the entirety of medical costs linked to stage IV NSCLC was used [55]. Based on real-world study data obtained from Dutch NSCLC patients between 2009-2011, all costs surrounding chemotherapy, concomitant medication, pathology, radiotherapy, surgery, targeted therapy, medical imaging services and procedures, laboratory testing, medical consultations, day-care, in-patient hospital days and intensive care unit days made over a timespan of 12.6 moths were included [55]. This cost component implicates cost for stable disease as well as progressed disease, and was converted to three-weekly cycle cost per patient [55]. For SoC, this totals €28,502, which was indexed to €32,708.38. Its standard deviation was €4,755 and was indexed to €5,465.75 (Table 2.5). For pembrolizumab, the same cost input was used after subtracting costs related to chemotherapy, concomitant medication, radiotherapy, surgery and targeted therapy, and totaled €16,752 or €19,224.29 after indexation. Its standard deviation was €1,991 and was indexed to €2,284.84 (Table 2.5). To achieve a final cost estimate for the pembrolizumab arm, its unit price (€1,430.28) and a one-off anti-PD-L1-test costs (€120.15) were added (see Table 2.5). Total acquisition costs per cycle for pembrolizumab (€4,290.84) were based on a dose of 2 mg/kg a patient and an average weight of 71 kg as estimated by the ZIN [17].

Similarly, a single end-of-life cost of €1243 or €1,357.71 after indexation per patient was considered for all patients as described by ZIN in literature in 2015 [17].

Type of cost	Unit Price	SD	Frequency	Source	Index year
Standard of Care					
Medical costs	€ 32,708.38	€ 5,456.75	One-off per patient	Derived from Table 3 in [55]	2012
Pembrolizumab					
Medical costs	€ 19,224.29	€ 2,284.84	One-off per patient	Derived from Table 3 in [55]	2012
Unit price per vial (50 mg)	€ 1,430.28	€ 286.06	Used to calculate total drug acquisition	Derived from [56]	NA
Total drug acquisition	€ 4,290.84	-	Per patient per cycle	Calculated based on [56] and [17]	NA
Anti-PD-L1 test	€ 120.15	€ 24.03	One-off per patient	Derived from Table 10 in [17]	2014
Both treatment arms					
Adverse events	€ 2,415.66	€ 4,905.91	One-off per patient	Derived from Table 4 in [55]	2012

End-of-life cost	€ 1,357.71	€ 271.54	One-off per patient	Derived from Table 10 in [17]	2012

Table 2.5: All cost inputs of the base case scenario of the KEYNOTE-024 trial. Abbreviations: SD, standard deviation; PD-L1, programmed cell death-ligand 1.

As requested by the VWS, this cost-effectiveness analysis adopted a societal perspective. This dictates that all relevant costs, both within and outside the healthcare sector will be taken into account as they apply in the Netherlands [26]. However, only direct medical costs were included in this current analysis. This choice will be further reflected upon in Chapter 4.

Adverse events

A single cost component for grade III or higher adverse events in stage IV NSCLC according to real-world data of 2015 was applied to the model, regardless of adverse event incidence reported in the KEYNOTE-024 trial [55]. The total one-off adverse event costs per patient for SoC were €2,105 or €2,415.66 after indexation (see Table S.3 for index rates). For pembrolizumab, no adverse events of grade III or higher with an incidence of 10% or more were observed during the KEYNOTE-024 trial [34]. Nevertheless, to adhere to real-world clinical plausibility and to uphold a conservative base-case scenario, the same adverse event costs of SoC were incorporated in the model for treatment with pembrolizumab as well.

Utility inputs

Utility values for each treatment arm and each disease state were taken from published utility values by the ZIN (Table 2.6) [17]. Based on calculations using EQ-5D data from the KEYNOTE-010 trial, they used Dutch index values to calculate and extrapolate representative utilities for the Dutch population [17], [30]. As no official standard deviation of these utilities were disclosed, 20% of their base case value was assumed to be their standard deviation input values. No utility decrement was assumed for adverse events. Effects were discounted at an annual rate of 1.5% [26].

Disease state	Pembrolizumab (SD)	Standard of Care (SD)	Source
Stable disease	0.797 (0.1594)	0.765 (0.1530)	Derived from page 27 and Table 6 in [17], [30]
Progressed disease	0.706 (0.1412)	0.708 (0.1416)	

Table 2.6: Utility inputs of the KEYNOTE-024 trial, based on disease state and treatment arm.

Sensitivity Analyses

In order to address uncertainty surrounding the surrounding the input parameters, two sensitivity analyses were performed. First, a probabilistic sensitivity analysis (PSA) was conducted to test the robustness and validity of the deterministic inputs and the base case outcomes. Gamma distributions were used for cost inputs that ranged from zero to positive infinity. Alternatively, beta distributions were applied to utility input parameters ranging from zero to one. If not provided by the original source, standard errors for gamma distributions were estimated as 20% of the input parameter, and were calculated for beta distributions using the following equation:

$SE = \sqrt{input\ parameter \cdot \frac{(1-input\ parameter)}{n}}$. All base case input values as well as their distributions and standard deviations can be found in Table 2.7 and 2.8.

Input	Value	Frequency	Distribution
Stable Disease			
Pembrolizumab cycle cost	€ 5,343.07	Per patient per cycle	Gamma
SoC cycle cost	€ 1,790.28	Per patient per cycle	Gamma
Adverse events	€ 2,415.66	One-off per patient	Gamma
Anti-PD-L1 test (pembrolizumab only)	€ 120.15	One-off per patient	Gamma
Progressive disease			
Pembrolizumab and SoC cycle cost	€ 1,790.28	Per patient per cycle	Gamma
End-of-life cost	€ 1,357.71	One-off per patient	Gamma

Table 2.7: All cost inputs of the base case scenario and PSA screening of the KEYNOTE-024 trial, and their distribution. Abbreviations: SoC, standard of care; PD-L1, programmed cell death-ligand 1.

Utility Inputs	Value	Standard Deviation	Rationale	Distribution
SD pembrolizumab	0.797	0.1594	20% of base case input	Beta
PD pembrolizumab	0.706	0.1412	20% of base case input	Beta
SD SoC	0.765	0.1530	20% of base case input	Beta
PD SoC	0.708	0.1416	20% of base case input	Beta

Table 2.8: All utility inputs of the base case and PSA screening of the KEYNOTE-024 trial, and their distribution. Abbreviations: SoC, standard of care; SD, stable disease; PD, progressed disease.

Using a 1 000x iteration Monte Carlo simulation which exploited the uncertainty surrounding all cost and utility input parameters, a cost-effectiveness plane as well as a cost-effectiveness acceptability curve were obtained to assess cost-effectiveness and possibly affect decision making in terms of reimbursement at various WTP-thresholds (Figure S1 and 2.3).

Additionally, to uncover the possible impact of parameter changes on the ICER, a one-way sensitivity analysis was performed in which the ranges of input parameters with regard to acquisition costs, hospital and healthcare costs, and adverse event costs were varied by -20% and +20%. These results are published using a Tornado diagram (Figure 2.4).

Scenario analyses

Finally, several distinct scenario changes were applied to the model so as to correspond more completely to real-world clinical practice as it transpires in the Netherlands. First of all, the exponential distribution of the OS curve of the base case scenario was exchanged for the curve belonging to the Weibull distribution. This progressive OS curve attributes more optimistic survival benefits to patients in the pembrolizumab treatment arm while doing the opposite for patients receiving standard of care (Figure 2.2A-B). In a second scenario,, a previously reported price reduction of 50% was applied to the list price of pembrolizumab in order to take into consideration the undisclosed discounts often offered to the Dutch government by the drug manufacturer [57].

Alternatively, in an attempt to preserve the continuity of the conservative base case approach when extrapolating model inputs of this principal indication to the other indications of pembrolizumab, SD and PD utility values of both treatments were equalized to the SoC utility values to examine a possible effect of canceling out utilities. The outcome of this scenario will determine whether the utilities as described in this principal model will be used during extrapolation, or whether all utilities will be assumed to be equal among the pembrolizumab and standard of care treatment arms in all future investigated indications.

Results

Base case scenario

Over a lifetime horizon, treatment with pembrolizumab produced a total of 2.16 QALY's for €174,039, whereas treatment with SoC produced 1.22 QALYs for € 54,150. Taken together, these numbers yield an ICER of €126,474 (Table 2.9). This implies that treatment with pembrolizumab is often more expensive compared to SoC, but does offer more QALYs in return, which is reflected in Figure S1. Using a WTP-threshold of €80,000, the cost-effectiveness acceptability curve illustrates that the probability of treatment with pembrolizumab being more cost-effective than treatment with SoC is approximately 3% (Figure 2.3).

	Pembrolizumab	Standard of Care	Increment
Life years	2.88	1.66	1.22
Quality-adjusted life years	2.16	1.22	0.95
Costs	€ 174,039	€ 54,150	€ 119,889
ICER – LY	**€ 98,332 / LY**		
ICER - QALY	**€ 126,474 / QALY**		

Table 2.9: Results of the base case scenario of the KEYNOTE-024 trial. Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

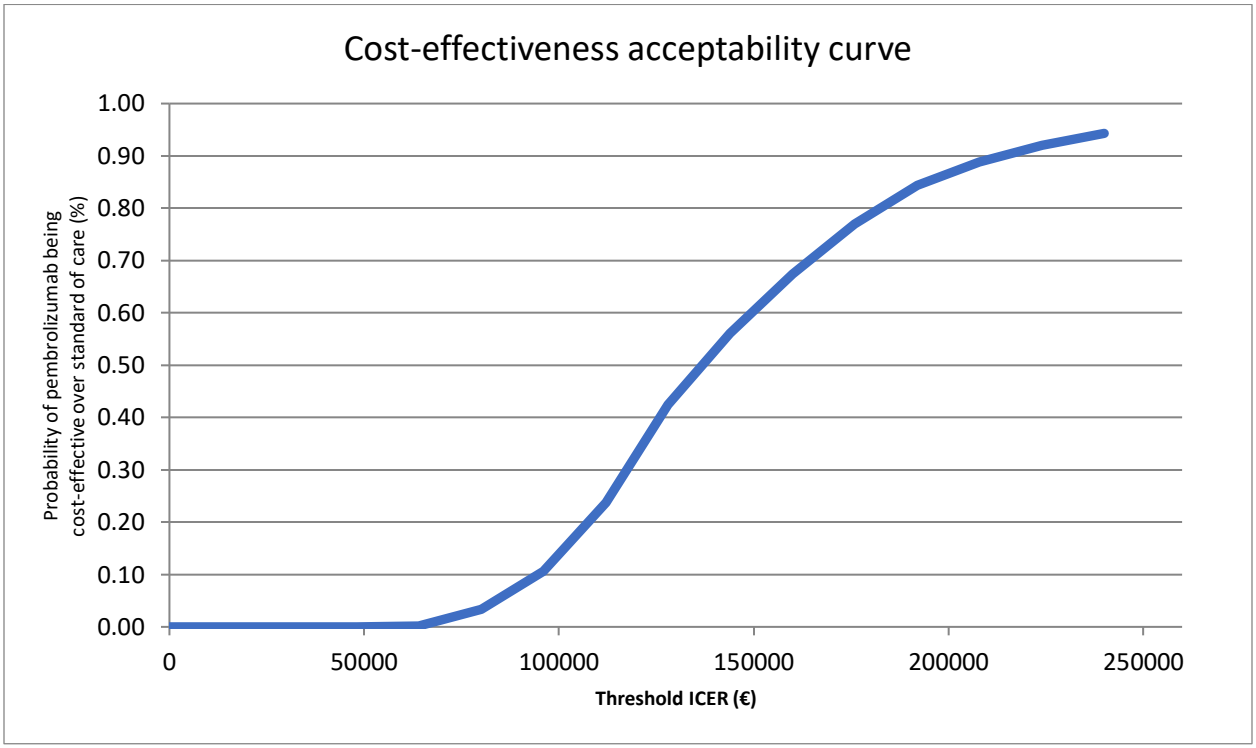

Figure 2.2: The cost-effectiveness curve acceptability curve (CEAC) of pembrolizumab versus standard of care of the KEYNOTE-024 trial. Abbreviations: ICER, incremental cost-effectiveness ratio.

Sensitivity analyses

Having changed all cost input parameters with +20% and -20%, the acquisition costs of pembrolizumab were identified as the main drivers of the ICER, altering the ICER with about 20% (Figure 2.4). In addition, healthcare costs of pembrolizumab and SoC altered the ICER with approximately 5% and 2%, respectively. Finally, adding 20% to the body weight of patients receiving treatment leads to the use of an extra vial of pembrolizumab, increasing the ICER with 28%. On the other hand, lowering the body weight with 20% was not enough to spare a vial of pembrolizumab, leading to no change in the ICER.

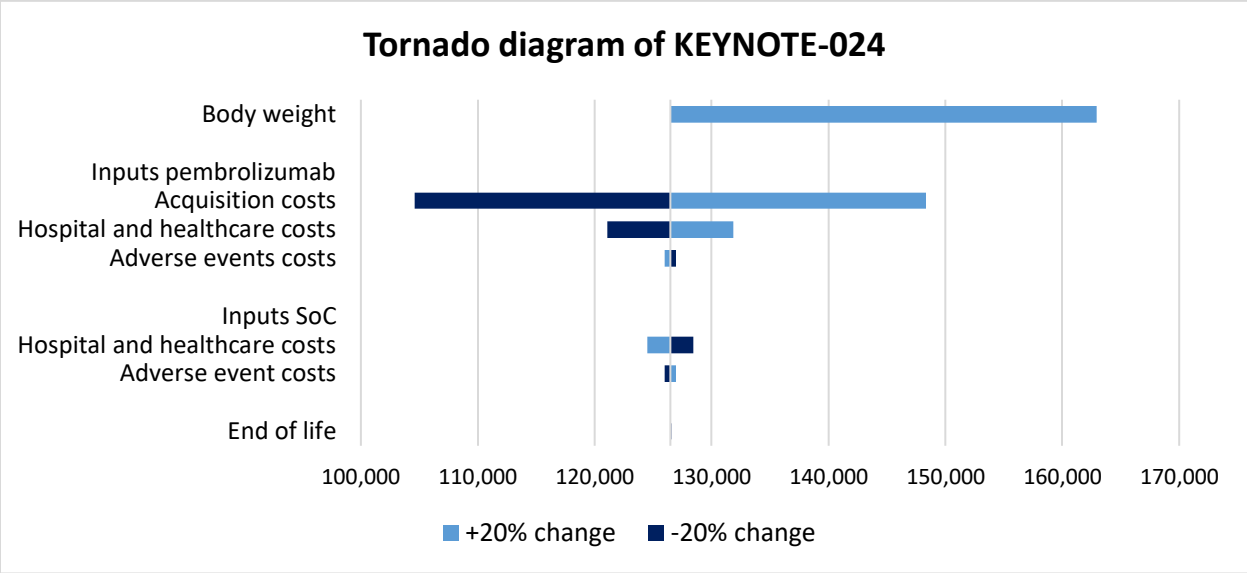

Figure 2.3: Tornado diagram of the KEYNOTE-024 trial depicting the absolute changes of the incremental cost-effectiveness ratio when changing cost input parameters with +20% and -20%. Abbreviations: SoC, standard of care.

Scenario analyses

Under a Weibull distribution for OS, patients receiving pembrolizumab gain more QALYs as compared to the base case scenario (2.16 versus 2.48), whereas patients receiving SoC lose QALYs (1.22 versus 1) (see Table 2.9 and 2.10). As the costs of both treatments increase with a similar absolute amount, the first scenario analysis resulted in a final ICER of €93,824 per QALY. The second scenario, including a price reduction of 50% for pembrolizumab, total costs associated with treatment with pembrolizumab decreased to €122,212, yielding an ICER of €71,787 per QALY.

	Pembrolizumab	Standard of Care	Increment
Life years	3.33	1.36	1.97
Quality-adjusted life years	2.48	1.00	1.48
Costs	€ 184,823	€ 45,830	€ 138,993
ICER	**€ 93,824 / QALY**		

Table 2.10: Results of the scenario analysis of the KEYNOTE-024 trial after adopting a Weibull distribution as input parameter for the OS curves of both treatment arms. Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years.

After equalizing both utility inputs to the initial utility inputs of the SoC of NSCLC, the QALYs obtained after treatment with pembrolizumab decreased minimally compared to the base case scenario (2.16 vs. 2.12) (Table 2.6, 2.11). For that reason, utilities will be extrapolated to the other models as they are described in Table 2.6.

	Pembrolizumab	Standard of Care	Increment
Life years	2.88	1.66	1.22
Quality-adjusted life years	2.12	1.22	0.91
Costs	€ 174,039	€ 54,150	€ 119,889
ICER		**€ 132,433 / QALY**	

Table 2.11: Results of the scenario analysis of the KEYNOTE-024 after adopting the same utility inputs for both treatment arms.

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years.

Chapter 3: Cost-effectiveness of multiple indications of pembrolizumab in The Netherlands

General approach

To assess the cost-effectiveness of pembrolizumab in the Dutch clinical setting as a whole, the cost-effectiveness of pembrolizumab in several other currently approved indications in The Netherlands will be roughly investigated. At the time of this writing, as many as 13 indications of pembrolizumab were approved according to the Farmacotherapeutisch Kompas, all of which were evaluated by KEYNOTE-trials (Table 0.1).

Nevertheless, not every indication lent itself to deeper examination, predominantly as a result of the absence or inaccessibility of suitable data corresponding to clinical practice in the Netherlands. For instance, the OS and PFS curves of the SoC of two KEYNOTE-studies of urothelial carcinoma did not match Dutch treatment guidelines, and required KM-curves of the OS and PFS of palliative care only in order to apply to the Dutch patient population [58], [59]. However, these curves have not yet been described in literature for urothelial carcinoma, or any other type of cancer histology for that matter. Since the available curves in the original KEYNOTE-trials would consequently not paint an accurate picture of the OS and PFS of SoC as expected in the Netherlands, these indications were not taken into account. In addition, the KEYNOTE-studies of first-line treatment of colorectal cancer and adjuvant therapy in melanoma were too premature and did not include an OS survival estimate at all and were therefore not included in this study [60], [61]. Finally, for practical reasons, it was decided to exclude Hodgkin lymphoma given its hematological character in the list of otherwise solid cancer histologies. In addition, hematological cancers fall outside the clinical scope of the cieBOM [12]. Ultimately, a total of 7 indications in 4 different cancer histologies were reviewed (Table 3.1).

Cancer	Full Indication	KEYNOTE-trial
Head & Neck Squamous Cell Carcinoma (HNSCC)	Monotherapy of recurrent or metastasized HNSCC with PD-L1 expression (TPS ≥ 50%) with disease progression on or after platinum-containing chemotherapy	KEYNOTE-040
	Monotherapy as first line treatment of metastasized or unresectable recurrent HNSCC with PD-L1 expression (CPS ≥ 1), combined with 5-fluoro-uracil and platinum-containing chemotherapy	KEYNOTE-048
Melanoma	Monotherapy of unresectable or advanced melanoma	KEYNOTE-006
Non-Small Cell Lung Cancer (NSCLC)	Monotherapy of locally advanced or metastasized NSCLC with PD-L1 expression (TPS ≥ 1%) and disease progression on or after previous chemotherapy. Patients with EGFR- or ALK-positive	KEYNOTE-010

	genomic mutations should have disease progression after receiving approved therapy for these mutations prior to pembrolizumab	
	Combination therapy as first line treatment of metastasized NSCLC with no EGFR- or ALK- positive genomic mutations, with Pemetrexed and platinum-containing chemotherapy	KEYNOTE-189
	Combination therapy as first line treatment of metastasized NSCLC, with carboplatin and either paclitaxel or (nab-)paclitaxel	KEYNOTE-407
Renal Cell Carcinoma (RCC)	Combination therapy as first line treatment of advanced RCC with axitinib	KEYNOTE-426

Table 3.1: All indications of pembrolizumab which will be considered in Chapter 3 and are currently approved in The Netherlands. Abbreviations: PD-L1, programmed death-ligand 1; TPS, tumor proportion score; CPS, combined positive score; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

Model properties

Like the principal indication, all cost-effectiveness models use the same Markov model with the same properties (Figure 2.1). As mentioned in Chapter 2, the principal indication and its key input parameters will be extrapolated to these indications to obtain a general notion of their cost-effectiveness should an extensive cost-effectiveness analysis have been performed. All unchanged parameters can be found in table A.1. An extensive overview the rationale behind changing the parameters can be found throughout this chapter, and in Tables 3.2 through 3.5.

Pembrolizumab regimens

In all the trials of Table 3.1, pembrolizumab of 200 mg per 3 weeks was compared to the SoC of each respective indication. In order to estimate the real-world treatment costs of pembrolizumab as accurately as possible, the treatment duration of each indication followed the reported OS and PFS of its KEYNOTE-trial (Table A.2).

Comparator regimens

Unlike the KEYNOTE-024 trial, not every SoC arm evaluated in the KEYNOTE-trials mentioned in Table 3.1 perfectly corresponded to the Dutch guidelines. More specifically, the SoC of KEYNOTE-040 and KEYNOTE-189 did not match clinical practice in the Netherlands (Table 3.3). For KEYNOTE-040, its own SoC KM curve was used to fit the parametric distributions regardless of its mismatch, which will be discussed thoroughly in Chapter 4. For KEYNOTE-189, the final choice of KM-curve for SoC deviated from the one obtained in the KEYNOTE-trial to adhere to Dutch clinical practice as accurately as possible (Table 3.3). Consulted sources for the Dutch SoC were recommendations made by the cieBOM and current online guidelines on www.richtlijnendatabase.nl [31], [62]–[68].

KEYNOTE-trial	Line of treatment	SoC in KEYNOTE-trial	SoC in Dutch guidelines	Match?	Rationale of SoC KM
KEYNOTE-040	Second	Investigator's choice of MTX, docetaxel or cetuximab	MTX monotherapy	No	SoC KM of KEYNOTE-trial was used regardless
KEYNOTE-048	First	Cetuximab with carboplatin or cisplatin and 5-fluorouracil	Cisplatin, carboplatin, 5-fluouracil and cetuximab	Yes	SoC KM of own KEYNOTE-trial could be used
KEYNOTE-006	First	Ipilimumab	Ipilimumab	Yes	SoC KM of own KEYNOTE-trial could be used
KEYNOTE-010	Second	Docetaxel	Docetaxel	Yes	SoC KM of own KEYNOTE-trial could be used
KEYNOTE-189	First	Placebo	Platinum-based chemotherapy	No	SoC KM of KEYNOTE-407 was used
KEYNOTE-407	First	Platinum-based chemotherapy with paclitaxel and placebo	Platinum-based chemotherapy with paclitaxel	Yes	SoC KM of own KEYNOTE-trial could be used
KEYNOTE-426	First	Sunitinib	Sunitinib	Yes	SoC KM of own KEYNOTE-trial could be used

Table 3.2: All indications of pembrolizumab with their respective SoC as investigated in the KEYNOTE-trials and their equivalent according to Dutch clinical standard. Abbreviations: SoC, standard of care; MTX, methotrexate; KM, Kaplan Meier curve.

Efficacy Inputs

Similar to the model of the principal indication in Chapter 2, decisions with regard to the efficacy input of the Markov trace of the other indications were made based on their clinical and statistical plausibility while pursuing a conservative base case approach for pembrolizumab (Table 3.3). Importantly, obtained parametric distributions were validated against the reported OS and PFS data of each KEYNOTE-trial, and enabled individually calculating the treatment duration and costs of each indication in particular (Table A.2). All choices of efficacy estimator that were not congruent both clinically, statistically and for the two treatment arms are reviewed individually in this section. In addition, Table 3.3 displays whether or not trials allowed crossing over of patients in the second-line treatment of their study. This phenomenon is discussed in more detail in Chapter 4. Statistical details, original KM curves and all fitted OS and PFS parametric distributions per indication can be found in Supplemental Tables S.4-S.17 and Figures

S.3-S.9. A detailed account of the rationale behind the choice of efficacy curves per indication can be found in the Appendix.

KEYNOTE-trial	Best clinical fit* (pembro/SoC)	Best statistical fit (pembro/SoC)	Final choice	Crossing over allowed?
KEYNOTE-040	OS: Weibull PFS: Loglogistic	OS: Exponential PFS: Loglogistic	OS: Weibull PFS: Loglogistic	No
KEYNOTE-048	OS: Weibull PFS: Weibull	OS: Lognormal/Weibull PFS: Weibull	OS: Weibull PFS: Weibull	No
KEYNOTE-006	OS: Weibull PFS: Weibull	OS: Loglogistic/Weibull PFS: Weibull	OS: Weibull PFS: Weibull	Yes, after 12 months
KEYNOTE-010	OS: Weibull PFS: Loglogistic/Weibull	OS: Weibull PFS: Loglogistic/Weibull	OS: Weibull PFS: Loglogistic	No
KEYNOTE-189	OS: Weibull PFS: Weibull	OS: Weibull PFS: Weibull	OS: Weibull PFS: Weibull	Yes
KEYNOTE-407	OS: Weibull PFS: Exponential	OS: Weibull PFS: Weibull	OS: Weibull PFS: Weibull	Yes, after 24 months
KEYNOTE-426	OS: Weibull PFS: Weibull	OS: Weibull PFS: Weibull	OS: Weibull PFS: Weibull	No

Table 3.3: Efficacy inputs for the OS and PFS curves of all investigated KEYNOTE-trials subdivided into best clinical fit, best statistical fit and final choice, along with their crossing-over status. Abbreviations: SoC, standard of care; OS, overall survival; PFS, progression-free survival. *Based on two indicators: clinical plausibility given a crude death rate of 8.5% in the Netherlands [44], and pursuing clinical conservatism with regard to the pembrolizumab treatment arm.

Medical Cost Inputs

As for all the healthcare cost inputs, amounts are displayed in 2021 Euro and discounted at 4% annually (Table 3.4) [26]. Costs made in previous years were indexed according to official inflation percentages as published by the CBS (Table S.3) [54]. The exact cost calculation of the SoC and pembrolizumab treatment arm each indication can be found in the Appendix.

KEYNOTE-trial	SoC Cost Input Parameter	SoC Cost Input Standard Deviation	P Cost Input Parameter	P Cost Input Standard Deviation	Source
KEYNOTE-040	€ 39,750.93	€ 7,950.19	€ 27,613.72	€ 5,522.74	Derived from Table 1 in [69], indexed from 2001
KEYNOTE-048	€ 31,447.96	€ 6,289.59	€ 22,237.15	€ 4,447.43	
KEYNOTE-006	€ 87,596.95	€ 29,133.05	€ 7,158.25	€ 7,688.17	Derived from Table 4 in [70], indexed from 2016
KEYNOTE-010	€ 32,708.38	€ 5,456.75	€ 19,224.29	€ 2,284.84	Derived from Table 3 in [55], indexed from 2012
KEYNOTE-189	€ 32,708.38	€ 5,456.75	€ 22,265.39	€ 2,893.05	
KEYNOTE-407	€ 32,708.38	€ 5,456.75	€ 22,607.21	€ 2,961.42	Derived from Table 3 in [55] and Table 1 and 3 in [49]. Indexed from 2012 [55] and 2005 [49].
KEYNOTE-426	€ 237,697.56	€ 47,539.51	€ 305,971.73	€ 61,194.35	Derived from Table 4 in [71] and [72]. Indexed from 2018.

Table 3.4: All cost inputs of the base case scenarios of all investigated KEYNOTE-trials. Abbreviations: SoC, standard of care; P, pembrolizumab.

Sensitivity analyses

Similar to the principal indication, a PSA was performed for every indication mentioned in this chapter, yielding a cycle cost for each base case scenario (Table 3.5). Costs associated with adverse events, end of life and the anti-PD-L1 test applicable to KEYNOTE-040, -048 and -010 were identical to the costs described in Table 2.5. All utilities were identical to the utilities described in Table 2.6.

KEYNOTE-trial	Input	Value	Frequency	Distribution
KEYNOTE-040	Stable Disease			
	Pembrolizumab cycle cost	€ 5,087.39	Per patient per cycle	Gamma
	SoC cycle cost	€ 1,146.66	Per patient per cycle	Gamma
	Progressive disease			
	Pembrolizumab and SoC cycle cost	€ 1,146.66	Per patient per cycle	Gamma
KEYNOTE-048	Stable Disease			
	Pembrolizumab cycle cost	€ 4,932.30	Per patient per cycle	Gamma
	SoC cycle cost	€ 907.15	Per patient per cycle	Gamma
	Progressive disease			
	Pembrolizumab and SoC cycle cost	€ 907.15	Per patient per cycle	Gamma

KEYNOTE-006	Stable Disease			
	Pembrolizumab cycle cost	€ 5,078.20	Per patient per cycle	Gamma
	SoC cycle cost	€ 9,635.04	Per patient per cycle	Gamma
	Progressive disease			
	Pembrolizumab and SoC cycle cost	€ 9,635.04	Per patient per cycle	Gamma
KEYNOTE-010	Stable Disease			
	Pembrolizumab cycle cost	€ 5,343.07	Per patient per cycle	Gamma
	SoC cycle cost	€ 1,790.28	Per patient per cycle	Gamma
	Progressive disease			
	Pembrolizumab and SoC cycle cost	€ 1,790.28	Per patient per cycle	Gamma
KEYNOTE-189	Stable Disease			
	Pembrolizumab cycle cost	€ 5,509.53	Per patient per cycle	Gamma
	SoC cycle cost	€ 1,790.28	Per patient per cycle	Gamma
	Progressive disease			
	Pembrolizumab and SoC cycle cost	€ 1,790.28	Per patient per cycle	Gamma
KEYNOTE-407	Stable Disease			
	Pembrolizumab cycle cost	€ 5,343.07	Per patient per cycle	Gamma
	Carboplatin-Paclitaxel cycle cost	€ 3,382.92	Per patient per cycle	Gamma
	SoC cycle cost	€ 1,790.28	One-off per patient	Gamma
	Progressive disease			
	Pembrolizumab and SoC cycle cost	€ 1,790.28	Per patient per cycle	Gamma
KEYNOTE-426	Stable Disease			
	Pembrolizumab cycle cost	€ 13,116.95	Per patient per cycle	Gamma
	SoC cycle cost	€ 6,856,66	Per patient per cycle	Gamma
	Progressive disease			
	Pembrolizumab and SoC cycle cost	€ 6,856,66	Per patient per cycle	Gamma

Table 3.5: All cost inputs of the base case scenarios and PSA screening of all investigated KEYNOTE-trials, and their distribution. Abbreviations: SoC, standard of care.

Results

For each KEYNOTE-trial, the amount of incurred life years, quality-adjusted life years and costs were calculated, producing an ICER associated with both life years and quality-adjusted life years (Table 3.6). The percentage of chance that reimbursing pembrolizumab over SoC would be cost-effective given a WTP of €80,000 in the Netherlands is also displayed in Table 3.6 [21]. In addition, each KEYNOTE-trial's PSA screening yielded a cost-effectiveness plane (Figure 3.1, Figure 3.2). All individual cost-effectiveness planes and – curves can be found in the Supplement (Figure S.10-S.23).

		Pembrolizumab	Standard of Care	Increment
KEYNOTE-040	Life years	1.25	0.74	0.51
	Quality-adjusted life years	0.94	0.54	0.40
	Costs	€ 72,826	€ 18,720	€ 54,105
	ICER – LY	**€ 105,852 / LY**		
	ICER - QALY	**€ 136,723 / QALY**		
	% chance of reimbursement given a WTP of € 80,000	**± 9%**		
KEYNOTE-048		**Pembrolizumab**	**Standard of Care**	**Increment**
	Life years	1.36	1.17	0.19
	Quality-adjusted life years	1.04	0.89	0.14
	Costs	€ 83,733	€ 22,178	€ 61,555
	ICER – LY	**€ 317,357 / LY**		
	ICER - QALY	**€ 426,508 / QALY**		
	% chance of reimbursement given a WTP of € 80,000	**± 3%**		
KEYNOTE-006		**Pembrolizumab**	**Standard of Care**	**Increment**
	Life years	1.25	1.11	0.14
	Quality-adjusted life years	0.97	0.83	0.13
	Costs	€ 136,843	€ 190,612	- € 53,769
	ICER – LY	**- € 396,792 / LY**		
	ICER - QALY	**- € 400,542 / QALY**		
	% chance of reimbursement given a WTP of € 80,000	**> 30%**		
KEYNOTE-010		**Pembrolizumab**	**Standard of Care**	**Increment**
	Life years	1.08	0.94	0.13
	Quality-adjusted life years	0.80	0.71	0.09
	Costs	€ 63,862	€ 33,430	€ 30,432
	ICER – LY	**€ 229,341 / LY**		
	ICER - QALY	**€ 337,885 / QALY**		
	% chance of reimbursement given a WTP of € 80,000	**± 1%**		
KEYNOTE-189		**Pembrolizumab**	**Standard of Care**	**Increment**
	Life years	1.24	1.25	- 0.01
	Quality-adjusted life years	0.97	0.94	0.03
	Costs	€ 113,221	€ 42,684	€ 70,537
	ICER – LY	**- € 4,183,701 / LY**		
	ICER - QALY	**€ 2,600,719 / QALY**		
	% chance of reimbursement given a WTP of € 80,000	**± 0%**		
KEYNOTE-407		**Pembrolizumab**	**Standard of Care**	**Increment**
	Life years	1.15	1.25	-0.10
	Quality-adjusted life years	0.91	0.94	-0.03

	Costs	€ 177,003	€ 39,634	€ 137,369
	ICER – LY	**- € 1,282,553 / LY**		
	ICER - QALY	**- € 4,322,049 / QALY**		
	% chance of reimbursement given a WTP of € 80,000	**± 0%**		
KEYNOTE-426		**Pembrolizumab**	**Standard of Care**	**Increment**
	Life years	2.11	1.78	0.33
	Quality-adjusted life years	1.61	1.33	0.28
	Costs	€ 397,555	€ 212,598	€ 184,956
	ICER – LY	**€ 566,723 / LY**		
	ICER - QALY	**€ 662,678 / QALY**		
	% chance of reimbursement given a WTP of € 80,000	**± 0%**		

Table 3.6: Results of all investigated KEYNOTE-trials. Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; WTP, willingness to pay.

Overall, the obtained ICERs display a very wide range (Table 3.6): while KEYNOTE-040 appears to have the most favorable ICER of €136,732/QALY in terms of approaching cost-effectiveness, KEYNOTE-407 seems to be the furthest removed with an ICER of - €4,322,049/QALY. Surprisingly, no ICER was found to sit below the WTP-threshold of €80,000. This finding is reiterated in the PSA screenings (Figure 3.1, Figure 3.2, Table 3.6). Most indications of pembrolizumab would never be reimbursed given a WTP-threshold of €80,000. Surprisingly, PSA results of the KEYNOTE-006 trial show that this indication has a 30% or higher chance of reimbursement. This is mainly due to the combination of lower incurred costs and higher obtained QALYs compared to the SoC treatment arm.

Cost-effectiveness planes

KEYNOTE-trials were plotted according to their distribution in costs and QALYs (Figure 3.1, Figure 3.2). In accordance with their obtained ICERs, the PSA screening results of KEYNOTE-010, -189, -407 and -426 are associated with relatively high costs, while their QALY revenue often does not exceed 0.10 (Table 3.6). In some cases, they yield a negative amount of QALYs, indicating that treatment with pembrolizumab would incur a health loss compared to treatment with SoC. On the other hand, KEYNOTE-048, -040 and -024 show similar but somewhat decreased costs, but they accumulate more QALYs in the meantime. Individual cost-effectiveness planes can be found in Supplemental Figures S.2, S.10, S.12, S.14, S.16, S.18, and S.20.

Looking for clues

Upon closer examination, there seems to be little connection between the relatively favorable and the relatively unfavorable ICERs (Table 3.6). It appears that the cost-effectiveness results do not change evidently in response to the line of treatment. For example, the two aforementioned extremes in terms of ICER level and PSA acceptability

(KEYNOTE-006 and KEYNOTE-407) are both first-line treatment indications for pembrolizumab. In addition, the results of the only two second-line indications do not resemble each other. The context of treatment does not obviously influence the results either. For instance, the two most extreme ICERs belong to combination therapies of pembrolizumab with already existing anti-cancer compounds such as platinum-based chemotherapy or paclitaxel (KEYNOTE-189 and KEYNOTE-407, respectively) and the combination therapy of pembrolizumab with axitinib neither approaches the WTP-threshold (KEYNOTE-426). Whereas the ICERs of the monotherapies of NSCLC or HNSCC (KEYNOTE-010 and KEYNOTE-048, respectively) seem more favorable in comparison with the ICERs of the combination treatments at first glance, there is no clinical or economic rationale to distinguish them on this basis alone.

Finally, even the cancer histology cannot be identified as a driving factor behind the level of the found ICERs. While the costs of treatment belonging to each treatment arm of the two HNSCC histologies are very similar, the KEYNOTE-048 study shows a smaller QALY increment compared to SoC than the KEYNOTE-040 (Table 3.6). This seems to occur predominantly due to a smaller clinical benefit associated with pembrolizumab in the former trial, which could be regarded as unexpected given the context of first-line treatment with pembrolizumab in the KEYNOTE-048 trial versus the second-line treatment in the KEYNOTE-040 trial. Similarly, all investigated indications of NSCLC show such a wide range in their ICERs and PSA acceptability percentages that any relation between their cancer histology and results appear to be far-fetched (Table 2.9, Table 3.6).

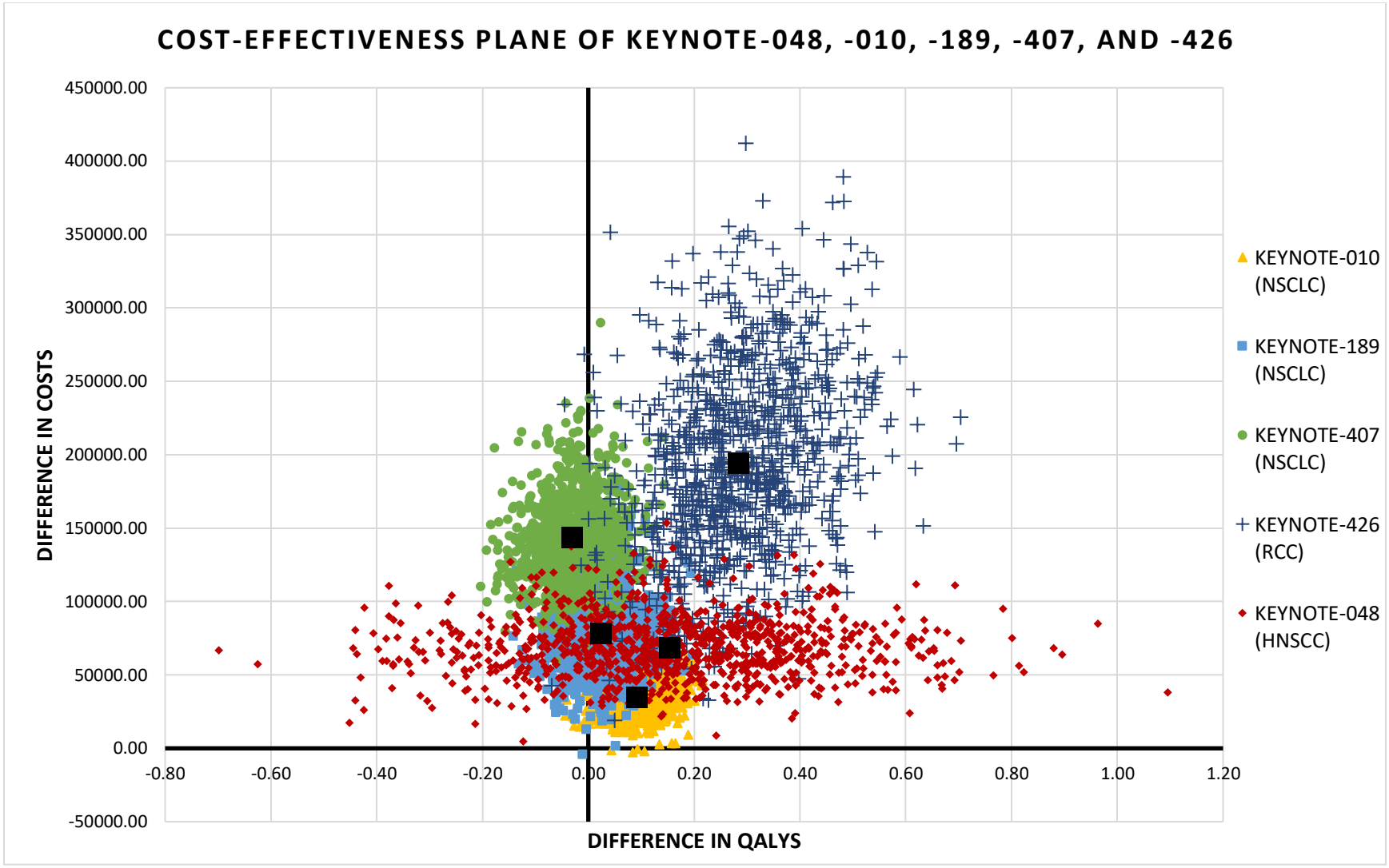

Figure 3.1: The cost-effectiveness plane of KEYNOTE-studies -010 (NSCLC), -189 (NSCLC), -407 (NSCLC), -048 (HNSCC) and -426 (RCC), depicting the results of the PSA screening. Black squares indicate the mean costs per QALY for each KEYNOTE. Costs are depicted in Euros. Abbreviation: QALY, quality-adjusted life year.

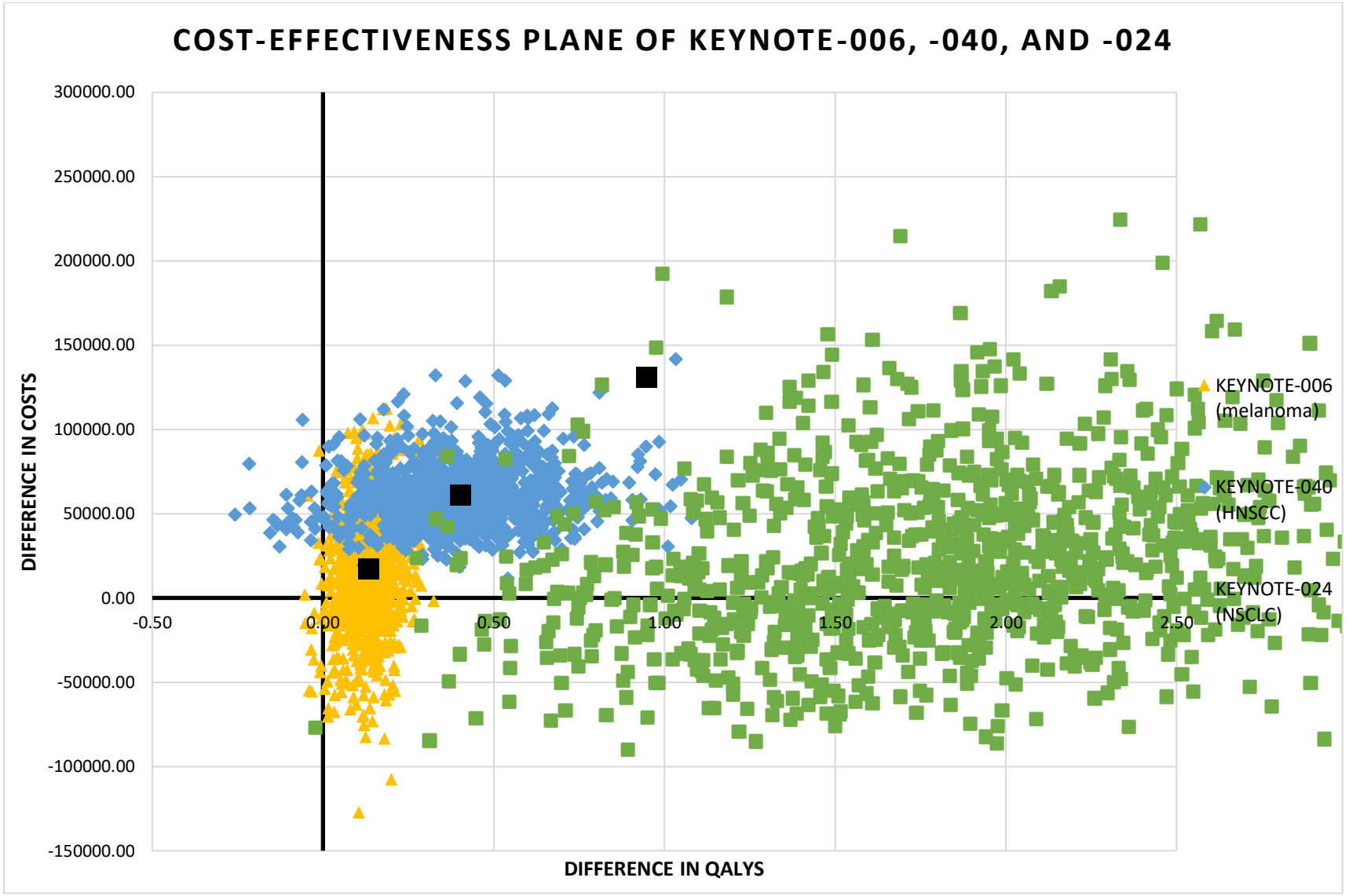

Figure 3.2: The cost-effectiveness plane of KEYNOTE-studies -006 (melanoma), -040 (HNSCC) and -024 (NSCLC), depicting the results of the PSA screening. Black squares indicate the mean costs per QALY for each KEYNOTE. Costs are depicted in Euros. Abbreviation: QALY, quality-adjusted life year.

Chapter 4: The place and role of the cost-effectiveness of pembrolizumab in the reimbursement landscape of the Netherlands

General discussion

In this study, the general cost-effectiveness of pembrolizumab in the Netherlands was assessed extensively by means of performing a cost-effectiveness analyses of 8 distinct indications of pembrolizumab in 4 different cancer histologies as they were approved and are currently adopted to treat oncology patients in Dutch clinical practice. First, a full cost-effectiveness model was built for the first-line treatment of pembrolizumab in NSCLC as the principal indication. Subsequently, these inputs and results served as guidance for the body and the inputs of the cost-effectiveness models of 7 other indications of pembrolizumab.

Applying a WTP-value of €80,000 given the relatively high disease burden of cancer, it was revealed that none of the 8 investigated indications of pembrolizumab would be worthwhile to reimburse in their base case scenarios, given their ICERs which range from €126,474 (KEYNOTE-024) to €2,600,719 (KEYNOTE-189) or take on a negative value of - €4,322,049 (KEYNOTE-407) (Table 3.7) [73]. Simultaneously, PSA screenings showed a low probability of treatment with pembrolizumab being cost-effective, with >30% being the highest probability of treatment with pembrolizumab being more cost-effective than the standard of care (SoC) (KEYNOTE-006) and half of the studied indications never demonstrating any cost-effectiveness of pembrolizumab at 0-1% chance of reimbursement (KEYNOTE-010, -189, -407, and -426). After having chosen a less conservative approach for the OS of the pembrolizumab treatment arm, the ICER of €93,824 (KEYNOTE-024) slightly approached the WTP-value, but not enough to warrant reimbursement. Only in the case of a 50% price reduction of the acquisition price of pembrolizumab the ICER of €71,787 (KEYNOTE-024) was found to be low enough to be accepted given a the WTP-value of €80,000 in the Netherlands. Taken together, almost all estimated ICERs of this study were substantially less cost-effective compared to the ICER obtained by the ZIN in its initial cost-effectiveness analysis during the first evaluation of the pharmaceutical dossier of pembrolizumab in 2016 in absence of any price discounts for pembrolizumab [17]. In addition, the wide range of obtained ICERs suggests that the cost-effectiveness of pembrolizumab can differ substantially between the line of treatment, the context of treatment, or most importantly, the cancer histology.

Throughout all 8 indications, similar input decisions and assumptions collectively influenced the extent of cost-effectiveness of treatment with pembrolizumab with respect to each SoC, or at least contributed in part to the uncertainty thereof. Nevertheless, the search for an as conservative base case scenario as possible ran like a thread through all cost-effectiveness models. The remainder of this chapter will touch upon each of these input decisions.

Efficacy Inputs

In order to adhere to a lifetime horizon as requested by WVS, the first assumptions made in all cost-effectiveness models were the fitted parametric survival curves of OS and PFS based on the survival data of each individual KEYNOTE-trial [26]. By way of RCT design and length of follow-up, official published survival data often ranged to approximately 30 months, after which extrapolation was required. With a conservative approach for treatment with pembrolizumab in mind, the extrapolated distributions were selected based on a combination of their statistical fit, as well as the worst-case scenario within the scope of clinical plausibility for pembrolizumab. Specifically, with respect to the estimation of PFS, the best statistical fit was assumed to correspond most accurately to clinical practice according to a 2021 retrospective study reporting comparable PFS times between clinical trials and real-world data [45]. Regarding the estimation of OS, the conservative choice for pembrolizumab was established on both statistical fit as well as clinical plausibility estimated through visual fit. For example, even though the exponential distribution and Weibull distribution as an OS estimator of treatment with pembrolizumab in the KEYNOTE-024 trial were both statistically and clinically viable, the decision between these two options eventually fell on the exponential distribution because of the relative overestimation of survival in the tail of the Weibull curve as compared to the exponential curve (Figure S.1). By that same rationale, the Weibull distribution was ultimately chosen over the lognormal distribution in the KEYNOTE-048 trial extrapolation (Figure S.5, Figure S.8). As corroborated by the same retrospective real-world data, this approach was proven to bear most resemblance to the observed clinical practice given that OS time was noted to be significantly shorter in real life compared to the trial setting, a finding attributed to the hypothesis that trials generally favor recruiting patients in a better clinical condition [45]. Several other cost-effectiveness studies of treatment with pembrolizumab report the use of the same parametric distributions to estimate survival data beyond the observed KM-curves [46]–[48].

Then, the selected parametric curves were validated against reported median OS and PFS data from the original KEYNOTE-trials, and served as an estimation of the treatment duration of both treatment arms to specifically calculate treatment costs tailored to each indication. Given this lifetime horizon and the varying histologies and subsequent clinical prognosis, these efficacy inputs constitute the most important drivers for the wide range of ICERs obtained throughout the various indications. Unfortunately, this approach did not yield fruitful results for every indication. For example, the obtained extrapolation for the KEYNOTE-407 systematically overestimated PFS duration for the pembrolizumab and SoC treatment arms, while underestimating the OS of the pembrolizumab treatment arm to the extent that it almost equals SoC OS values (Figure S.8). As this indication currently demonstrates a negative (QA)LY increment even though trial data clearly indicate a superior OS and PFS duration for the pembrolizumab treatment arm, the obtained ICER of this indication remains questionable. In addition, the OS of the pembrolizumab treatment arm of two indications (KEYNOTE-006 and KEYNOTE-426) were not yet reached at the time of analysis (Table A.2). This complicates verifying the applicability of the extrapolated curves and affects the accuracy of their (QA)LY increments and ICERs, even though the most conservative fit for treatment with

pembrolizumab was selected each time. Subsequently, these three mentioned indications will not receive the same weight in terms of relevance and representation as the other indications with validated efficacy inputs.

Utilities

A second assumption affecting all investigated indications concerns the use of utilities derived from the KEYNOTE-010 trial, which served as utility inputs for the stable disease and disease progression health states in each cost-effectiveness model in the scope of this study. The main motivation behind this decision is twofold. The first reason is merely a practical one: given the number of indications to be studied and the scarcity of available quality of life data from other KEYNOTE-trials suitable for translation to utility inputs representative of the Dutch patient population, it was decided to exercise the already published utility values of the KEYNOTE-010 trial. More specifically, these utility values were extracted from the KEYNOTE-010 trial to match Dutch clinical practice by the ZIN as part of the official cost-effectiveness study of pembrolizumab used to inform the VWS in 2016 [17]. As such, their extrapolation to patients in the other KEYNOTE-trials was assumed to be substantiated.

In addition, the second reason behind the use of the KEYNOTE-010 utilities as published in all cost-effectiveness models of this study relates to the impact of in- or excluding these utilities in the cost-effectiveness model as a whole. Despite decisions made by ZIN to pool quality of life data per health state in the absence of any statistical or clinical difference between the two treatment arms, utility values used in this study did differ depending on health state and treatment arm, albeit their relatively small discrepancy (0.797 vs. 0.765 in stable disease, 0.706 vs. 0.708 in disease progression, Table 2.6). The exact impact of this scenario was tested in a separate analysis which examined the effect of equalizing utilities of both treatment arms to the utilities associated with the SoC treatment arm. This resulted in a small utility decrement for treatment with pembrolizumab, but did not significantly alter the obtained ICER compared to the base case scenario (Table 2.11). In that light, it could be argued that leaving out utilities altogether would not alter any reimbursement recommendations made based on the obtained ICERs of the models. Nevertheless, upholding a conservative scenario for treatment with pembrolizumab, pooling quality of life data or not taking them into account at all would forego the fact that only acknowledging the life years gained in the pembrolizumab arm without weighing those years in terms of quality does not accurately reflect clinical practice and will overestimate the health benefit following treatment with pembrolizumab altogether.

However, using the KEYNOTE-010 utility values for the stable disease and disease progression health states in each cost-effectiveness model might distort the obtained ICERs. Several important discrepancies between the KEYNOTE-010 study and the other KEYNOTE-trials need to be addressed in order to understand the possible emerging ramifications. First, utilities from the KEYNOTE-010 trial represent the quality of life assessed in patients undergoing their second line of treatment with anti-cancer compounds. While applying this estimation might be appropriate with regard to KEYNOTE-040, another second-line trial, all other KEYNOTE-trials included in this study consist of the

assessment of patients undergoing first-line treatment (Table 3.2). In their case, using utilities from the KEYNOTE-010 study as a proxy of their own will presumably underestimate the quality of life, given that patients usually enjoy a better overall performance score in the first line of treatment compared to the second line of treatment. Taking into account that treatment with pembrolizumab was found to be associated with a longer time to clinical deterioration and a higher quality of life considering its therapeutic benefit over SoC, the underestimation of quality of life resulting from using utilities of the KEYNOTE-010 trial could affect estimation of patients in the pembrolizumab treatment arm to a greater extent than patients in the SoC treatment arm [74]. Ultimately, this could lead to wrongfully assigning less QALYs to the pembrolizumab treatment arm, overestimating the ICER associated with treatment with pembrolizumab versus treatment with SoC, and even alter reimbursement recommendations. The latter specifically refers to KEYNOTE-024 and -040, which are on the brink of reimbursement and whose ICERs would benefit from a bigger QALY increment as they approach the €80,000 WTP threshold (Table 3.7).

Another point of discussion regarding the use of KEYNOTE-010 utilities in all other cost-effectiveness models pertains to the differences in cancer histology across all investigated KEYNOTE-trials. KEYNOTE-010 utilities represent the quality of life of patients suffering from advanced NSCLC, a type of cancer known for its bleak prognosis with a 5-year survival of approximately 5-23% [35]. According to official data by the Dutch cancer registry, the 5-year survival of the KEYNOTE-trials in other histologies investigated in this study range from 23-68% for advanced melanoma (KEYNOTE-006), 11-64% for advanced RCC (KEYNOTE-426) and 37-41% for advanced HNSCC (KEYNOTE-040 and KEYNOTE-048) [75]–[78]. Extrapolating KEYNOTE-010 utilities to the other investigated cancer histologies with a more optimistic forecast can negatively impact the quality of life of cancer treatment in the other KEYNOTE-trials, particularly of the pembrolizumab arm for the same reasons as mentioned above.

Finally, the KEYNOTE-010 trial exerts patient stratification through the selection of patients with elevated PD-L1 levels in their tumor tissue. As described in Chapter 1, the main reason was the lack of clinical effect in patients whose tumors did not bear any PD-L1 expression. While KEYNOTE-024, -040 and -048 apply the same stratification, the other included KEYNOTE-trials examined treatment with pembrolizumab versus SoC in all patients regardless of PD-L1 status. Subgroup analyses of the KEYNOTE-010 and KEYNOTE-040 trials suggest that patients with PD-L1 levels of ≥50% have a better OS and PFS compared to patients with PD-L1 levels between 1-49%, and as a result might experience and report better overall quality of life scores [30], [79]. However, this finding is not reiterated in the KEYNOTE-048 trial, which reports similar median survival data in patients with both low and high PD-L1 tumor levels [80]. No subgroup analyses were performed in the KEYNOTE-024 trial. Currently, the exact role of PD-L1 expression as a biomarker for response to treatment with pembrolizumab continues to be a highly debated topic [81]. Not all KEYNOTE-trials ascribe more promising survival statistics to patients with higher PD-L1 levels, and not all promising survival statistics only pertain to patients with high PD-L1 expression levels [81]. Moreover, the present selection of different cut-off points for the amount of expression of PD-L1 seems rather arbitrary and carries little scientific

rationale [81]. In short, more research is needed to predict the impact of stratifying according to PD-L1 expression on efficacy inputs and resulting quality of life of cancer patients across different histologies. Therefore, any consequences of extrapolating the utilities of PD-L1 positive patients of the KEYNOTE-010 trial to the other KEYNOTE-trials, or any effect on their final ICERs and subsequent reimbursement recommendations will not be discussed further.

Adverse Events

In terms of adverse events, all costs incurred by both treatment arms were assumed to be equal in all cost-effectiveness models. Driven by the conservative base case scenario of the pembrolizumab treatment arm, this particular decision came into being through several steps. Even though the reported incidence of grade 3 or higher adverse events of treatment with pembrolizumab in the KEYNOTE-024 trial did not exceed 10% of the treated patients and would therefore not be incorporated in the cost-effectiveness models in the first place, it was deemed unlikely and clinically inaccurate not to include any costs associated with adverse events for the pembrolizumab treatment arm. In addition, only considering costs of adverse events in the SoC treatment arm would illegitimately shed a more positive light on treatment with pembrolizumab. Nonetheless, a brief literature review revealed a scarcity of accurate and up-to-date data on the costs of adverse events associated with treatment with pembrolizumab that could serve as a trustworthy source of cost inputs for the cost-effectiveness models. For that reason, adverse events costs of the SoC treatment arm described by a real-world NSCLC study in Dutch patients were used as cost inputs for both the SoC and the pembrolizumab treatment arm regardless of their incidence, essentially eliminating their effect on the obtained ICERs [55].

Even though little can be concluded about the financial aspect of adverse events following pembrolizumab treatment, several studies have attempted to determine their incidence. One meta-analysis assessing the incidence of adverse events of 125 clinical trials involving PD-L1 inhibitors found that 1 in 7 patients suffered from a grade 3 or higher adverse event upon treatment, the majority of which were immune-related [82]. In a real-world cohort of NSCLC patients similar to the population of the KEYNOTE-024 trial, approximately 10% of patients experienced grade 3 or higher immune-related adverse event [83]. In general, treatment with pembrolizumab elicits a smaller number of regular adverse events compared to treatment with SoC, but compensates in the form of a higher rate of immune-related adverse events [82], [83]. Since these immune-related adverse events are often more debilitating and require more frequent emergency department visits or even hospitalization, it is hypothesized that costs of adverse events after treatment with pembrolizumab as a collective will exceed those of treatment with SoC [48], [84]. However, the precise extent to which these costs will affect the ICER in favor of treatment with SoC in the Dutch patient population demands more research.

On a final note, possible utility decrements arising from adverse events in either treatment arm were disregarded completely due to time constraints and for practical reasons. Should Dutch utility values associated with (immune-related) adverse events following treatment with pembrolizumab have been available in literature, it is likely that they would have outweighed utility decrements of the SoC treatment arm given their relatively severe nature [82]–[84]. In the same way as costs of its adverse events, this excess of utility decrement on the side of the pembrolizumab treatment arm would benefit the SoC treatment arm, albeit to an unknown degree.

Societal perspective

Even though all cost-effectiveness studies in the Netherlands ought to be performed from the viewpoint of a societal perspective, several societal arguments were not included in this study in consideration of practical feasibility. All cost-effectiveness analyses only incorporated direct medical costs for several reasons. First, indirect medical costs incurred by patients in the intervention or comparator arm were not assumed to differ significantly. For example, as the majority of patients diagnosed with stage IV NSCLC are bordering or past the retirement age (67 in the Netherlands), the opportunity cost will not change depending on the treatment arm of the patient [85]. In addition, given that patients in the pembrolizumab arm had a higher probability of vanquishing the disease or significantly improving their quality of life, they could theoretically have been more likely to (partly) return to work. Should they have exercised that option, the change in opportunity cost would positively impact costs related to treatment with pembrolizumab. For that reason, not incorporating opportunity cost adds to the conservative purpose of the base case scenario.

Considering the centralization of specialized treatment centers of pembrolizumab as advised by the ZIN in their recommendation to the VWS, it could be possible that patients in the pembrolizumab treatment arm would incur additional travel expenses to receive treatment. At the time of their package advice, these costs were estimated at € 23 per treatment cycle per patient, which could alter each ICER with a couple of thousands of Euros in favor of the SoC treatment arm [17]. Nevertheless, more recent data suggest a steady increase in the amount of treatment centers offering treatment with pembrolizumab, implying that travel time and travel expenses have been declining and will presumably continue to do so in the future [20]. Therefore, travel expenses were excluded in the cost-effectiveness models of this study.

Another excluded expense consists of the future (non-)medical costs of both treatment groups. As patients receiving pembrolizumab generally are reported to live longer, it seems probable that this group has a higher probability of incurring (medical) costs in their ‘added life years’ (Table A.2). In other words, the opportunity costs of the pembrolizumab treatment arm are underestimated to a greater extent compared to the SoC treatment arm, and omitting these costs subsequently favors the treatment arm that extends life over the treatment arm that improves quality of life [86]. This implies that ignoring future (medical) costs in this study puts costs related to treatment with

pembrolizumab in a better light, and could render these interventions even more cost-ineffective. The exact effect of this omission depends on the reported OS and PFS durations of each indication and the extent of disability of each cancer histology.

Other indirect medical costs made by both the patient and their family, such as costs associated with mental health services, or any type of informal care were not found to vary substantially across the two treatment arms and were therefore not included [17].

Crossing Over

Lastly, KEYNOTE-024, -006, and -407 allowed treatment cross-over from SoC to pembrolizumab after signs of disease progression in the former treatment group. Only KEYNOTE-024 and KEYNOTE-407 have attempted to correct for the resulting overestimation of the OS of the SoC treatment arm. Also mentioned in Chapter 2, the KEYNOTE-024 trial utilized several statistical methods, while the KEYNOTE-407 trial merely performed a single two-stage model to rectify this bias [36]–[40]. Accordingly, these adjusted OS curves were integrated in their respective cost-effectiveness models as efficacy input as the OS of SoC instead of the principal published OS curve containing crossed over patients. On the other hand, KEYNOTE-006 did not include such corrections, unfairly attributing second-line survival benefits of treatment with pembrolizumab to first-line treatment with SoC. Unfortunately, no subgroup analysis or other statistical revision of the KEYNOTE-006 data exploring a possible rectification is currently published.

KEYNOTE-specific discussion

Several specific input decisions related to two distinct KEYNOTE-trials and their overall effect on the results of their cost-effectiveness studies warrant a separate elaboration.

KEYNOTE-040

In the KEYNOTE-040 trial, the SoC treatment arm consisted of either MTX, docetaxel or cetuximab at the discretion of the investigator, whereas patients are usually administered a monotherapy of MTX in Dutch clinical practice [63], [79]. Unfortunately, no other OS or PFS data following monotherapy of MTX in a Dutch setting was available in literature, and the KEYNOTE-040 paper did not perform any subgroup analyses. Therefore, the KM-curve as published in the original paper was used anyway to extrapolate efficacy inputs for the KEYNOTE-040 model, as it did technically include the standard of care as delivered in the Netherlands. In addition, data derived from the original paper was used to give a positive recommendation for the use of pembrolizumab in HNSCC by the cieBOM in spite of the absence of entirely representative efficacy data [63].

As one of the only investigated KEYNOTE-trials whose results approaches the WTP-threshold of € 80,000, critically reflecting on and attempting to substantiate the details of its efficacy inputs could prove fruitful, as even a slight change in QALY increment could border reimbursement (Table 3.7). In that regard, However, according to some head-to-head clinical trials, patient suffering from recurrent HNSCC receiving either docetaxel or MTX monotherapy did not show significant differences in their OS and PFS rates, while treatment with MTX versus cetuximab merely elicited an extended PFS time, but no difference in OS [87], [88]. Consequently, it is implausible that the published OS and PFS curves for SoC in the KEYNOTE-040 trial would overestimate the survival benefit of the SoC treatment arm. As a result, the slightly disparate published SoC curves are assumed to be an accurate representation of the Dutch clinical setting and are not expected to lead to any change in the current reimbursement recommendation of this KEYNOTE-trial.

KEYNOTE-407 and -189

Similarly, the SoC treatment of KEYNOTE-189 is not compatible with Dutch clinical practice either [67], [89]. While Dutch patients would usually receive platinum-based chemotherapy, this trial merely investigated administering a placebo regimen to patients in the SoC treatment arm. In the absence of any other available SoC survival estimates in literature representative for the Dutch patient population, survival data extracted from the KEYNOTE-407 trial were used to estimate the OS and PFS of the SoC treatment arm [90]. Like the KEYNOTE-189 trial, the KEYNOTE-407 also revolves around the administration of platinum-based chemotherapy in the SoC treatment arm. Given the similarity between the indications of these trials with regards to their tumor type and staging, their line of treatment, and the lack of patient stratification based on PD-L1 tumor expression, the KEYNOTE-407 was deemed the best candidate to replace OS and PFS values for the SoC treatment arm of the KEYNOTE-189 out of all the other mentioned KEYNOTE-trials in this study.

Besides the platinum-based chemotherapy, the KEYNOTE-407 trial also involves the administration of paclitaxel to the SoC treatment arm, while the KEYNOTE-189 does not. Since the combination of these compounds might prove more effective in its anti-cancer capability, it should be taken into account that using the survival data of the KEYNOTE-407 trial could attribute an illegitimate survival benefit to the SoC arm of the KEYNOTE-189 trial. Nevertheless**,** the total achieved survival benefit following the combination treatment of platinum-based chemotherapy and paclitaxel versus platinum-based chemotherapy only was found to amount to a mere 4 months in terms of OS, and 1.6 months in terms of PFS [90]. Therefore, while the addition of paclitaxel to the platinum-based chemotherapy regimen will elicit some additional survival benefit over platinum-based chemotherapy alone, this effect will probably not affect the ICER of the KEYNOTE-189 trial sufficiently to drop below the € 80,000 WTP-threshold.

Ramifications and lessons following the reimbursement of pembrolizumab in the Netherlands

In conclusion, this study of the cost-effectiveness of a selection of indications of pembrolizumab found that not a single indication currently meets the WTP-value of € 80,000 as applied in the Netherlands. Consequently, all off the investigated indications of pembrolizumab would receive a negative reimbursement recommendation from the ZIN. Nevertheless, it should be noted that the first reimbursement decision of pembrolizumab made by the VWS was accompanied by a confidential price discount of 17.5% upwards, possibly amounting up to 30% or even 50% [32]. Naturally, this would favor the cost-effectiveness of several indications investigated in this work and positively impact their reimbursement recommendation. However, some of the obtained ICERs are so cost-ineffective that even a price reduction of that extent would not suffice. This implies that these indications of pembrolizumab would not have been included in the basic care package even in presence of a considerable price discount, albeit their clinical benefit. As a result, the present reimbursement of these cost-ineffective indications of pembrolizumab could suggest a misallocation of the national inpatient healthcare budget of the Netherlands.

Crowding out

Most often, economic theory hypothesizes that reimbursing healthcare interventions that were proven to be cost-ineffective leads to a misallocation of resources, which puts cost-effective healthcare interventions at a disadvantage and consequently leads to a health loss of a given population [91]. After all, resources, and particularly healthcare budgets, can only be spent one time. However, it is a challenge to identify what this so-called 'crowding out' of cost-effective healthcare interventions entails specifically, or estimate the magnitude of this population-wide health loss. For example, could a particular type of care be disproportionally displaced compared to others, or could this health loss be expressed in QALYs?

Recently, an elaborate Dutch investigation has attempted to answer these questions as they relate to the Dutch healthcare landscape [92]. Importantly, their results show that reimbursing cost-ineffective healthcare does not lead to the direct displacement of other care. Instead, the budgetary pressure resulting from the implementation of cost-ineffective healthcare is diffusely distributed among different departments of one hospital, or several hospitals of the same region. In that way, crowding out of cost-effective healthcare happens gradually over time. Still, it eventually does lead to a decreased accessibility of the healthcare sector: constraints of certain types of healthcare with regards to the available budget or treatable patient populations, shortages in relating healthcare resources such as labor, and a general lower supply of healthcare altogether. In an attempt to counter these consequences and improve efficiency of the workplace, the study found that hospitals often face an increasing workload among their personnel both within and outside clinical practice. Alarmingly, it seems that, in the event of crowding out,

patients undergoing elective care or suffering from benign conditions encounter the biggest repercussions. Given that treatment of patients needing acute care or suffering from oncologic diseases are prioritized over the treatment of other patient populations in times of scarcity, the latter often experience longer waiting lists, more referrals and longer referral times. In short, while displacement of cost-effective healthcare interventions might be subtle and might accumulate slowly, the side effects of the strain put on the healthcare sector to continue to reimburse cost-ineffective healthcare interventions do exist, and its limit might soon be reached [92].

Improving cost-effectiveness

However, this does not signify that the reimbursement of a healthcare intervention with an unfavorable ICER automatically initiates a cascade of displacement of cost-effective care as mentioned in the previous paragraph. Within the scope of its indication(s), there is room to improve the cost-effectiveness of a given compound in clinical practice. Besides their reimbursement recommendation, the ZIN usually also offers pragmatic advice concerning the most efficient use of a new healthcare intervention in Dutch clinical practice. Ever since the evaluation of its pharmaceutical dossier, several pragmatic points have been highlighted concerning the clinical application of pembrolizumab that could enhance its cost-effectiveness [17], [20].

In its initial indication of second-line treatment of locally advanced or metastasized NSCLC, pembrolizumab was approved at a dosage of 2 mg/kg every three weeks according to its administration in the KEYNOTE-trial [30]. Given the dose of 50 mg per vial of pembrolizumab and a mean estimated weight of 71 kg for Dutch patients, this implies that at least three vials of pembrolizumab are used every cycle at a unit price of €1,430.28, amounting to a total acquisition cost of €4,290.84 (Table 2.5) [17]. Additionally, a univariate sensitivity analysis shows that these acquisition costs could increase up to four vials or €5,721.12 per cycle should 20% be added to the patients' mean weight, substantially impacting the ICER in favor of treatment with SoC (Figure 2.4). To combat these costs, several new dosing strategies have been identified, such as dose-capping, which rounds the patient's dose depending on the content of used vials, or dose-banding, in which the dose is rounded by the amount of patients in a certain treatment cohort in order to correspond to the content of used vials [20]. Another dosage regiment that is currently being investigated in NSCLC consists of simply reducing the dose of pembrolizumab from 2 mg/kg to 1.5 kg/mg [93]. Estimations find that these creative ways to go about dosing of pembrolizumab could save up to tens of millions of euros each year [20]. Currently, it is too early to draw conclusions about any possible clinical benefit of this strategy. Still, the tumor-agnostic feature of pembrolizumab and other immunotherapies to follow might complicate new dosing strategies in practice. Even in the event of identical clinical benefit of pembrolizumab after administration of a lower dose in NSCLC, it remains to be elucidated whether or not the other cancer histologies will follow this example. Probably, this will require clinical trials to be carried out in several more indications and consequently will take considerably more time, both of which are very costly in this case. In addition, it is unclear what happens should one indication display promising clinical effects following a lower dose, while another does not. Will the higher dose

of pembrolizumab still be administered, even though that would imply accepting its unfavorable cost-effectiveness in the process? Or will the lower costs associated with the lower dose be accepted in exchange for the loss of QALYs? Will new cost-effectiveness studies need to be reperformed to assess the value for money in the latter case?

Another potentially lucrative feature of the current treatment of pembrolizumab could be the selection of its patient population and the treatment duration thereof [20]. One proposed mechanism is discontinuing treatment with pembrolizumab at an earlier stage both in patients that react poorly as in patients that respond well. In the first population, costs related to drug acquisition and occurring adverse events are saved while no clinical harm is done. In the latter population, studies are still assessing whether a shorter duration of treatment with pembrolizumab induces the same tumor response, which would also diminish total treatment costs per patient [94]. Nevertheless, in order for this strategy to work timely and most efficiently, there needs to be a system in place that is able to determine which patient populations can expect tumor response and which cannot. As mentioned earlier, no adequate biomarker is currently able to predict treatment response to pembrolizumab, or any immunotherapy for that matter [81]. Either way, both in absence and in presence of a biomarker, the exact code of conduct of treatment duration for each indication remains ambiguous. Should a biomarker ever be identified, could it be used for all indications of pembrolizumab or any other given immunotherapy? If so, can the same stratification thresholds be used throughout all these indications, or does each indication call for a different threshold to maximize the clinical benefit of the treated patient population? How much additional research is needed to determine this threshold for every different cancer histology? And if a biomarker will never be found, will all patients be continued to be treated with immunotherapy, even though many of them will never see clinical response?

At the time of its package advice, the centralization of treatment and research centers was named as another one of the main preconditions for reimbursement of pembrolizumab [17]. With this measure, pembrolizumab would only be administered in specialized centers that meet specific quality and patient volume criteria drawn up by the NVALT. These specialized centers could then use their experience to maximize cost-effectiveness by identifying the appropriate patient populations, minimizing drug spillage and optimizing treatment duration. Together, this centralization would ensure the quality of care, and guarantee its financial sustainability at the same time. Nonetheless, the amount of treatment centers for melanoma and NSCLC in particular has been rising steadily. For example, more than half of these new treatment centers for NSCLC and melanoma care for less than 100 patients a year, raising questions as to their quality and ability to treat in a cost-effective manner [20]. In addition, many new indications of pembrolizumab have entered the market in the meantime. Eventually, the rise in newly eligible patients that fall within these new indications could put a strain on the degree of centralization of treatment centers. While the subsequent increase in treatment centers might benefit the accessibility of pembrolizumab to patients throughout the Netherlands, it remains to be seen whether this development would also still contribute to maximizing its cost-effectiveness in practice.

Lastly, the abovementioned attempts at improving cost-effectiveness are predominantly based on advice issued after the first couple of years of the clinical use of pembrolizumab for its initial indication of NSCLC and subsequently that of melanoma [20]. Given the relative favorable ICER calculated for one indication of first-line NSCLC in this study, even small practical measures could be enough to yield a better cost-effectiveness outcome, or indeed change reimbursement recommendations by the ZIN (Table 3.7). On the other hand, it becomes more difficult to justify trying to enhance cost-effectiveness for indications whose ICERs were found to exceed €200,000 or more, or take on a negative value. This was the case for five out of the eight studied indications of pembrolizumab. Realistically, none of the presently proposed mechanisms would be able to reduce the ICER sufficiently to approach the WTP-threshold of €80,000 for these indications.

In conclusion, while many strategies for cost containment concerning the clinical use of pembrolizumab have been proposed which could have proven fruitful in the case of a single cancer histology to be treated by pembrolizumab or any other immunotherapy, the tumor-agnostic nature of these compounds brings considerable uncertainty regarding the practical feasibility and desirability of improving their cost-effectiveness in real-life. In other words, this approach cannot and should not be used as a means to condone the unfavorable outcomes of the cost-effectiveness analyses of tumor-agnostic therapies.

Theoretical formality

Instead, a more careful approach could have been taken during the process of reimbursement and establishment of financial agreements of any indication of pembrolizumab. As per official criteria by the ZIN, two detailed financial limits have been installed to determine whether a healthcare intervention or an indication thereof should be placed in The Lock, as described in Chapter 1 [8]. These criteria allow that both a healthcare intervention itself, as well as subsequent new indications of said healthcare interventions can be placed in The Lock independently. So, even if the healthcare intervention itself has been placed in The Lock and has passed a reimbursement decision, possible new indications of the same intervention can still meet the criteria to be placed in The Lock as well if their estimated annual budget impact is too large. Essentially, this measure protects the Dutch national inpatient healthcare budget from being spent on new and expensive applications of a healthcare intervention that was once accepted for reimbursement.

In the case of pembrolizumab, this last criterium might have been overlooked. Following the instituted financial agreement after its first approved indication, pembrolizumab left The Lock once and for all in 2017. Ever since, no new indications of pembrolizumab have been placed in The Lock, even though sufficient evidence exists that suggests that the budget impact of several indications might have met the financial limitations of the second criterium. First of all, the brief breakdown of treatment costs outlined by the cieBOM in their PASKWIL-criteria

already revealed that the annual expenditures associated with the vast majority of their assessed indications exceed €50,000 per patient, including all but two indication that was investigated in this study [31], [32], [59], [62]–[68], [95]–[97]. Only treatment costs per patient associated with the KEYNOTE-040 and KEYNOTE-010 trials were sufficiently low to securely assume that a placement in The Lock would not be necessary. In addition, the treatment costs of indications of pembrolizumab that emerged after its removal from The Lock as listed in the HG report the same excess in costs [98], [99]. Often, the estimated total annual budget impact substantially exceeds the limit of €10 million and the annual treatment costs per patient are approximated to range between €40,000 and €60,000.

Formally, these indications should have been placed in The Lock. Not only would this have warranted an extensive review and evaluation of their pharmaco-economic dossier for each indication to elucidate its cost-effectiveness individually, it also would have offered the VWS with more opportunities to engage in new financial negotiations with the manufacturer each time a new Lock placement is established. After all, a more expansive application of pembrolizumab in clinical practice and a subsequent better market position for this compound could justify a greater price reduction. In any case, it would have increased the budgetary transparency in terms of the value for money of the indications of pembrolizumab that have been approved to today and will be approved in the future, leading to an improved ability of critical decision-making regarding the role of pembrolizumab in the Dutch cancer treatment landscape.

Practical reasonability

Still, acknowledging the pragmatic circumstances under which the reimbursement of these indications come into being is imperative in this issue. While pleading for an ideal reality where all indications are assessed based on their cost-effectiveness, it should be considered that conducting detailed pharma-economic studies and drawing up a complete pakketadvies of each indication takes time and money. For example, the KEYNOTE-010 pakketadvies was released approximately 4 months after its placement in The Lock. In the light of providing the most optimal oncologic treatments to patients as quickly as possible, delaying the clinical availability of pembrolizumab or other innovative anti-cancer compounds for several indications and patient populations while waiting for this evidence seems undesirable and could also affect the quality of the Dutch healthcare system.

Another point of uncertainty regarding the practical cost-effectiveness of pembrolizumab is the lack of transparency surrounding its financial arrangement. As mentioned earlier, it is known that the price discount of pembrolizumab amounted to at least 17.5%, but could have added up to 30% or 50% as well. Another possibility is that VWS negotiated a population-level expenditure cap. In that case, the pharmaceutical company receives a fixed price for their product in exchange for a limitless supply, and it would be unnecessary to place new indications in The Lock. Either way, the fact of the matter is that the real-world cost-effectiveness of pembrolizumab remains uncertain as long as details of its financial situation are not released.

Future prospects

In order to estimate the effects and ramifications of disregarding financial aspects when deciding upon the reimbursement of new and expensive oncologic compounds in the Dutch healthcare setting, this study presents the first global cost-effectiveness study of a tumor-agnostic immunotherapy in the current clinical practice of the Netherlands. Overall, it was found that failure to consider the cost-effectiveness of new indications of an already reimbursed tumor-agnostic immunotherapy during approval decisions leads to the application of cost-ineffective healthcare treatments in the absence of financial agreements with the manufacturer. Consequently, this could result in crowding-out of existing cost-effective healthcare, a decreased accessibility of healthcare in general and a potential health loss for the Dutch population. Given the increasing prevalence of cancer and the continuing rapid development of research into immunotherapy, this work could offer a glimpse into the possible results of reimbursing and approving new tumor-agnostic immunotherapies by way of the same process as described in Chapter 1 [100], [101].

Recently, the ZIN has issued several package advices for upcoming immunotherapies and their clinical use in the Netherlands following their placement in The Lock. Among these are avelumab, atezolizumab, nivolumab, and ipilimumab, all anti-PD-L1 compounds except for the latter, which is a cytotoxic T-lymphocyte-associated protein 4 (CTLA4) immune checkpoint regulator [102]–[105]. Similar to the case of pembrolizumab, serious doubts regarding their impact on the financial sustainability of the Dutch healthcare sector emerged upon the determination of their ICER or budget impact. Calculations show that the obtained ICERs exceed €110,000, and budget impacts range from €10 million to a remarkable €203 million for nivolumab in particular. Regardless, all are currently reimbursed in the Netherlands, and often have been approved for additional indications other than the one included in their initial assessment, even though their financial positions were never assessed again in different histologies, and no further proof of value for money exists. This implies that the path of pembrolizumab is not unique, has already repeated itself for other immunotherapies and will most likely do so in the future as well.

Taken together, this study aims to raise awareness of the current state of affairs of the reimbursement process of tumor-agnostic immunotherapy in the Netherlands. While the structure of the reimbursement system of expensive inpatient healthcare interventions appears adequate and sufficient to ensure the correct allocation of the Dutch national healthcare budget, past and present reimbursement pathways of pembrolizumab and other immunotherapies have shown that this might not be the case for tumor-agnostic therapies in practice. As shown by this study, their financial picture and subsequent cost-effectiveness can differ greatly between various indications, even if they pertain to the same cancer histology. Given this wide range in cost-effectiveness, continuing to grant approval for use in different cancer histologies after initial inclusion in the basic care package, essentially blindly assuming that all indications display cost-effectiveness because the first indication proved to do so, risks not

obtaining the most value for money in the end and could lead to a misallocation of the Dutch healthcare budget. This matter is further complicated by the lack of transparency regarding the financial agreements established between VWS and the manufacturers, which renders it impossible to accurately assess the real-world cost-effectiveness and value for money of immunotherapy. In short, this unsustainable course of action is testing the limits of the Dutch national healthcare budget and will plausibly continue to do so, potentially harming the quality, accessibility and affordability of healthcare in the Netherlands.

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Appendix

Unchanged parameters

To facilitate input translation from the principal indication to the other indications but maintain sight of clinical accuracy of each cancer histology in the process, the input parameters of the principal indication were slightly altered or replicated altogether depending on their clinical importance within each cancer histology and their impact on the ICER as highlighted by several sensitivity analyses performed in Chapter 2 (Table 2.9 – 2.11). Table A.1 shows a list of parameters that remained the same throughout all cost-effectiveness models mentioned in Table 3.1.

For every subsequent cost-effectiveness model, acquisition costs of pembrolizumab and the one-off anti-PD-L1-test costs (if applicable) were assumed to remain the same. In addition, each patient incurred a one-off cost for adverse events in both treatment arms, as well as an end-of-life cost parameter upon death. Based on the results of the scenario analysis in Chapter 2, the disease state utilities of both pembrolizumab and SoC will be left unchanged in all cost-effectiveness models (Table 2.11). Sources of these parameters and their indexation rates can be found in Tables 2.5, 2.6 and S.3.

Input parameter	Input Parameter	Standard deviation	Decision rationale
Cost Inputs			
Drug acquisition costs pembrolizumab	€ 4,290.84	-	Remains the same irrespective of cancer histology.
Anti-PD-L1-test pembrolizumab*	€ 120.15	€ 24.03	
Adverse events costs pembrolizumab and SoC	€ 2,415.66	€ 4,905.91	±20% change had minimal impact on ICER (Figure 2.4).
End-of-life cost pembrolizumab and SoC	€ 1,357.71	€ 271.54	
Utility Inputs			
SD pembrolizumab	0.797	0.1594	Equalizing utilities had minimal impact on ICER (Table 2.11). Therefore, the current utility benefit of pembrolizumab will remain.
PD pembrolizumab	0.706	0.1412	
SD SoC	0.765	0.1530	
PD SoC	0.708	0.1416	

Table A.1: Input parameters of the principal indication as described in Chapter 2 that remained unchanged during extrapolation to the other investigated indications of pembrolizumab. Abbreviations: SoC, standard of care; SD, stable disease; PD, progressive disease; PD-L1, programmed death-ligand 1. *Only applies to KEYNOTE-040, -048, and -010.

Overall survival and progression-free survival statistics

For each indication, incurred costs and utilities depended on the reported OS and PFS of their respective KEYNOTE-trials (Table A.2). Values of this table were used to validate the obtained parametric distribution curves.

KEYNOTE-trial	Median overall survival (95% CI) (months)		HR (95% CI), p-value	Progression-free survival (95% CI) (months)		HR (95% CI), p-value
	Pembrolizumab	SoC		Pembrolizumab	SoC	
KEYNOTE-040	11.6 (8.3 – 19.5)	6.6 (4.8 – 9.2)	0.53 (0.35 – 0.81), p=0.0014	3.5 (NP)	2.2 (NP)	NP
KEYNOTE-048	12.3 (10.8 – 14.9)	10.3 (9.0 – 11.5)	0.78 (0.64-0.96), p=0.0086	3.2 (2.2 – 3.4)	5.0 (4.8 – 5.8)	1.16 (0.96 – 1.39), NP
KEYNOTE-006	NR (23.5 – NR)	15.9 (13.3 – 22.0)	0.74 (0.59 – 0.92), p=0.0029	4.1 (2.9 – 7.2)	2.8 (2.8 – 2.9)	0.61 (0.50 – 0.75), p<0.0001
KEYNOTE-010	10.4 (9.4 – 11.9)	8.5 (7.5 – 9.8)	0.71 (0.58 – 0.88), p=0.0008	3.9 (3.1 – 4.1)	4.0 (3.1 – 4.2)	0.88 (0.74 – 1.05), p=0.07
KEYNOTE-189	22.0 (19.5 – 25.2)	10.7 (8.7 – 13.6)	0.56 (0.45 – 0.70), NP	9.0 (8.1 – 9.9)	4.9 (4.7 – 5.5)	0.48 (0.40 – 0.58), NP
KEYNOTE-407	17.1 (14.4 – 19.9)	11.6 (10.1 – 13.7)	0.71 (0.58 – 0.88), NP	8.0 (6.3 – 8.4)	5.1 (4.3 – 6.0)	0.57 (0.47 – 0.69), NP
KEYNOTE-426	NR	35.7 (33.3 – NR)	0.68 (0.55 – 0.85), p=0.0003	11.4 (12.7 – 18.9)	11.1 (9.1 – 12.5)	0.71 (0.60 – 0.84), p<0.001

Table A.2: Median OS and PFS of the pembrolizumab and the standard of care treatment arm of each KEYNOTE-trial investigated in Chapter 3. Abbreviations: SoC, standard of care; HR, hazard ratio; CI, confidence interval; NR, not registered; NP, not provided.

Rationale efficacy inputs

As for KEYNOTE-189 and KEYNOTE-426, the Weibull distribution was identified as the best overall fit for OS and PFS both statistically and clinically (Figures S.7-S.9, Tables S.13-S17). For the other KEYNOTE-trials, some grounded concessions were made. Only the trials that show discrepancy between their clinical and statistical fit will be discussed.

First of all, the best clinical fit found for the OS estimator of KEYNOTE-040 was a Weibull distribution, whereas the best statistical fit was an exponential distribution (Figure S.3, Table S.4). However, given the fact that a Weibull distribution was the second-best statistical fit for the OS estimator for treatment with both pembrolizumab and SoC, and considering its most conservative clinical fit, a Weibull distribution was the final choice for OS estimator.

For the OS of KEYNOTE-048, a Weibull distribution was determined as the best clinical fit, while the best statistical fit was a lognormal distribution for treatment with pembrolizumab and a Weibull distribution for treatment with SoC (Figure S.4, Table S.6). The final choice of Weibull for best overall fit was based on the fact that a Weibull distribution was the second-best statistical fit for the OS estimator of treatment with pembrolizumab. Considering that a Weibull distribution was the best clinical fit for treatment with both pembrolizumab and SoC, the best statistical fit for treatment with SoC and the second-best statistical fit for treatment with pembrolizumab, it was seen as the best overall choice for the OS estimator of this KEYNOTE-study.

Regarding KEYNOTE-006, overall survival following treatment with pembrolizumab best followed a Weibull distribution clinically, and a loglogistic distribution statistically (Figure S.5, Table S.8). The OS of SoC was best described using a Weibull distribution for both arguments. Taking into account that a Weibull distribution would be the second-best statistical choice for pembrolizumab and was the first choice for the other clinical and statistical distributions, the Weibull distribution was chosen as the final OS efficacy estimator for the KEYNOTE-006 trial.

Furthermore, data extracted from the PFS values of the KEYNOTE-010 trial indicate that a Weibull distribution would constitute the best clinical and statistical for the SoC treatment arm, while a loglogistic distribution would be best for the pembrolizumab treatment arm (Figure S.6, Table S.10). Given that the efficacy estimators all attempt to favor a conservative base case scenario for treatment with pembrolizumab, the final choice for the PFS estimator of the KEYNOTE-010 trial was a loglogistic distribution.

Finally, the PFS estimations of the KEYNOTE-407 trial overestimate the reported PFS of the trial data. For both treatment arms, the exponential distribution approaches the KM-curve most closely. However, statistical analysis points toward a Weibull distribution as the best statistical fit. Since real-world data have shown that estimated PFS duration in trials often mirrors in real clinical practice, it was decided to adopt the Weibull distribution as the PFS estimator for both treatment arms.

Rationale medical cost inputs

KEYNOTE-040 and KEYNOTE-048

Since KEYNOTE-040 and -048 both consisted of patients suffering from HNSCC, the same paper outlining the Dutch price tag of this cancer histology was used to calculate cost inputs [69]. This real-world 2001 study distinguishes all mean medical costs related to primary tumors (KEYNOTE-048) and recurrent tumors (KEYNOTE-040) related to outpatient visits, hospital days, therapies and diagnostics [69]. For SoC, this totaled €21,858 indexed to €31,447.96 for KEYNOTE-048, and €27,629 indexed to €39,750.93 for KEYNOTE-040 (Table 3.7). For pembrolizumab, the same one-off cost was used after subtracting costs for chemotherapy, adding up to €14,752 or €21,224.28 after indexation for KEYNOTE-048 and €19,193 or €27,613.72 after indexation for KEYNOTE-040 (Table 3.5) [69]. In accordance with the first-line combination therapy of the KEYNOTE-048 trial, costs belonging to chemotherapy only were added to the model, which amounted to €704 or €1,012.87 after indexation. In addition, both KEYNOTE trials required an anti-PD1 test, whose costs were added as well. These total one-off costs of almost 2 years of follow-up were then converted to a 3-weekly cycle cost to be used as the main cost input in the cost-effectiveness models. The standard deviation was assumed to be 20% of the cost parameter (Table 3.5).

Adhering to the outline of the indication and Dutch clinical practice, patients in the KEYNOTE-040 model first received pembrolizumab monotherapy in the pembrolizumab treatment arm or SoC in the SoC treatment arm. Upon disease progression, both treatment arms received SoC until death. As for KEYNOTE-048, patients in the pembrolizumab treatment arm first received pembrolizumab in combination with only chemotherapy of the SoC arm, whereas patients in the SoC arm received the full SoC treatment. Upon disease progression, both arms received SoC until death.

KEYNOTE-006

All cost inputs for the KEYNOTE-006 cost-effectiveness model were derived from a real-world study conducted in Euro 2016 [70]. This paper aimed to assess the healthcare costs associated with advanced melanoma and its treatment with ipilimumab in the Netherlands. Accrued over a period of 6.27 months, they estimated total healthcare costs of treatment with ipilimumab to be €81,484 with a standard deviation of €27,100, or €87,596.95 and €29,133.05 after indexation, respectively (Table 3.5) [70]. For treatment with pembrolizumab, the same cost input was used after subtracting costs associated with chemotherapy, surgery, and radiotherapy. Total healthcare costs amounted to €6,619 with a standard deviation of €7,109, or €7,158.25 and €7,688.17 after indexation, respectively (Table 3.5) [70]. As with the previous indications, these total costs were converted to a 3-weekly cycle cost as the main cost input of the cost-effectiveness model.

Patients either received pembrolizumab monotherapy or SoC consisting of ipilimumab depending on their treatment arm. Upon disease progression, all treatment arm received SoC until death.

KEYNOTE-010, -189 and -407

For all these NSCLC clinical trials, the same real-world cost study of NSCLC patients in the Netherlands used for the KEYNOTE-024 trial in Chapter 2 was used (Table 2.5) [55]. Healthcare costs for treatment with SoC were found to be €32,708.38, whereas treatment with pembrolizumab amounted to €19,224.29 in healthcare costs [55]. Depending on the specifics of each indication, different cost inputs were added to this one-off cost. All costs were reported to have been incurred over a period of 12.6 months and were converted to a 3-weekly cycle cost. The standard deviation of total healthcare costs for pembrolizumab was assumed to be the calculated €2,284.84 plus 20% of possible added cost inputs, whereas the standard deviation for costs associated with the SoC arm remained identical to the one calculated in Chapter 2 at €5,456.75 (Tables 2.7 and 3.5).

Given that KEYNOTE-010 implies monotherapy with pembrolizumab versus SoC, all cost input parameters remained unchanged as compared to the KEYNOTE-024 model. Excluding costs related to the anti-PD1 test which were later added as a one-off cost input, total healthcare costs for treatment with pembrolizumab or SoC stayed at €19,224.29 or €32,708.38, respectively (Table 2.5).

For KEYNOTE-189, costs associated with chemotherapy of the SoC treatment arm as reported in the previously mentioned real-world NSCLC cost study were added to the total healthcare costs of the pembrolizumab arm [55]. With a chemotherapy cost of €2,650 or €3,041.09 after indexation, total healthcare costs of the pembrolizumab arm amounted to €22,265.39 (Table 3.5).

To calculate the costs incurred by treatment combination of carboplatin and paclitaxel in addition to pembrolizumab for KEYNOTE-407, a retrospective Dutch NSCLC cost study was consulted [49]. Indexed to 2021 prices, they report a mean cycle use of 538 mg at €0.97/mg for carboplatin and 336 mg at €7.72 for paclitaxel. In addition, an administration cost of €269.33 per cycle was incorporated. In total, the 3-weekly cycle cost of the additional chemotherapy consisting of carboplatin and paclitaxel to be added to the pembrolizumab treatment arm was €3,382.92, yielding a total cost of €22,607.21 (Table 3.5).

In all NSCLC models, patients first received pembrolizumab monotherapy, or pembrolizumab in combination with another treatment if applicable to the indication, or SoC. Upon disease progression, all patients received SoC.

KEYNOTE-426

For costs associated with renal cell carcinoma investigated by the KEYNOTE-426 trial, results from a cost-effectiveness study performed in the Netherlands were consulted [71]. Reported in EUR 2018, this study included all costs stemming from treatment with the current Dutch SoC sunitinib over a time period of two years [64], [71]. In order to conform to the cost-effectiveness model outline of this thesis, costs of terminal care and adverse events were subtracted from the total published amount, yielding a final amount of €224,878 or €237,697.56 after indexation for the healthcare costs of the SoC treatment arm (Table 3.5). To obtain healthcare costs of the pembrolizumab treatment arm, drug acquisition costs were subtracted from the total SoC costs, totaling €194,467 or €205,552.93 after indexation (Table 3.5). As per Dutch clinical standards and the indication, acquisition costs of a daily dose of 10 mg of axinitib was added to the total costs of the pembrolizumab arm [64]. Given the cost of €68.78 for one pill of 5 mg, the total additional cost of axitinib over a two-year period equaled €100,418.80, increasing the healthcare costs of the pembrolizumab treatment arm to €305,971.73 [72] (Table 3.5). Both healthcare costs belonging to the pembrolizumab and SoC treatment arm were converted to a 3-weekly cycle cost, and their standard deviation was assumed to be 20%.

Supplemental Data

Introduction

New Indications of pembrolizumab since March 2021	
Tumor Type	**Full Indication**
Breast Cancer (BC)	Combination therapy with chemotherapy for local recurring inoperable or metastasized triple negative BC with PD-L1 expression (CPS ≥ 10) not previously treated for their metastasized disease
Endometrial Cancer (EC)	Combination therapy with lenvatinib for advanced ED with disease progression following prior systemic therapy in any setting, if ineligible for curative surgery or radiation
Esophageal Carcinoma (EG)	Combination therapy with platinum and fluoropyrimidine-based chemotherapy as first line treatment of locally advanced unresectable or metastatic EG with PD-L1 expression (CPS ≥ 10)
Hodgkin Lymphoma (cHL)	Monotherapy of recurrent or refractory cHL after two failed treatment cycles and ineligibility for autologous stem cell transplantations
Renal Cell Carcinoma (RCC)	Combination therapy as first line treatment of advanced RCC with lenvatinib

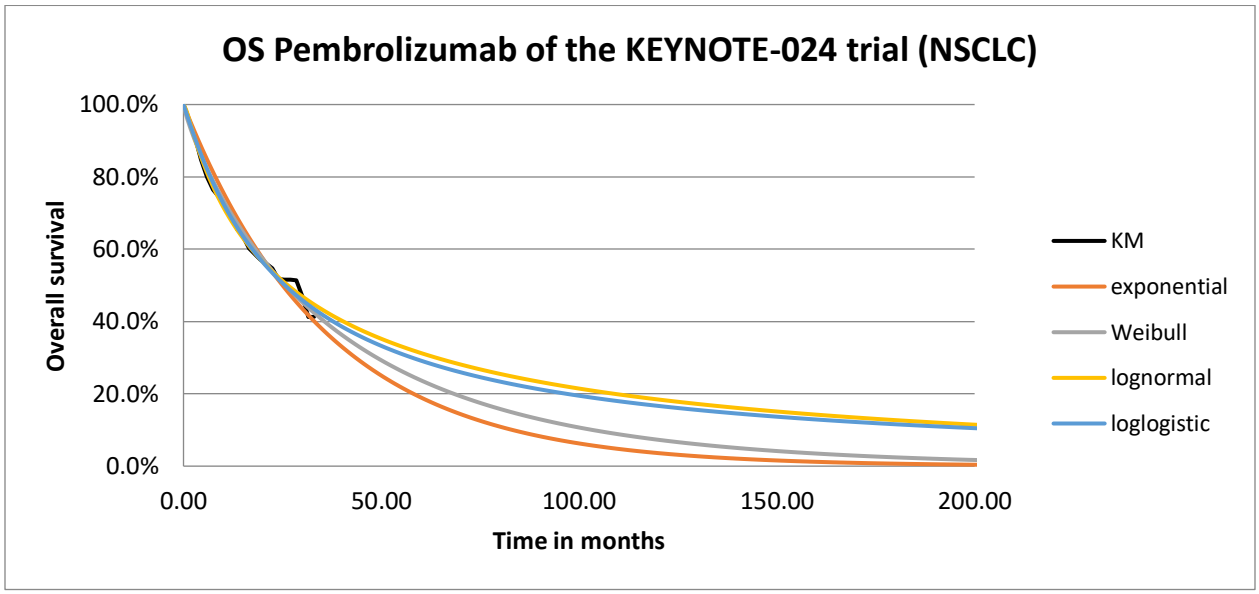
Table S.1: Current additional indications of pembrolizumab approved since March 2021, according to the Farmacotherapeutisch Kompas, accessed January 2022. Abbreviations: PD-L1, programmed death-ligand 1; TPS, tumor proportion score; CPS, combined positive score; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

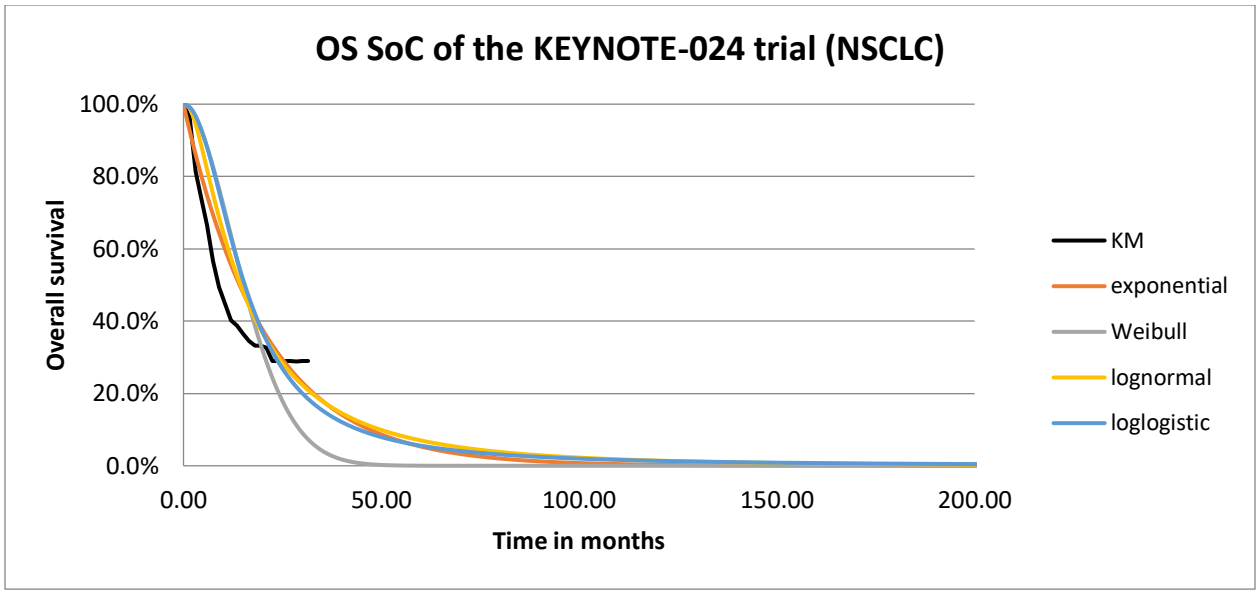
Future Indications of pembrolizumab		
Tumor Type	**Full Indication**	**Expected Approval**
Renal Cell Carcinoma (RCC)	Adjuvant monotherapy of RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions	February 2022
Breast Cancer (BC)	Combination therapy with chemotherapy as neoadjuvant treatment, then continued as adjuvant treatment after surgery of locally advanced, inflammatory, or early-stage triple negative BC at high-risk of recurrence	March 2022
Non-Small Cell Lung Cancer (NSCLC)	Combination therapy of locally advanced NSCLC, with chemoradiation	April 2022
Hepatocellular Carcinoma (HP)	Combination therapy as first line treatment of advanced HP, with lenvatinib	May 2022
Colorectal Cancer (CRC)	Monotherapy of unresectable or metastatic MSI-H or dMMR CRC after prior therapy	May 2022
Cervical Cancer (CC)	Combination therapy as first line treatment of persistent, recurrent or metastatic CC, with or without bevacizumab	June 2022

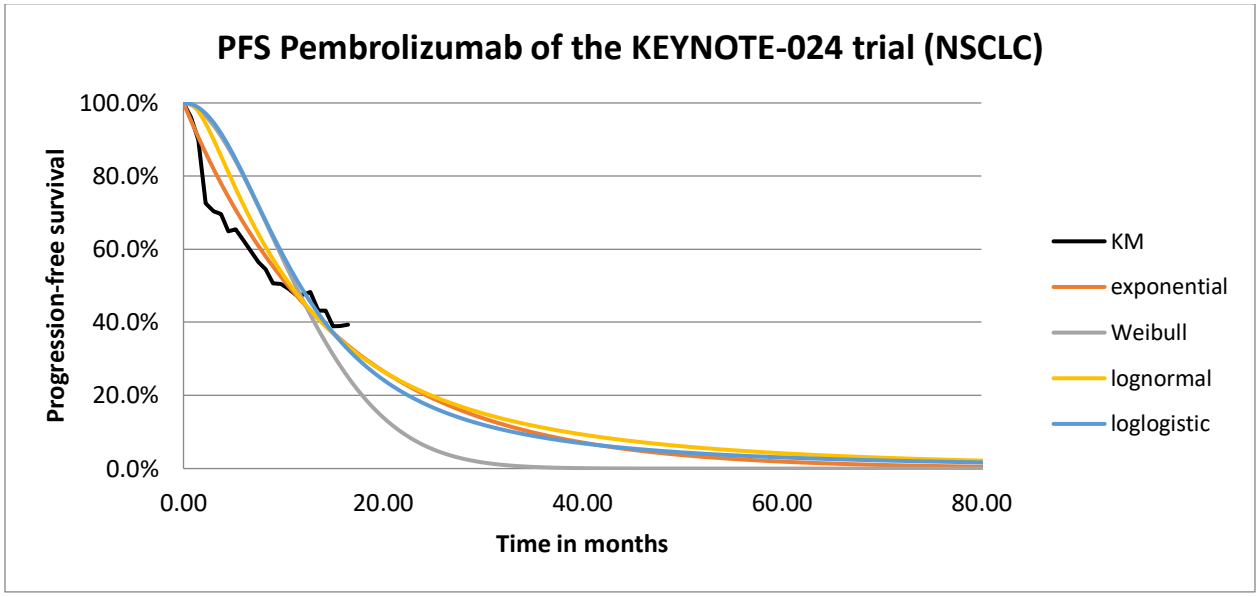
Melanoma	Adjuvant treatment of stage IIb, IIC or stage III melanoma, including patients ≥ 12 years of age	June 2022
	Combination therapy as first line treatment of advanced melanoma with lenvatinib	2023
Metastatic castration-resistant prostate cancer (mCRPC)	Combination therapy as third line treatment of extensively pre-treated mCRPC with olaparib	December 2022
Head & Neck Squamous Cell Carcinoma (HNSCC)	Combination therapy of locally advanced HSNCC with chemoradiation	May 2023

Table S.2: Future indications of pembrolizumab, according to the Farmacotherapeutisch Kompas, accessed January 2022. Abbreviations: MSI-H, microsatellite instability-high; dMMR, mismatch repair deficient.

Chapter 2




OS SoC of the KEYNOTE-024 trial (NSCLC)
Overall survival
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
0.00
50.00
100.00
150.00
200.00
Time in months
KM
exponential
Weibull
lognormal
loglogistic


PFS Pembrolizumab of the KEYNOTE-024 trial (NSCLC)
Progression-free survival
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
0.00
20.00
40.00
60.00
80.00
Time in months
KM
exponential
Weibull
lognormal
loglogistic

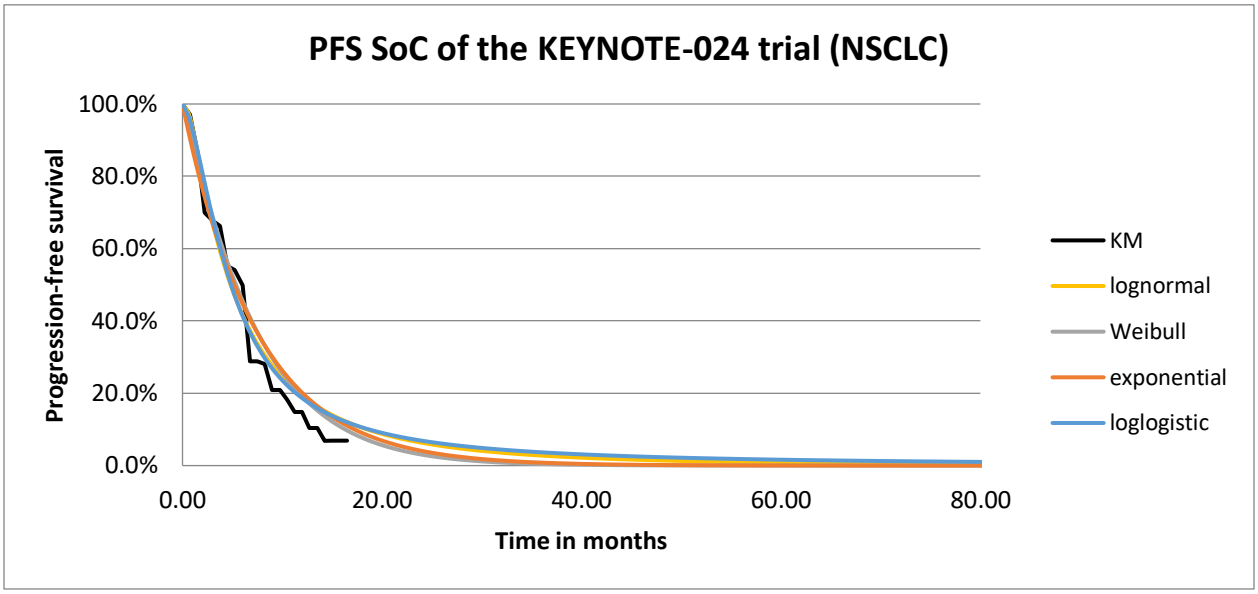


Figure S.1A-D: Original KM curves and their OS and PFS fitted parametric distributions for both treatment arms of the KEYNOTE-024 trial. Abbreviations: NSCLC, non-small cell lung cancer; SoC, standard of care; OS, overall survival; PFS, progression-free survival; KM, Kaplan-Meier.

Inflation percentages by the CBS			
Year 2001/2002	4.10%	**Year 2012/2013**	2.50%
Year 2002/2003	3.30%	**Year 2013/2014**	2.50%
Year 2003/2004	2.10%	**Year 2014/2015**	1.00%
Year 2004/2005	1.30%	**Year 2015/2016**	0.60%
Year 2005/2006	1.70%	**Year 2016/2017**	0.30%
Year 2006/2007	1.10%	**Year 2017/2018**	1.40%
Year 2007/2008	1.60%	**Year 2018/2019**	1.70%
Year 2008/2009	2.50%	**Year 2019/2020**	2.60%
Year 2009/2010	1.20%	**Year 2020/2021**	1.30%
Year 2010/2011	1.30%	**Year 2021/2022**	2.70%
Year 2011/2012	2.30%		

Table S.3: Indexation rates as issued by the Centraal Bureau voor Statistiek (CBS) [54].

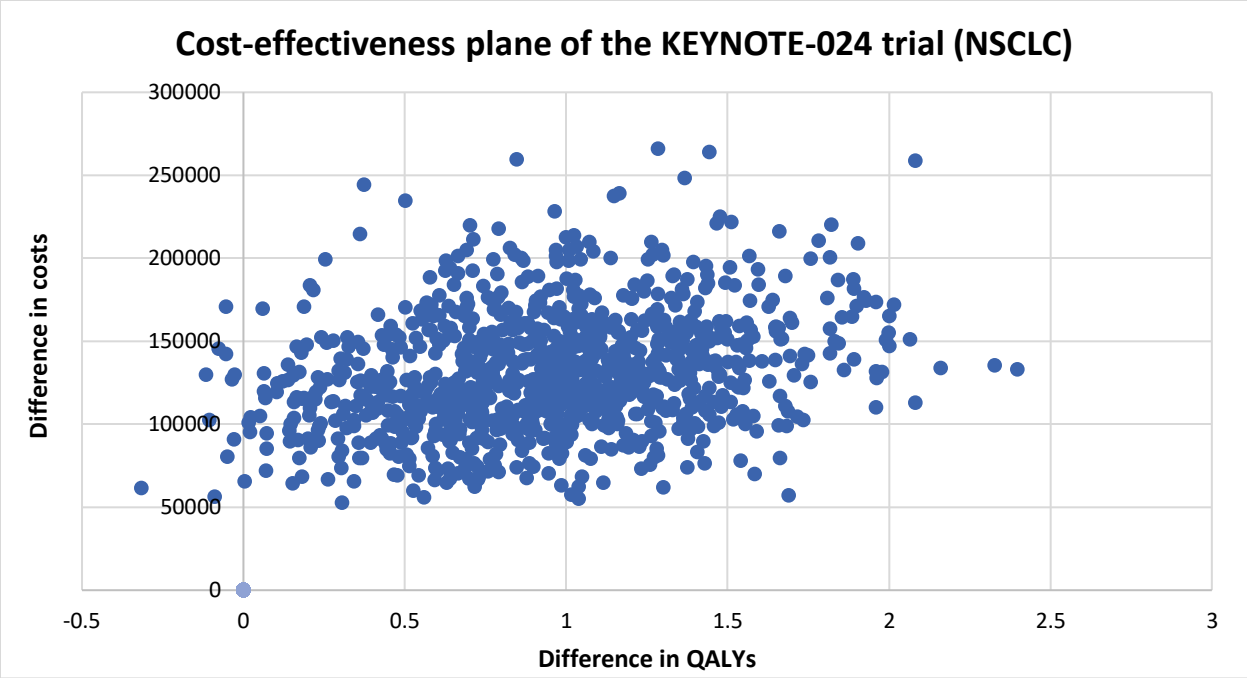


Figure S.2: The cost-effectiveness plane of pembrolizumab versus standard of care of the KEYNOTE-024 trial, depicting differences in QALYs over differences in cost (€). Abbreviations: SoC, standard of care; QALYs, quality-adjusted life years.

Chapter 3

Efficacy inputs

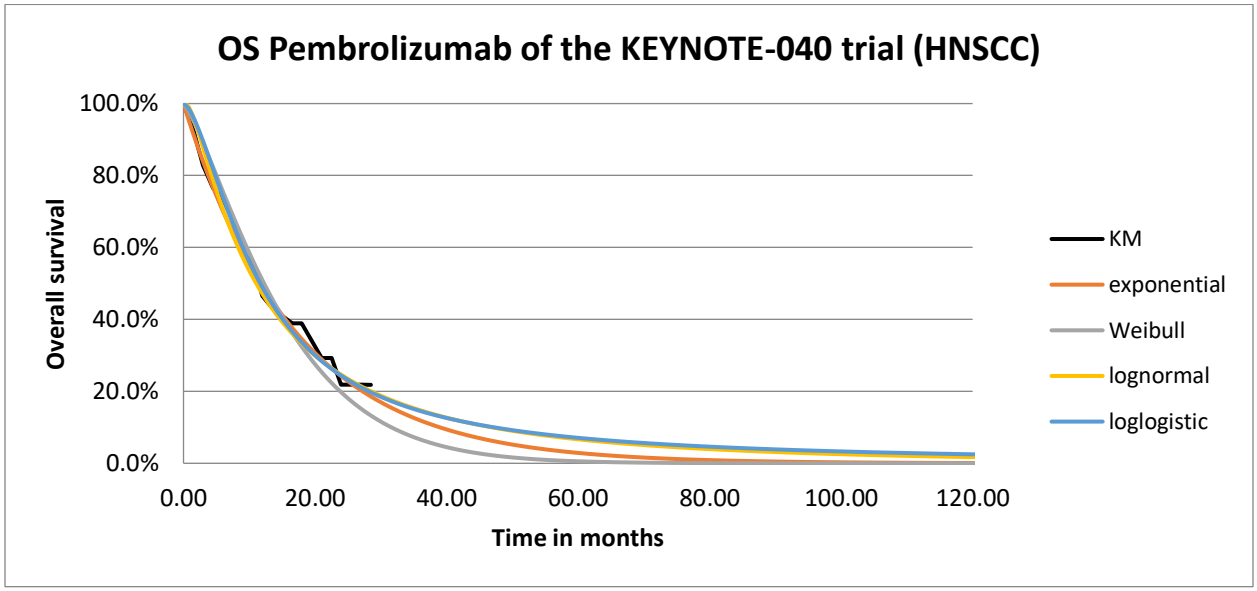
KEYNOTE-040 (HNSCC)

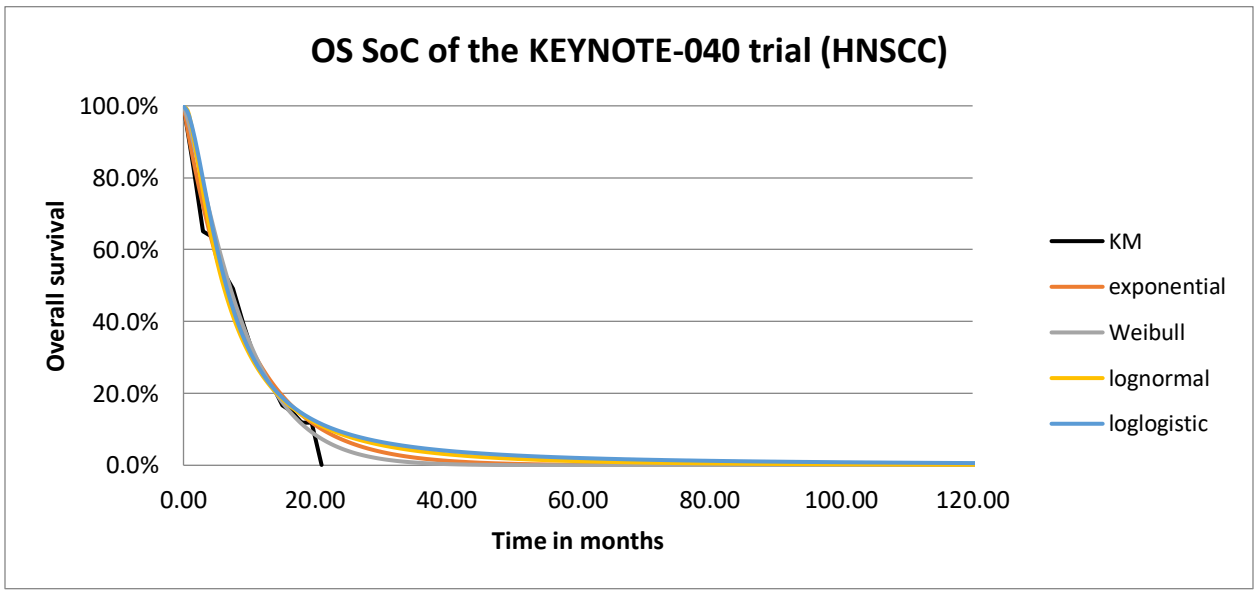
	OS pembrolizumab		OS Standard of Care		PFS pembrolizumab		PFS Standard of Care	
	AIC	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	*277.81*	*284.84*	*419.78*	*426.80*	253.95	260.97	295.21	302.24
Weibull	*276.69*	287.22	*418.01*	428.55	255.86	266.39	297.00	307.54
Lognormal	280.07	290.60	*418.00*	428.54	*241.89*	252.42	267.15	277.69
Loglogistic	279.82	286.84	*418.31*	*425.33*	*240.17*	*247.19*	*260.46*	*267.49*

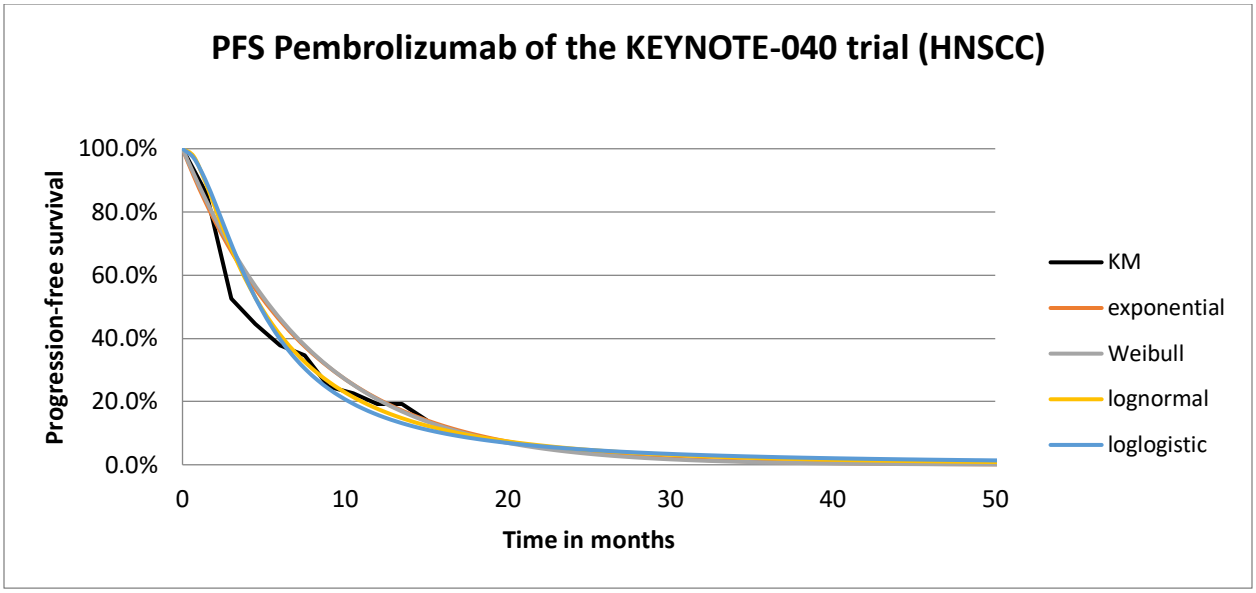
Table S.4: Aikake Information Criterion (AIC) and Bayesian Information Criterion (BIC) values of all four fitted parametric distributions of OS and PFS values of both pembrolizumab and SoC of KEYNOTE-040. Highlighted are the smallest AIC and BIC values of a given set of fitted parametric distributions for each treatment option.

	OS pembrolizumab		OS Standard of Care		PFS pembrolizumab		PFS Standard of Care	
	Intercept	Scale	Intercept	Scale	Intercept	Scale	Intercept	Scale
Exponential	2.8288	-	2.2140	-	2.0361	-	1.6538	-
Weibull	2.7953	-0.2366	2.2505	-0.1882	2.0445	-0.0318	1.6358	0.0402
Lognormal	2.4036	0.1192	1.8020	0.0099	1.5723	-0.0161	1.1722	-0.1196
Loglogistic	2.4575	-0.4530	1.8696	-0.5530	1.5627	-0.5956	1.1243	-0.7458

Table S.5: Intercept and scale of all four fitted parametric distributions of OS and PFS values of both pembrolizumab and SoC of KEYNOTE-040.







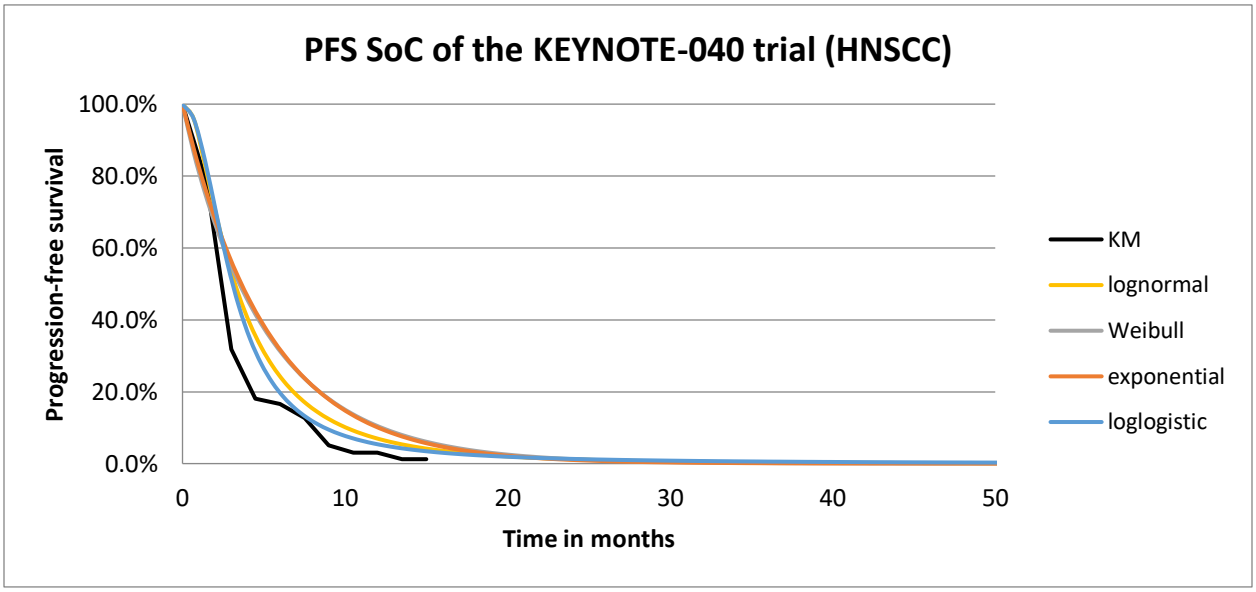


Figure S.3: Original KM curves and their OS and PFS fitted parametric distributions for both treatment arms of the KEYNOTE-040 trial.

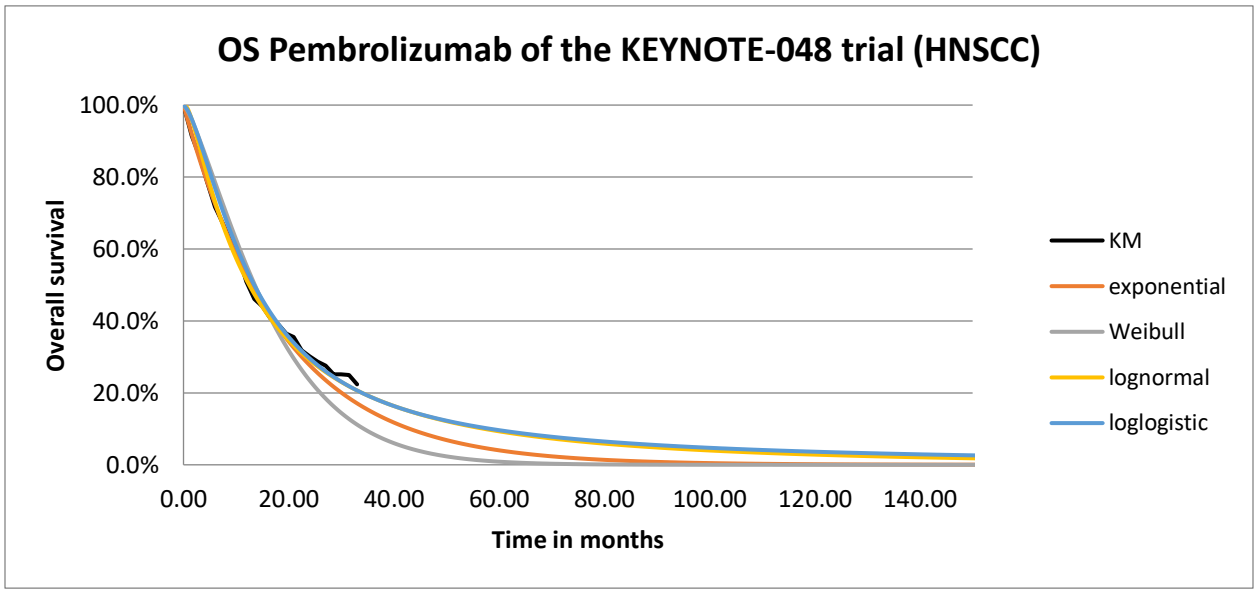
KEYNOTE-048 (HNSCC)

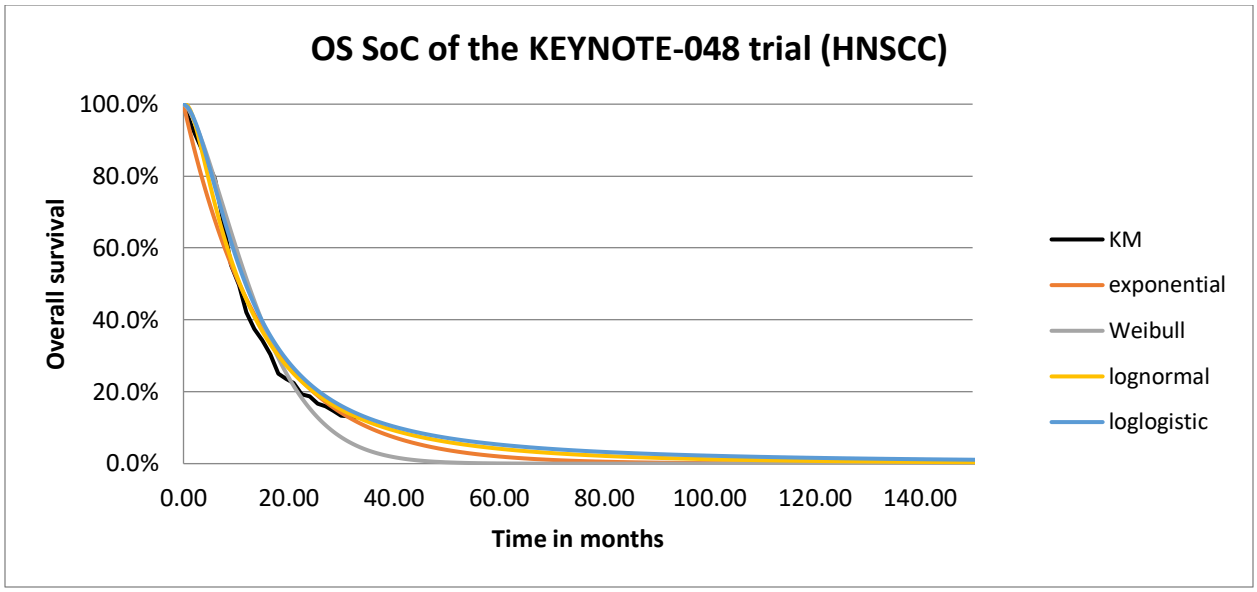
	OS pembrolizumab		OS Standard of Care		PFS pembrolizumab		PFS Standard of Care	
	AIC	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	1201.72	1216.80	1411.91	1419.01	1111.94	1119.36	1540.90	1548.00
Weibull	1189.68	1200.30	*1375.32*	*1385.97*	*1086.68*	*1097.80*	*1450.90*	*1461.55*
Lognormal	*1120.48*	*1131.10*	1425.43	1436.08	1131.28	1142.40	1580.78	1591.43
Loglogistic	1219.31	1226.39	1425.81	1432.91	1136.37	1143.78	1550.51	1557.61

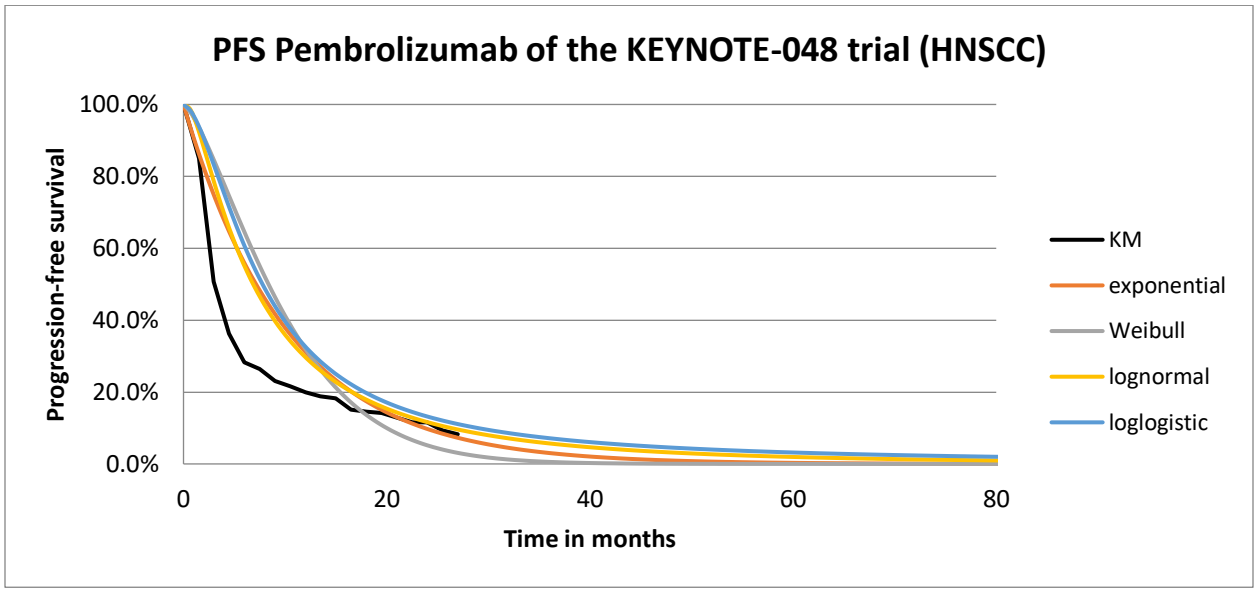
Table S.6: Aikake Information Criterion (AIC) and Bayesian Information Criterion (BIC) values of all four fitted parametric distributions of OS and PFS values of both pembrolizumab and SoC of KEYNOTE-048. Highlighted are the smallest AIC and BIC values of a given set of fitted parametric distributions for each treatment option.

	OS pembrolizumab		OS Standard of Care		PFS pembrolizumab		PFS Standard of Care	
	Intercept	**Scale**	**Intercept**	**Scale**	**Intercept**	**Scale**	**Intercept**	**Scale**
Exponential	2.9271	-	2.7295	-	2.3320	-	2.7738	-
Weibull	2.8900	-0.2578	2.7559	-0.3977	2.3901	-0.3206	2.8455	-0.6492
Lognormal	2.5250	0.1714	2.3726	-0.0066	1.9251	0.0483	2.4751	-0.0267
Loglogistic	2.5975	-0.4031	2.4690	-0.5727	2.0512	-0.5142	2.6700	-0.7464

Table S.7: Intercept and scale of all four fitted parametric distributions of OS and PFS values of both pembrolizumab and SoC of KEYNOTE-048.




OS SoC of the KEYNOTE-048 trial (HNSCC)
Overall survival
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
0.00
20.00
40.00
60.00
80.00
100.00
120.00
140.00
Time in months
KM
exponential
Weibull
lognormal
loglogistic


PFS Pembrolizumab of the KEYNOTE-048 trial (HNSCC)
Progression-free survival
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
0
20
40
60
80
Time in months
KM
exponential
Weibull
lognormal
loglogistic

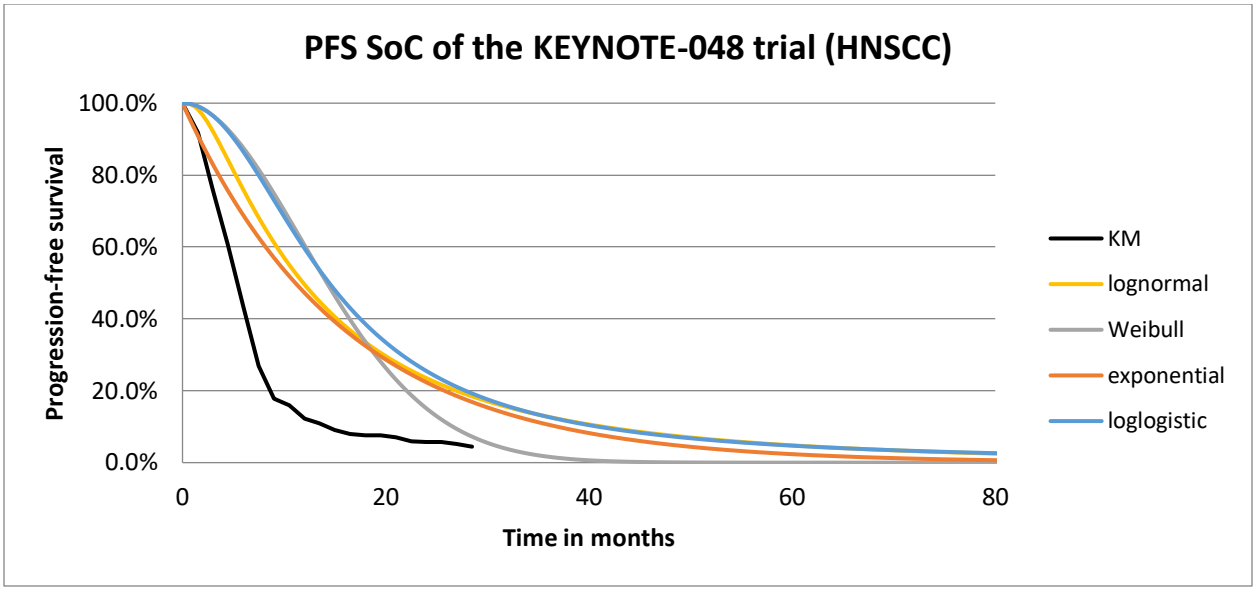


Figure S.4: Original KM curves and their OS and PFS fitted parametric distributions for both treatment arms of the KEYNOTE-048 trial.

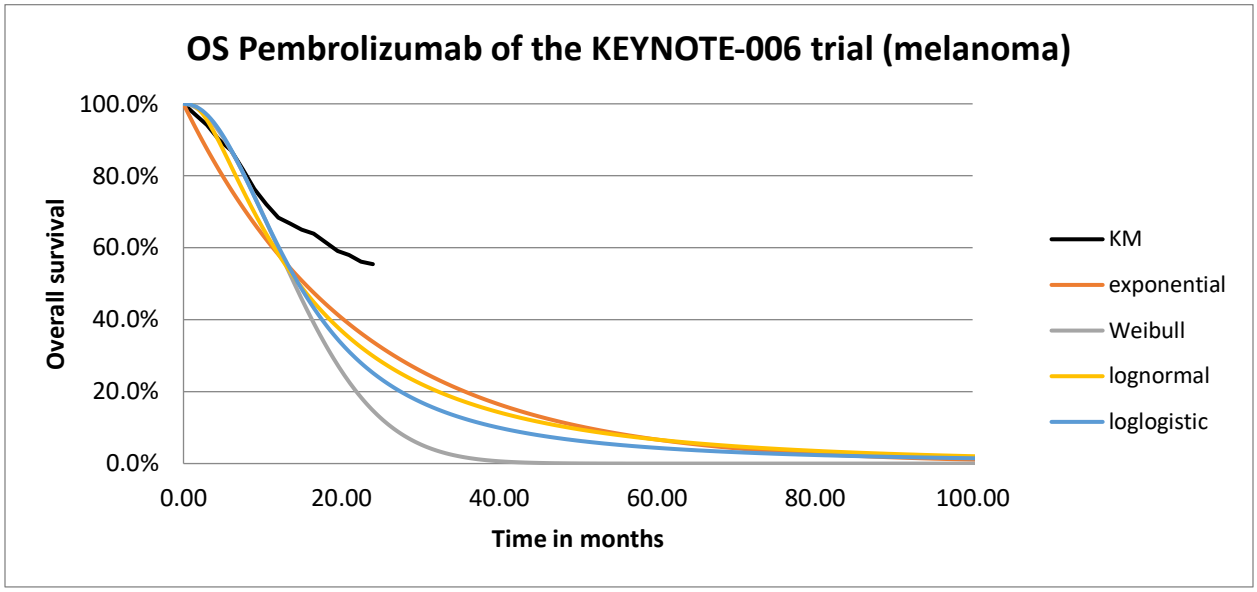
KEYNOTE-006 (melanoma)

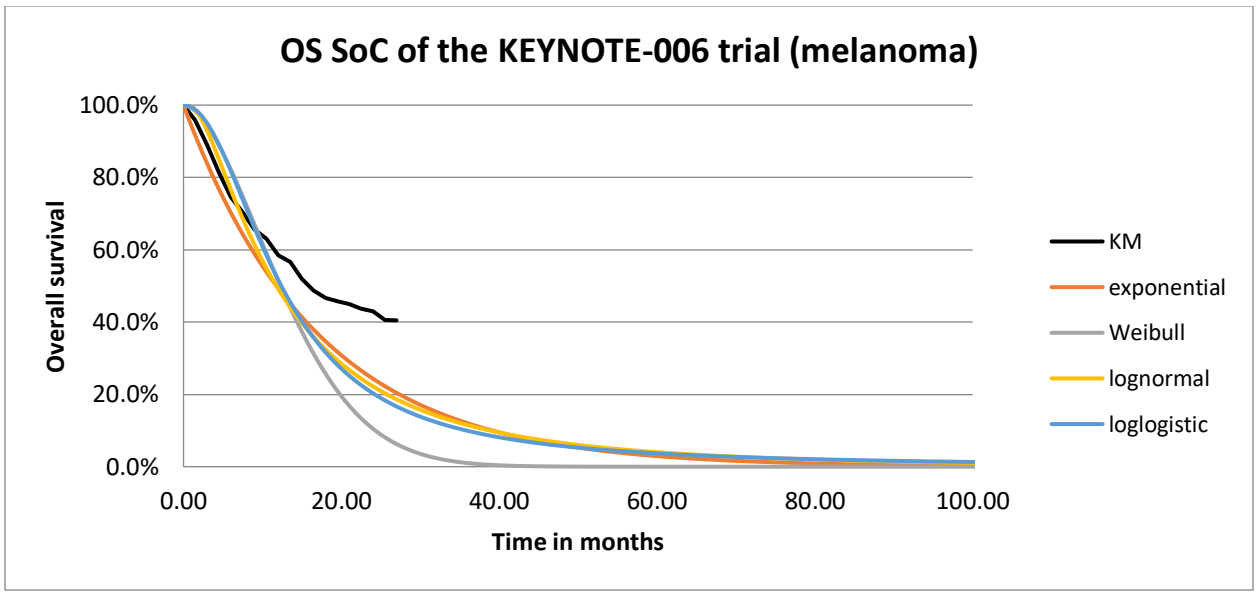
	OS pembrolizumab		OS Standard of Care		PFS pembrolizumab		PFS Standard of Care	
	AIC	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	806.69	813.94	971.22	978.48	862.40	869.65	910.67	917.93
Weibull	760.36	771.23	*923.59*	*934.47*	*836.07*	*846.94*	*901.84*	*912.72*
Lognormal	797.07	807.94	962.96	973.84	860.71	871.58	915.04	925.92
Loglogistic	*679.27*	*686.512*	948.49	955.75	855.78	863.03	924.27	931.53

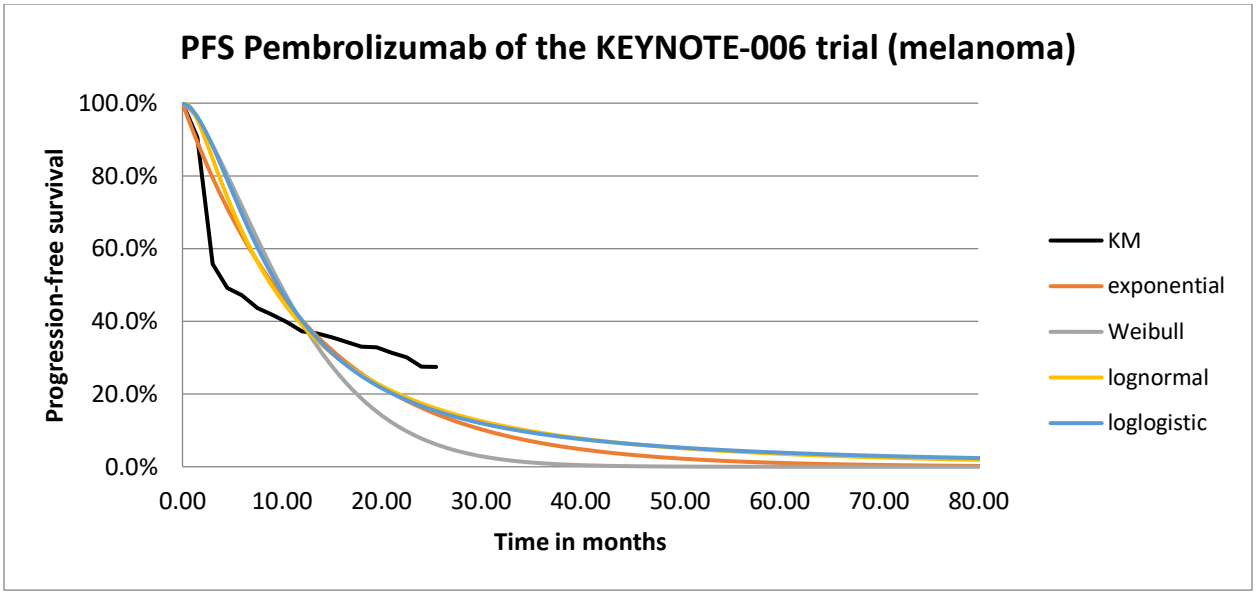
Table S.8: Aikake Information Criterion (AIC) and Bayesian Information Criterion (BIC) values of all four fitted parametric distributions of OS and PFS values of both pembrolizumab and SoC of KEYNOTE-006. Highlighted are the smallest AIC and BIC values of a given set of fitted parametric distributions for each treatment option.

	OS pembrolizumab		OS Standard of Care		PFS pembrolizumab		PFS Standard of Care	
	Intercept	**Scale**	**Intercept**	**Scale**	**Intercept**	**Scale**	**Intercept**	**Scale**
Exponential	3.0983	-	2.8330	-	2.5808	-	2.3062	-
Weibull	2.8362	-0.6411	2.7168	-0.5647	2.5382	-0.3806	2.3308	-0.2051
Lognormal	2.6827	-0.0612	2.4666	-0.0718	2.1898	0.0549	1.8479	0.1092
Loglogistic	2.6795	-0.7800	2.5181	-0.7276	2.2595	-0.5575	1.9248	-0.4218

Table S.9: Intercept and scale of all four fitted parametric distributions of OS and PFS values of both pembrolizumab and SoC of KEYNOTE-006.


OS Pembrolizumab of the KEYNOTE-006 trial (melanoma)
Overall survival
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
0.00
20.00
40.00
60.00
80.00
100.00
Time in months
KM
exponential
Weibull
lognormal
loglogistic


OS SoC of the KEYNOTE-006 trial (melanoma)
Overall survival
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
0.00
20.00
40.00
60.00
80.00
100.00
Time in months
KM
exponential
Weibull
lognormal
loglogistic



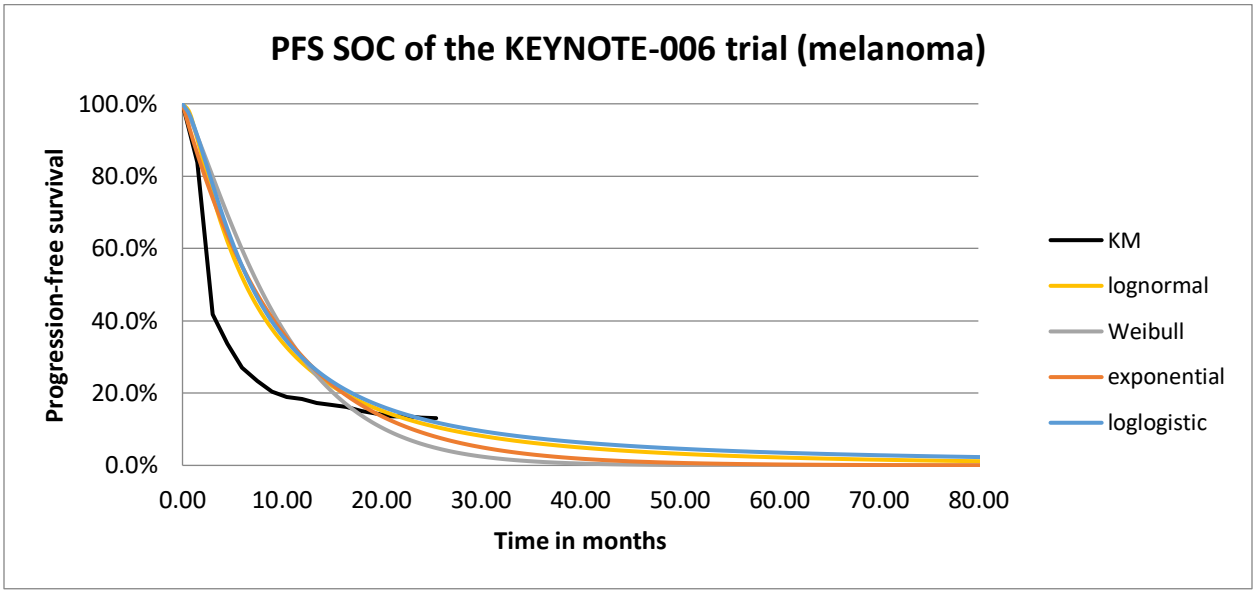


Figure S.5: Original KM curves and their OS and PFS fitted parametric distributions for both treatment arms of the KEYNOTE-006 trial.

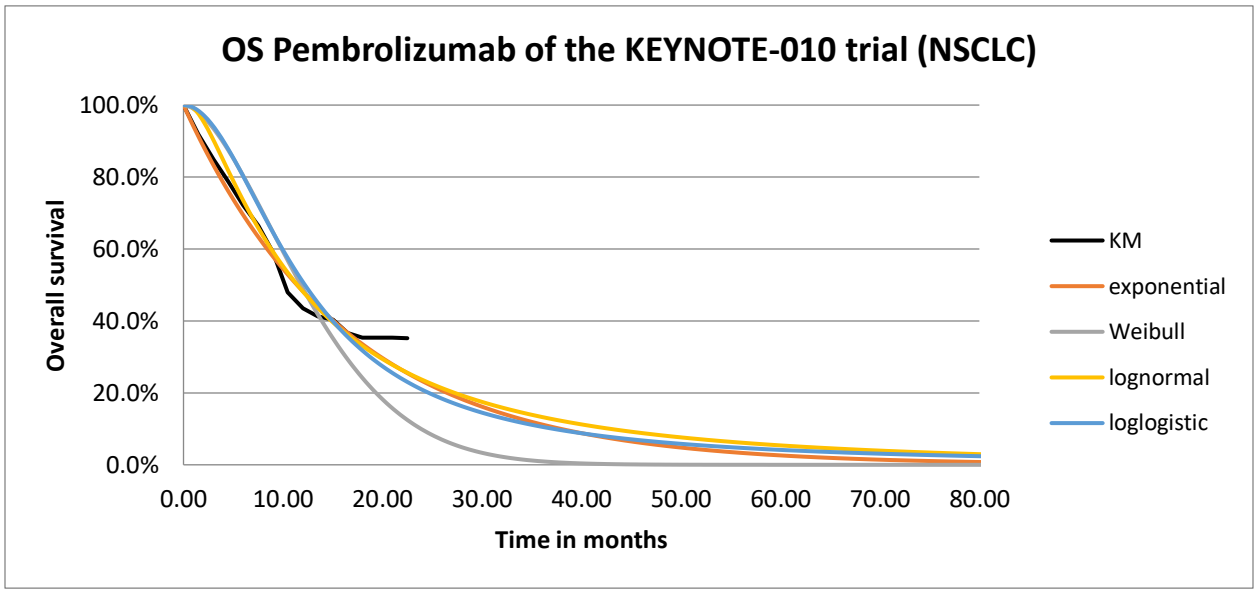
KEYNOTE-010 (NSCLC)

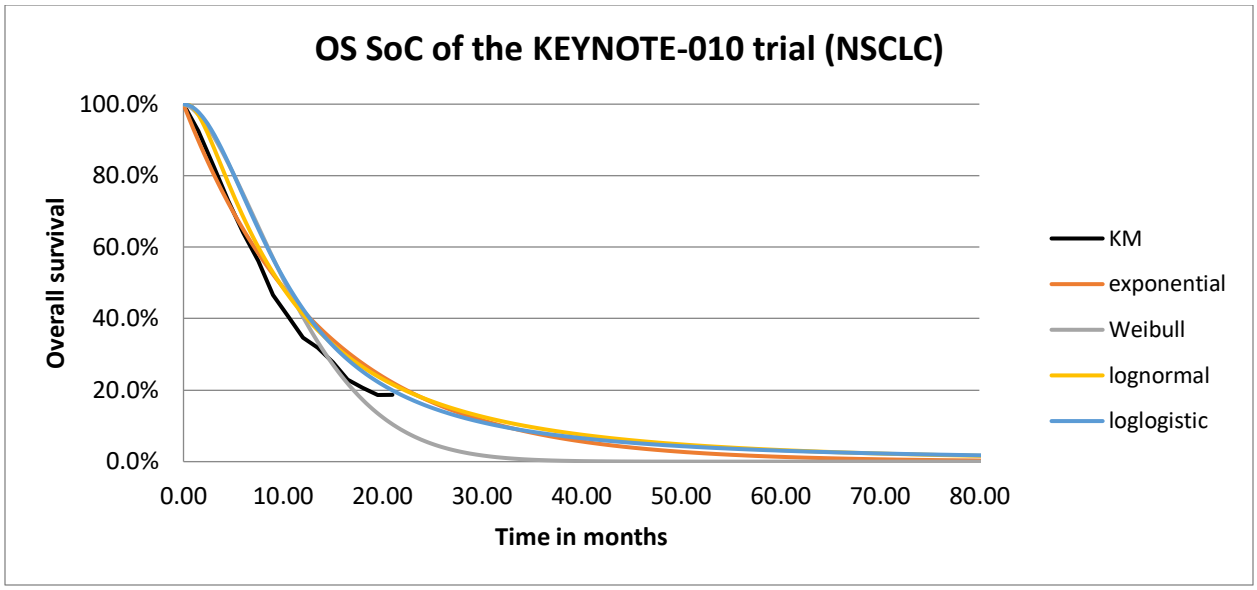
	OS pembrolizumab		OS Standard of Care		PFS pembrolizumab		PFS Standard of Care	
	AIC	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	1348.79	1356.47	1279.74	1287.41	1205.77	1213.18	1350.72	1358.40
Weibull	*1290.66*	*1302.19*	*1227.62*	*1239.13*	1172.54	1183.66	*1305.15*	*1316.67*
Lognormal	1357.12	1368.65	1276.55	1288.07	1110.79	1121.91	1332.86	1344.38
Loglogistic	1328.90	1336.59	1257.95	1265.62	*1105.20*	*1112.61*	1336.17	1343.84

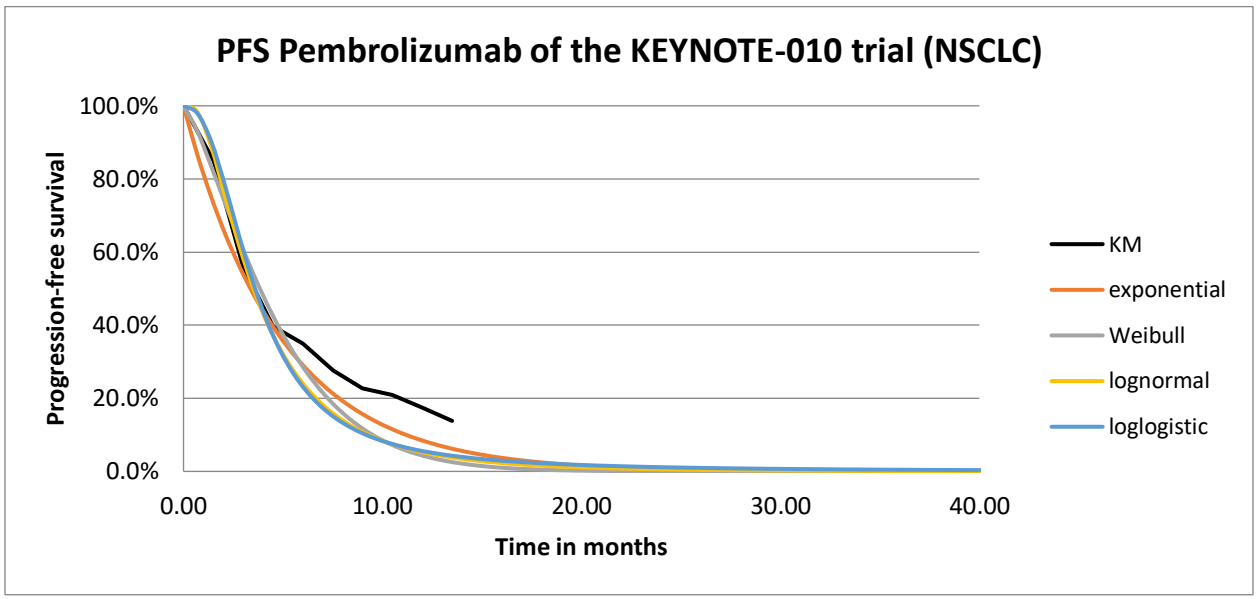
Table S.10: Aikake Information Criterion (AIC) and Bayesian Information Criterion (BIC) values of all four fitted parametric distributions of OS and PFS values of both pembrolizumab and SoC of KEYNOTE-010. Highlighted are the smallest AIC and BIC values of a given set of fitted parametric distributions for each treatment option.

	OS pembrolizumab		OS Standard of Care		PFS pembrolizumab		PFS Standard of Care	
	Intercept	**Scale**	**Intercept**	**Scale**	**Intercept**	**Scale**	**Intercept**	**Scale**
Exponential	2.8010	-	2.6338	-	1.5801	-	2.0161	-
Weibull	2.6834	-0.5334	2.5477	-0.4938	1.6218	-0.2820	2.0618	-0.3648
Lognormal	2.4379	0.0298	2.2685	-0.0107	1.2562	-0.2757	1.6667	-0.0812
Loglogistic	2.5016	-0.6793	2.3359	-0.6738	1.2802	-0.8534	1.7597	-0.6469

Table S.11: Intercept and scale of all four fitted parametric distributions of OS and PFS values of both pembrolizumab and SoC of KEYNOTE-010.




OS SoC of the KEYNOTE-010 trial (NSCLC)
Overall survival
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
0.00
10.00
20.00
30.00
40.00
50.00
60.00
70.00
80.00
Time in months
KM
exponential
Weibull
lognormal
loglogistic


PFS Pembrolizumab of the KEYNOTE-010 trial (NSCLC)
Progression-free survival
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
0.00
10.00
20.00
30.00
40.00
Time in months
KM
exponential
Weibull
lognormal
loglogistic

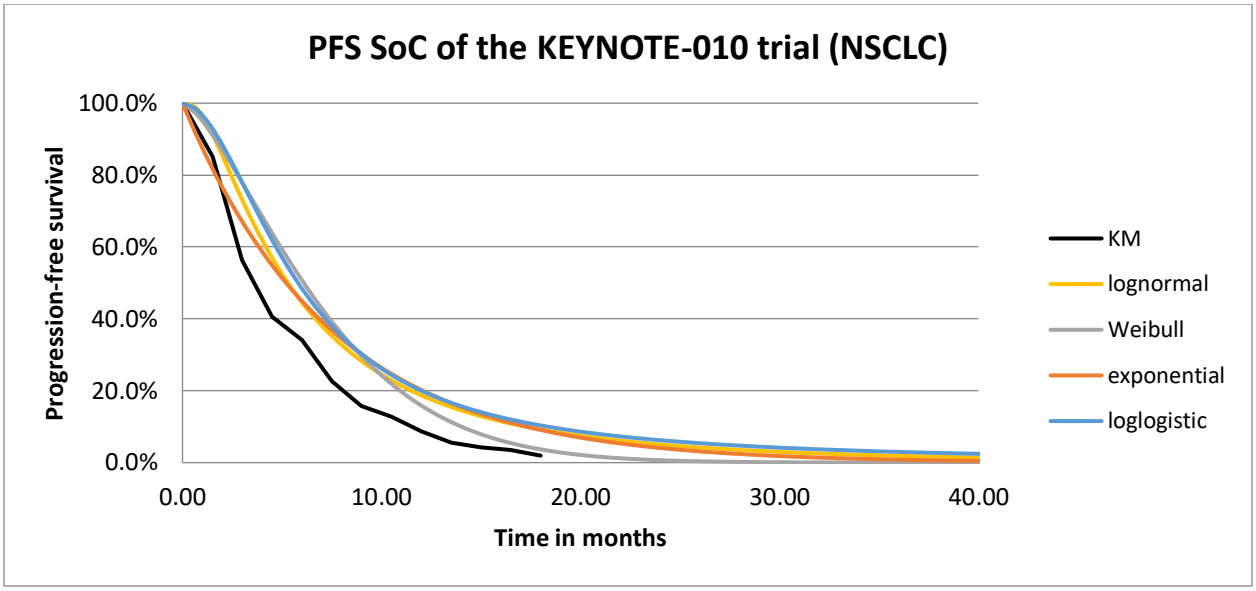


Figure S.6: Original KM curves and their OS and PFS fitted parametric distributions for both treatment arms of the KEYNOTE-010 trial.

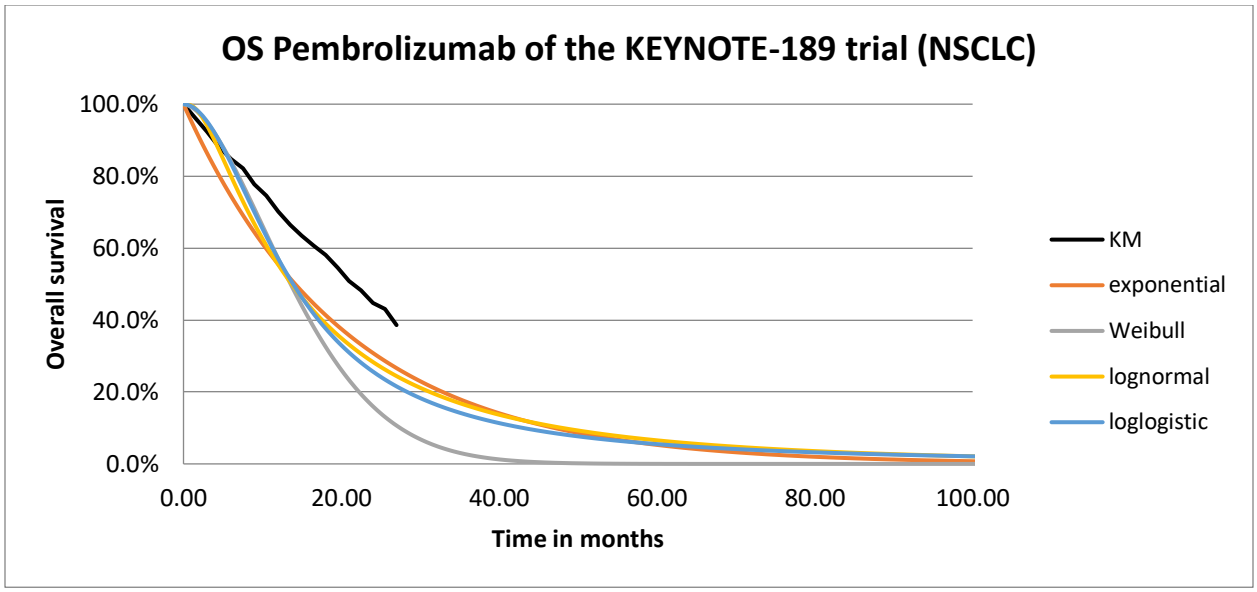
KEYNOTE-189 (NSCLC)

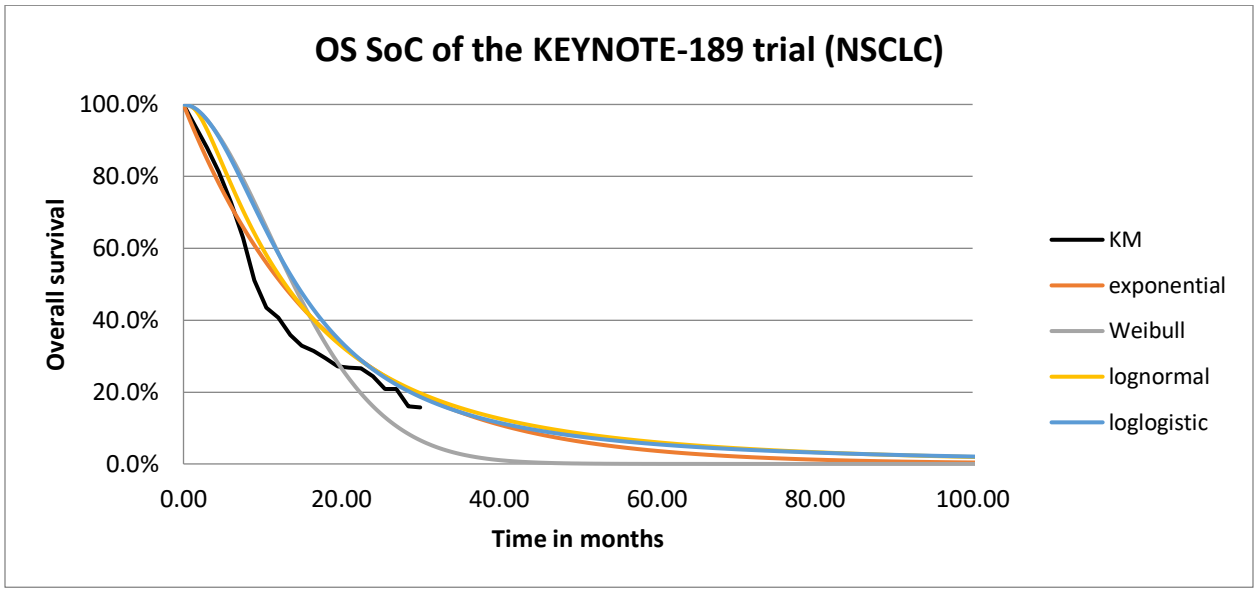
	OS pembrolizumab		OS Standard of Care		PFS pembrolizumab		PFS Standard of Care	
	AIC	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	1550.88	1558.92	1302.00	1309.28	1949.44	1957.47	1567.01	1574.29
Weibull	*1488.82*	*1500.87*	*1240.70*	*1251.62*	*1893.61*	*1905.65*	*1521.40*	*1532.32*
Lognormal	1533.73	1545.78	1316.33	1327.25	1980.90	1992.94	1618.56	1629.48
Loglogistic	1517.84	1525.88	1294.46	1301.74	1970.95	1978.98	1609.93	1617.21

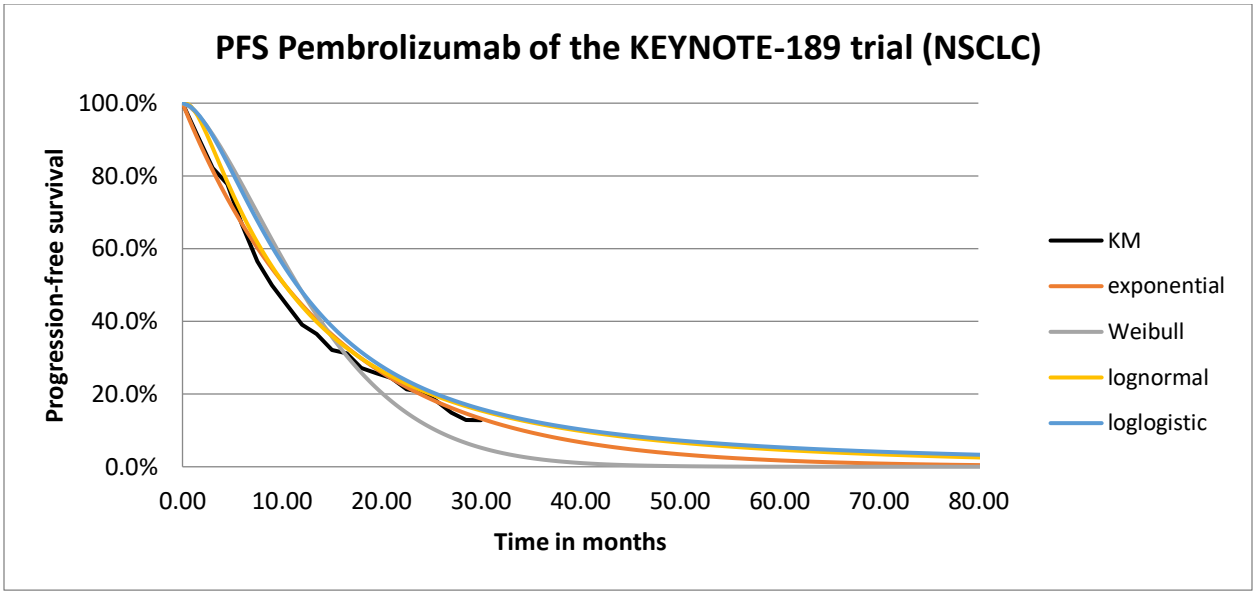
Table S.12: Aikake Information Criterion (AIC) and Bayesian Information Criterion (BIC) values of all four fitted parametric distributions of OS and PFS values of both pembrolizumab and SoC of KEYNOTE-189. Highlighted are the smallest AIC and BIC values of a given set of fitted parametric distributions for each treatment option.

	OS pembrolizumab		OS Standard of Care		PFS pembrolizumab		PFS Standard of Care	
	Intercept	**Scale**	**Intercept**	**Scale**	**Intercept**	**Scale**	**Intercept**	**Scale**
Exponential	3.0158	-	3.0180	-	2.2976	-	2.0136	-
Weibull	2.8233	-0.5339	2.9224	-0.6004	2.6909	-0.4202	2.0915	-0.0764
Lognormal	2.6180	-0.0223	2.6677	-0.0335	2.3315	0.0511	1.5746	0.0477
Loglogistic	2.6312	-0.6646	2.7414	-0.7388	2.4429	-0.5523	1.5824	-0.4899

Table S.13: Intercept and scale of all four fitted parametric distributions of OS and PFS values of both pembrolizumab and SoC of KEYNOTE-189.


OS Pembrolizumab of the KEYNOTE-189 trial (NSCLC)
Overall survival
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
0.00
20.00
40.00
60.00
80.00
100.00
Time in months
KM
exponential
Weibull
lognormal
loglogistic


OS SoC of the KEYNOTE-189 trial (NSCLC)
Overall survival
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
0.00
20.00
40.00
60.00
80.00
100.00
Time in months
KM
exponential
Weibull
lognormal
loglogistic



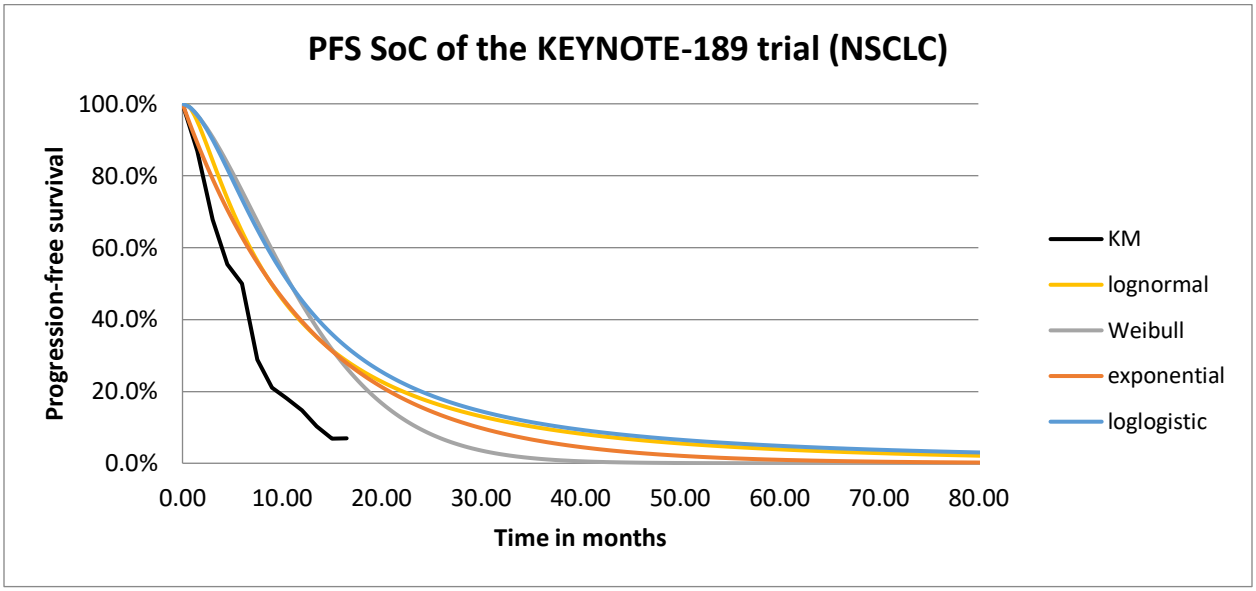


Figure S.7: Original KM curves and their OS and PFS fitted parametric distributions for both treatment arms of the KEYNOTE-189 trial.

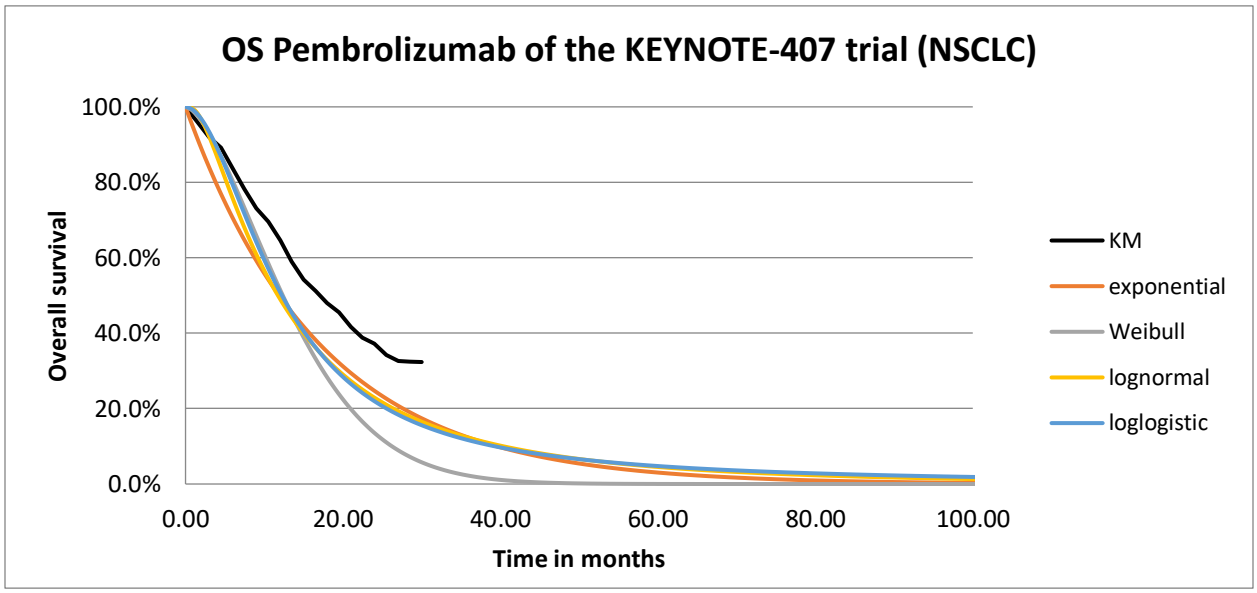
KEYNOTE-407 (NSCLC)

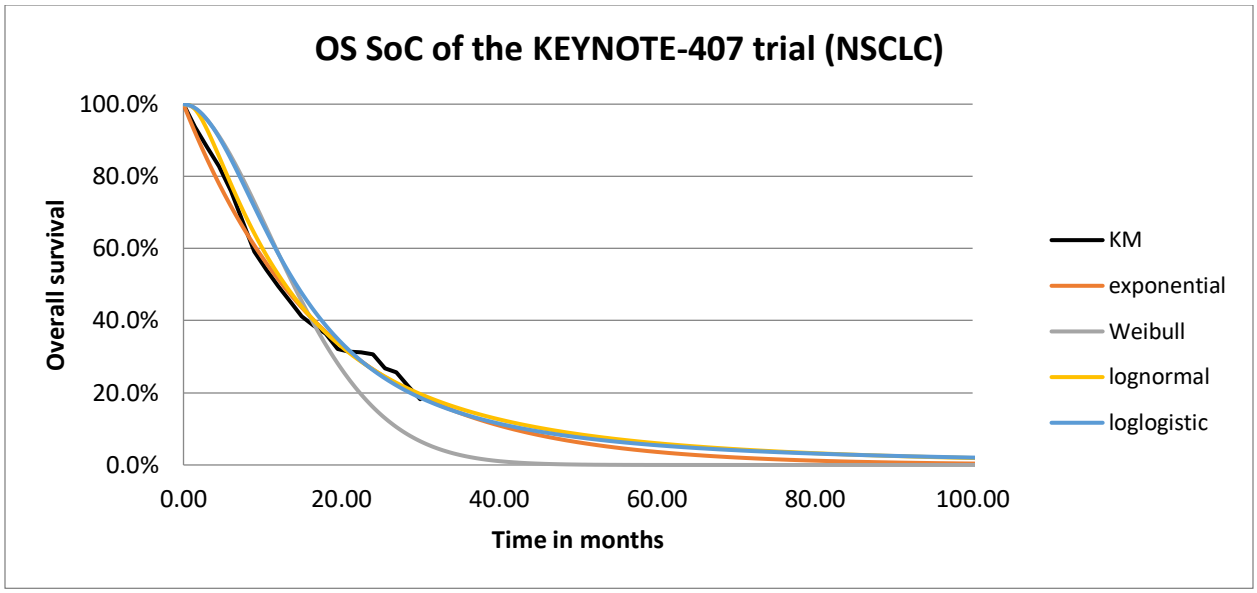
	OS pembrolizumab		OS Standard of Care		PFS pembrolizumab		PFS Standard of Care	
	AIC	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	1168.20	1175.46	1302.00	1309.28	1475.68	1482.93	1567.01	1574.29
Weibull	*1128.73*	*1139.61*	*1240.70*	*1251.62*	*1413.27*	*1424.15*	*1521.40*	*1532.32*
Lognormal	1157.89	1168.77	1316.33	1327.25	1502.94	1513.83	1618.56	1629.48
Loglogistic	1151.97	1159.23	1294.46	1301.74	1483.72	1490.97	1609.93	1617.21

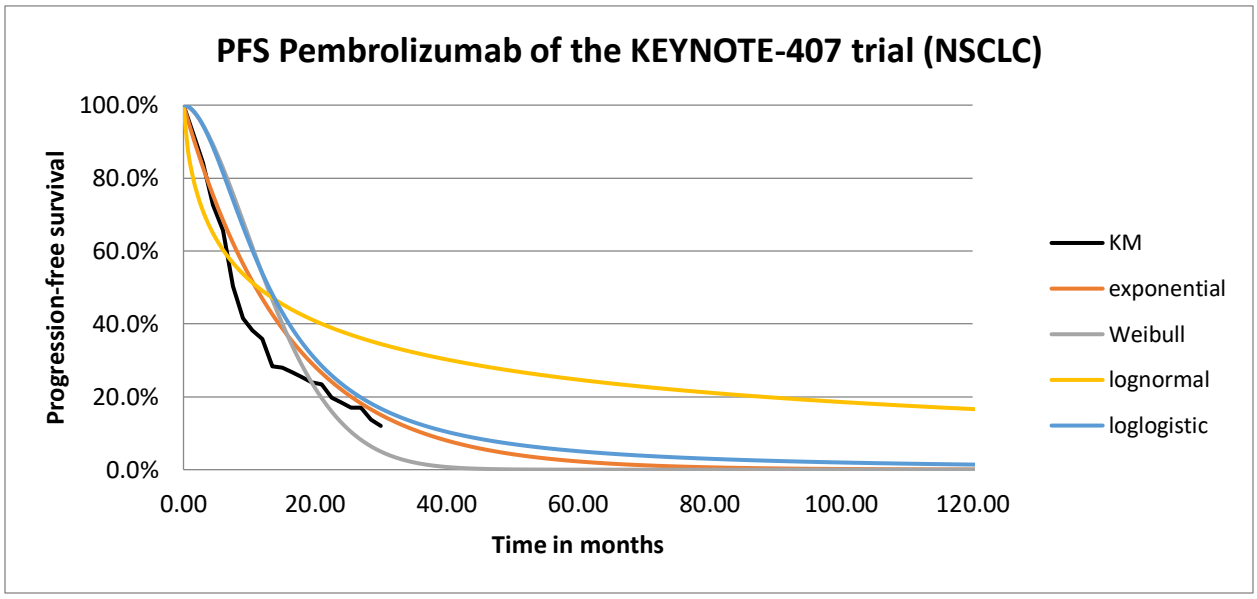
Table S.14: Aikake Information Criterion (AIC) and Bayesian Information Criterion (BIC) values of all four fitted parametric distributions of OS and PFS values of both pembrolizumab and SoC of KEYNOTE-407. Highlighted are the smallest AIC and BIC values of a given set of fitted parametric distributions for each treatment option.

	OS pembrolizumab		OS Standard of Care		PFS pembrolizumab		PFS Standard of Care	
	Intercept	**Scale**	**Intercept**	**Scale**	**Intercept**	**Scale**	**Intercept**	**Scale**
Exponential	2.8431	-	2.8945	-	2.7624	-	2.5585	-
Weibull	2.7437	-0.4669	2.8394	-0.5775	2.7614	-0.5406	2.6193	-0.4323
Lognormal	2.4627	-0.0368	2.5550	-0.0085	2.4289	0.8894	2.1888	0.07609
Loglogistic	2.5047	-0.6335	2.6597	-0.6864	2.5648	-0.6502	2.3762	-0.5493

Table S.15: Intercept and scale of all four fitted parametric distributions of OS and PFS values of both pembrolizumab and SoC of KEYNOTE-407.




OS SoC of the KEYNOTE-407 trial (NSCLC)
Overall survival
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
0.00
20.00
40.00
60.00
80.00
100.00
Time in months
KM
exponential
Weibull
lognormal
loglogistic


PFS Pembrolizumab of the KEYNOTE-407 trial (NSCLC)
Progression-free survival
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
0.00
20.00
40.00
60.00
80.00
100.00
120.00
Time in months
KM
exponential
Weibull
lognormal
loglogistic

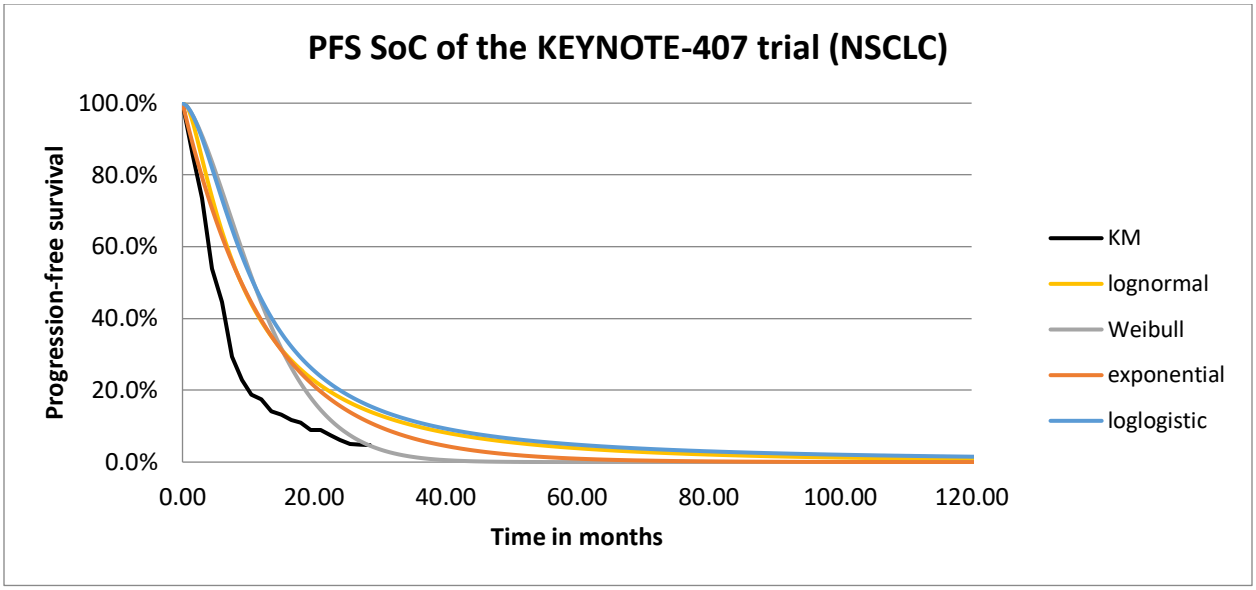


Figure S.8: Original KM curves and their OS and PFS fitted parametric distributions for both treatment arms of the KEYNOTE-407 trial.

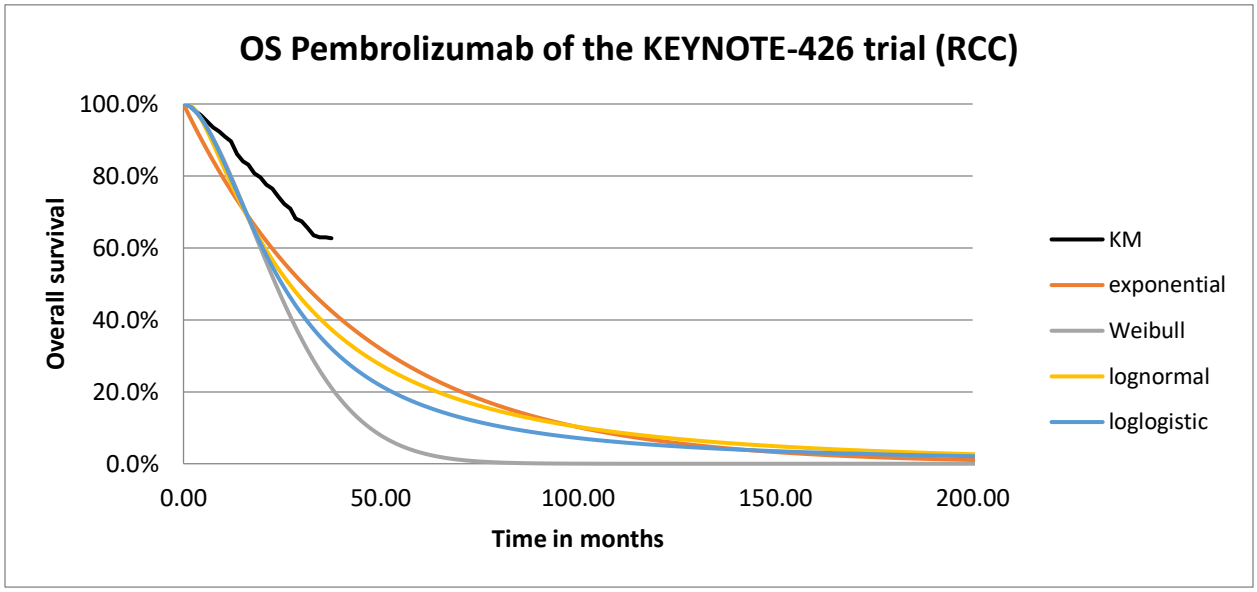
KEYNOTE-426 (RCC)

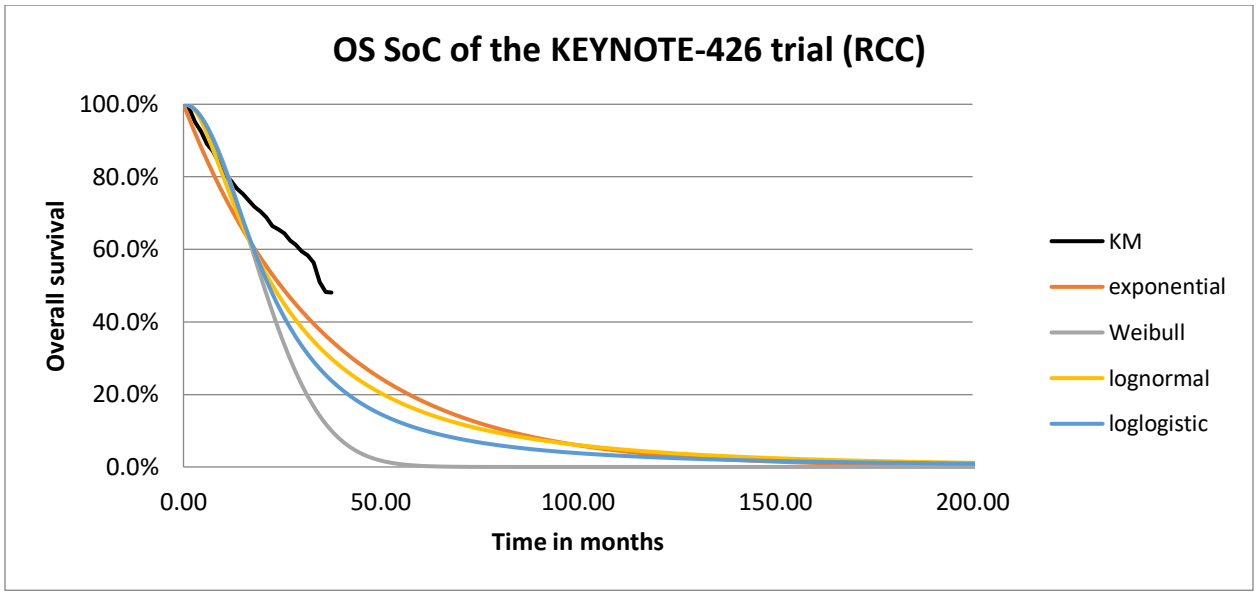
	OS pembrolizumab		OS Standard of Care		PFS pembrolizumab		PFS Standard of Care	
	AIC	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	1228.31	1236.45	1397.77	1405.89	1687.44	1695.58	1752.42	1760.54
Weibull	*1193.09*	*1205.30*	*1329.24*	*1341.42*	*1597.16*	*1609.37*	*1662.03*	*1674.21*
Lognormal	1202.90	1215.11	1371.29	1383.48	1637.77	1649.98	1736.39	1748.58
Loglogistic	1198.78	1206.91	1350.80	1358.92	1631.13	1639.26	1715.28	1723.40

Table S.16: Aikake Information Criterion (AIC) and Bayesian Information Criterion (BIC) values of all four fitted parametric distributions of OS and PFS values of both pembrolizumab and SoC of KEYNOTE-426. Highlighted are the smallest AIC and BIC values of a given set of fitted parametric distributions for each treatment option.

	OS pembrolizumab		OS Standard of Care		PFS pembrolizumab		PFS Standard of Care	
	Intercept	**Scale**	**Intercept**	**Scale**	**Intercept**	**Scale**	**Intercept**	**Scale**
Exponential	3.7790	-	3.5695	-	3.0554	-	2.9010	-
Weibull	3.3652	-0.5332	3.1984	-0.6716	2.9340	-0.5965	2.8584	-0.5665
Lognormal	3.2889	0.0384	3.1178	-0.0422	2.6833	-0.1574	2.5624	-0.0856
Loglogistic	3.2174	-0.6147	3.0727	-0.7456	2.7214	-0.7536	2.6365	-0.7305

Table S.17: Intercept and scale of all four fitted parametric distributions of OS and PFS values of both pembrolizumab and SoC of KEYNOTE-426.


OS Pembrolizumab of the KEYNOTE-426 trial (RCC)
Overall survival
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
0.00
50.00
100.00
150.00
200.00
Time in months
KM
exponential
Weibull
lognormal
loglogistic


OS SoC of the KEYNOTE-426 trial (RCC)
Overall survival
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
0.00
50.00
100.00
150.00
200.00
Time in months
KM
exponential
Weibull
lognormal
loglogistic

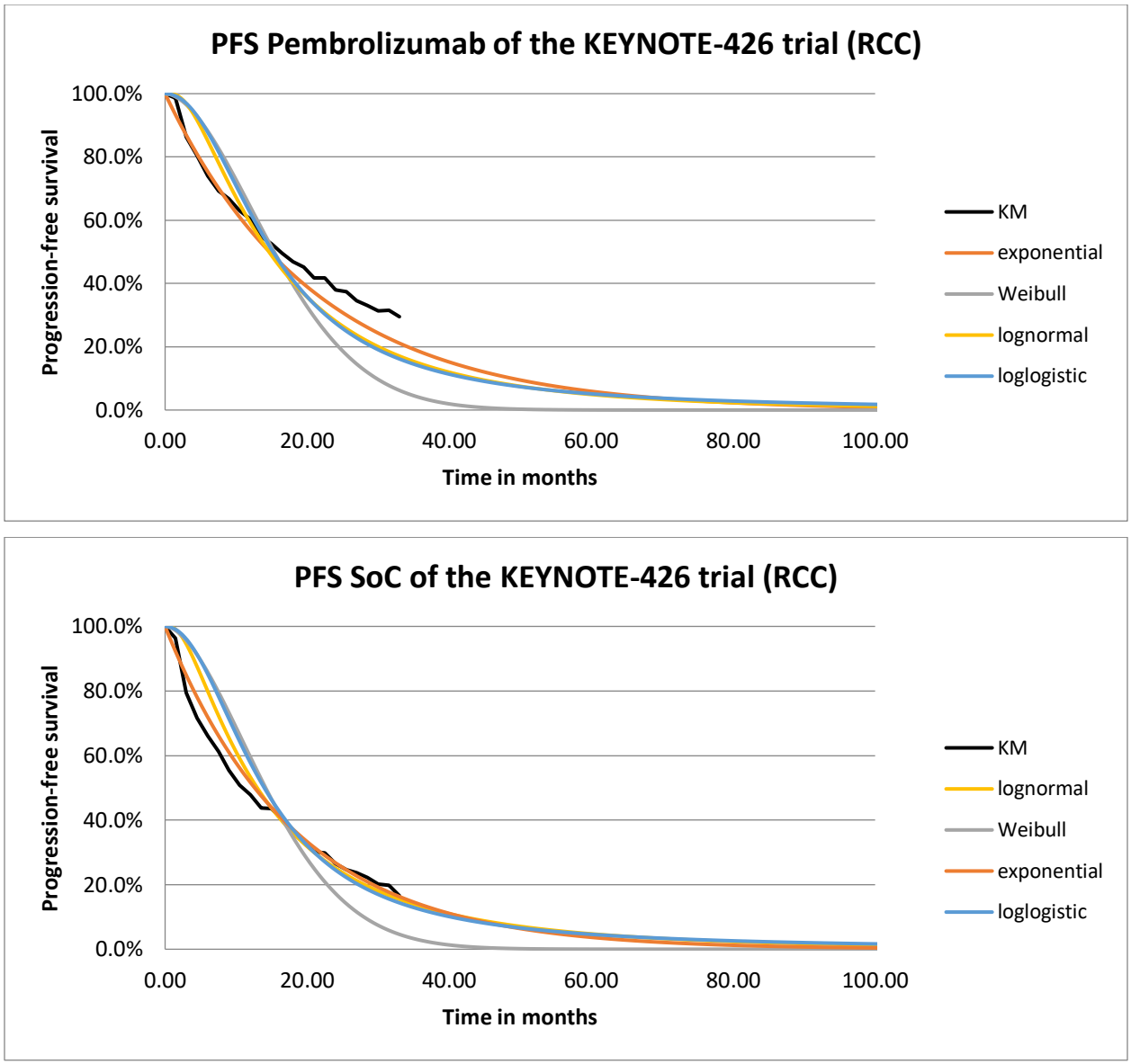


Figure S.9: Original KM curves and their OS and PFS fitted parametric distributions for both treatment arms of the KEYNOTE-426 trial.

Results

KEYNOTE-040 (HNSCC)

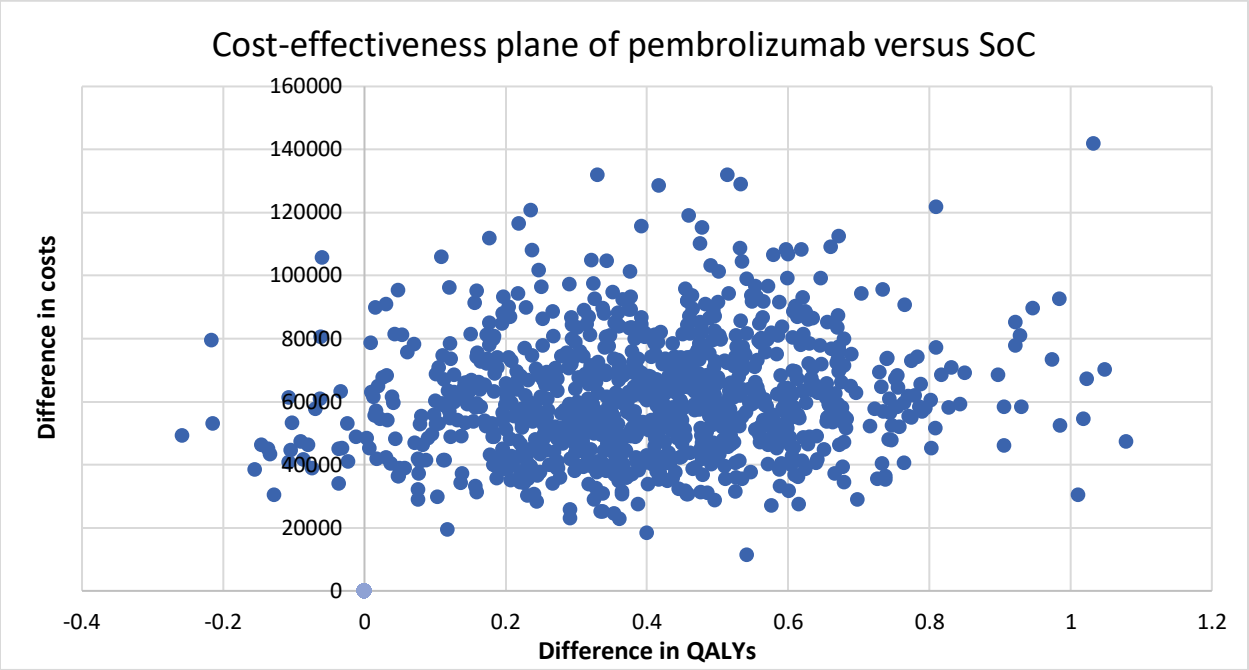


Figure S.10: the cost-effectiveness plane of pembrolizumab versus standard of care of KEYNOTE-040, depicting differences in QALYs over differences in cost (€). Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

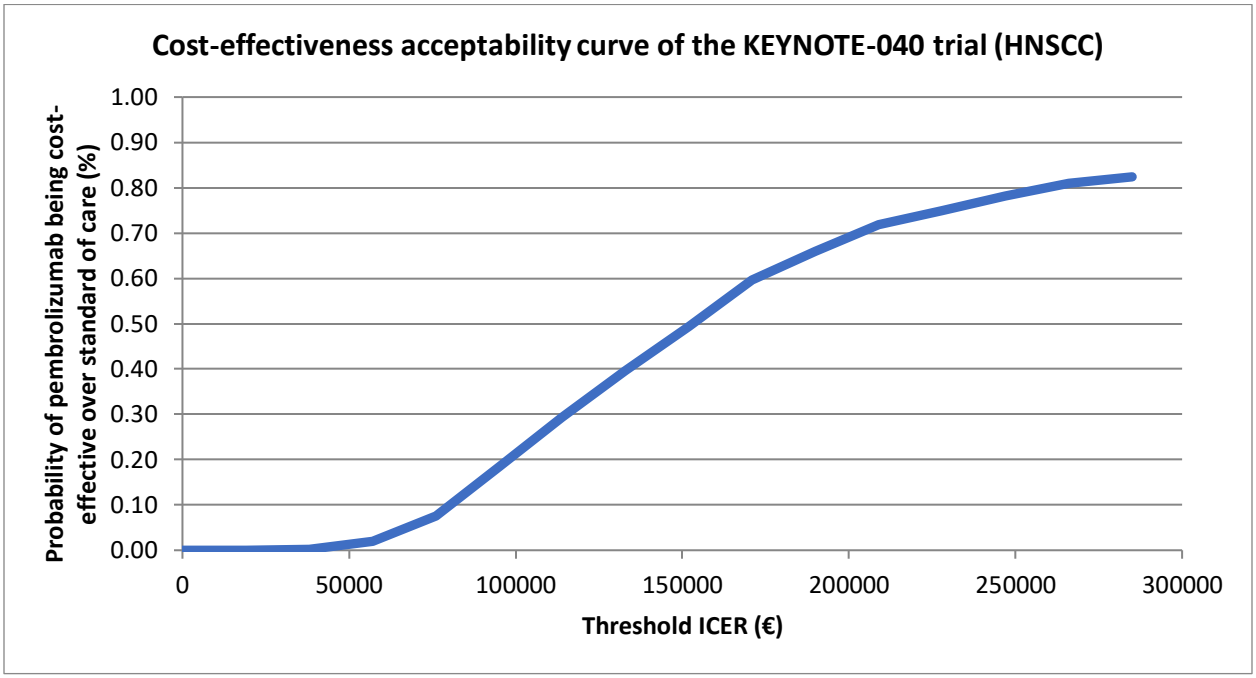


Figure S.11: The cost-effectiveness acceptability curve (CEAC) of pembrolizumab versus standard of care of the KEYNOTE-040 trial.

KEYNOTE-048 (HNSCC)

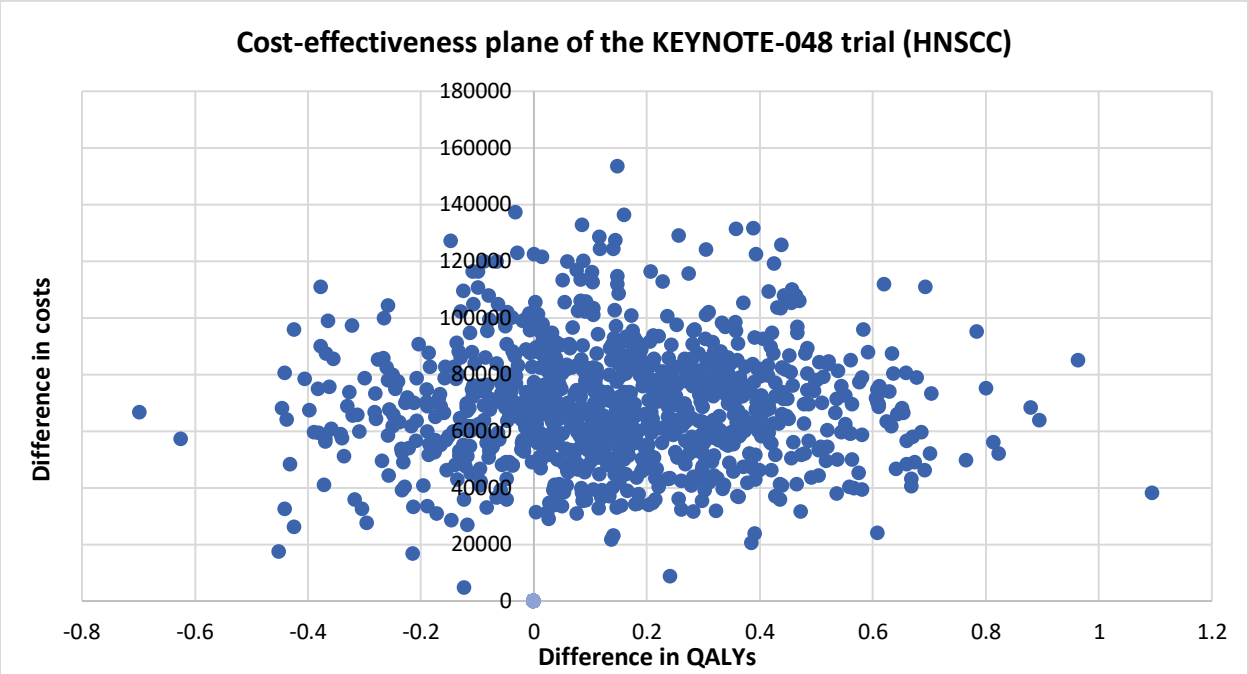


Figure S.12: The cost-effectiveness plane of pembrolizumab versus standard of care of the KEYNOTE-048 trial, depicting differences in QALYs over differences in cost (€).

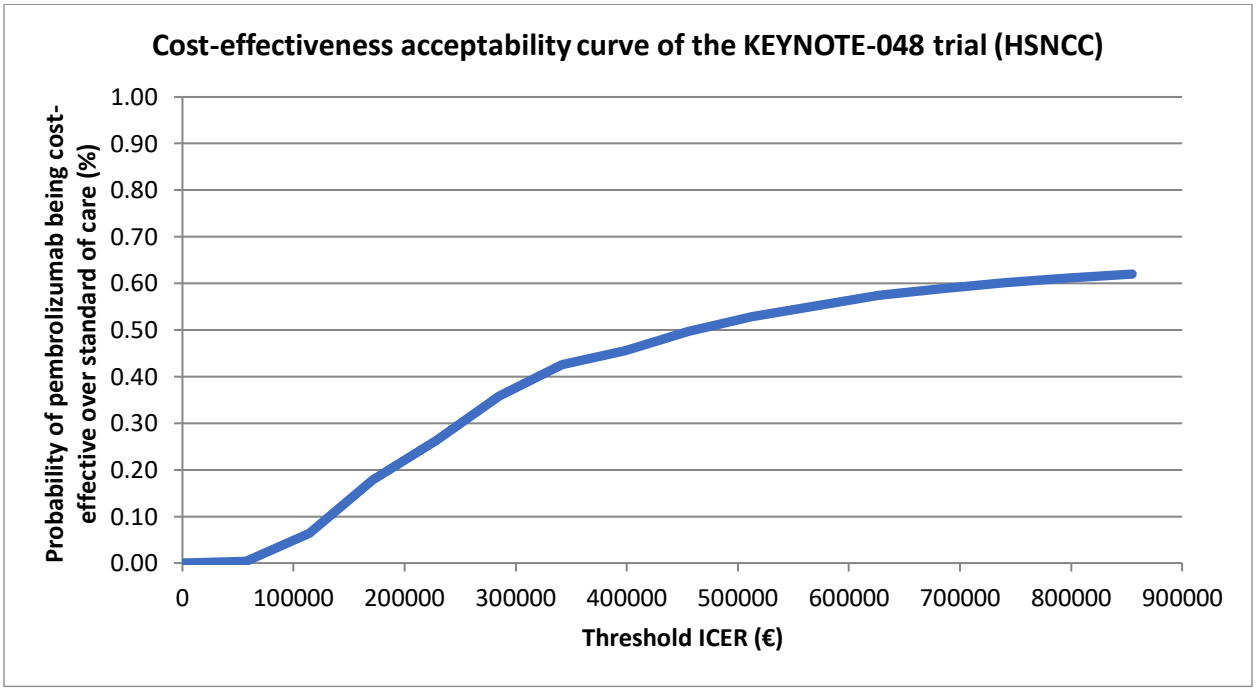


Figure S.13: The cost-effectiveness acceptability curve (CEAC) of pembrolizumab versus standard of care of the KEYNOTE-048 trial.

KEYNOTE-006 (melanoma)

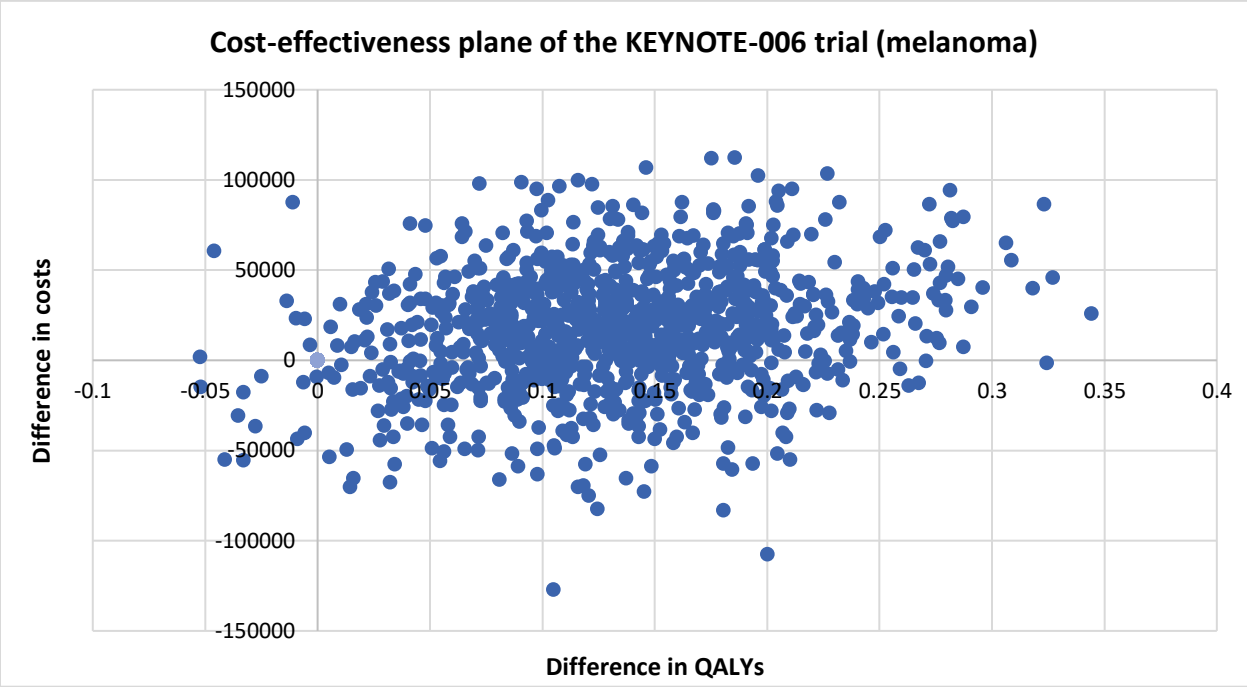


Figure S.14: The cost-effectiveness plane of pembrolizumab versus standard of care of the KEYNOTE-006 trial, depicting differences in QALYs over differences in cost (€).

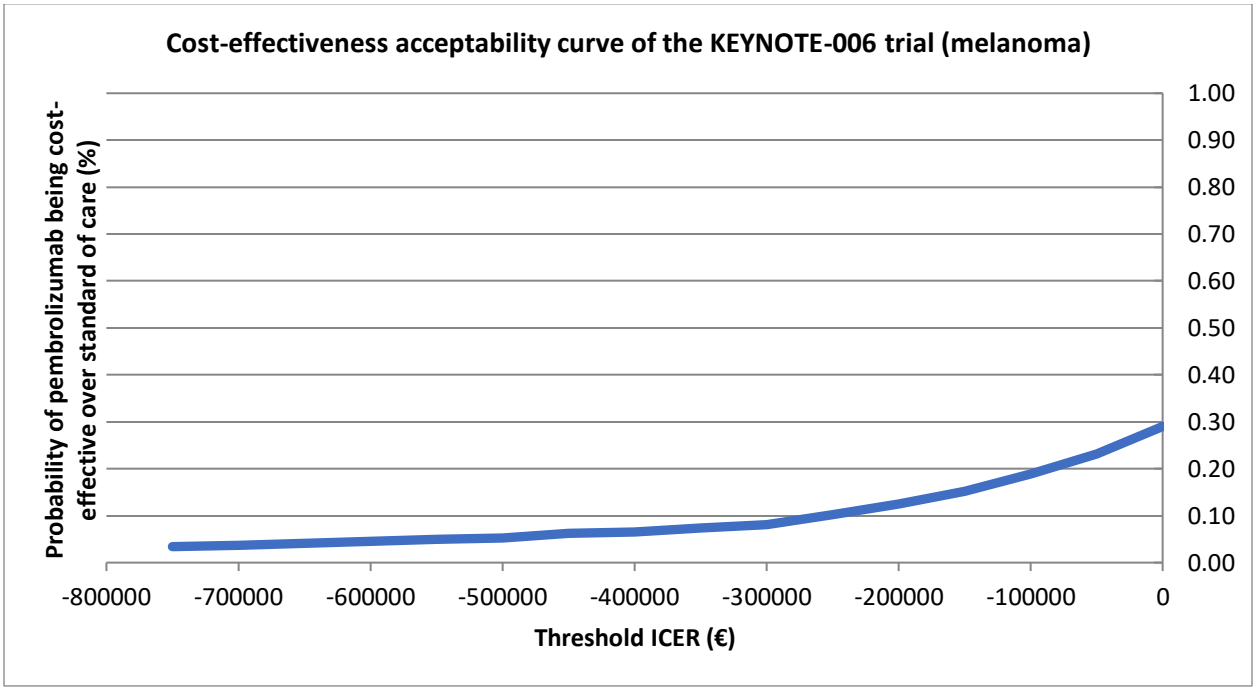


Figure S.15: The cost-effectiveness acceptability curve (CEAC) of pembrolizumab versus standard of care of the KEYNOTE-006 trial.

KEYNOTE-010 (NSCLC)

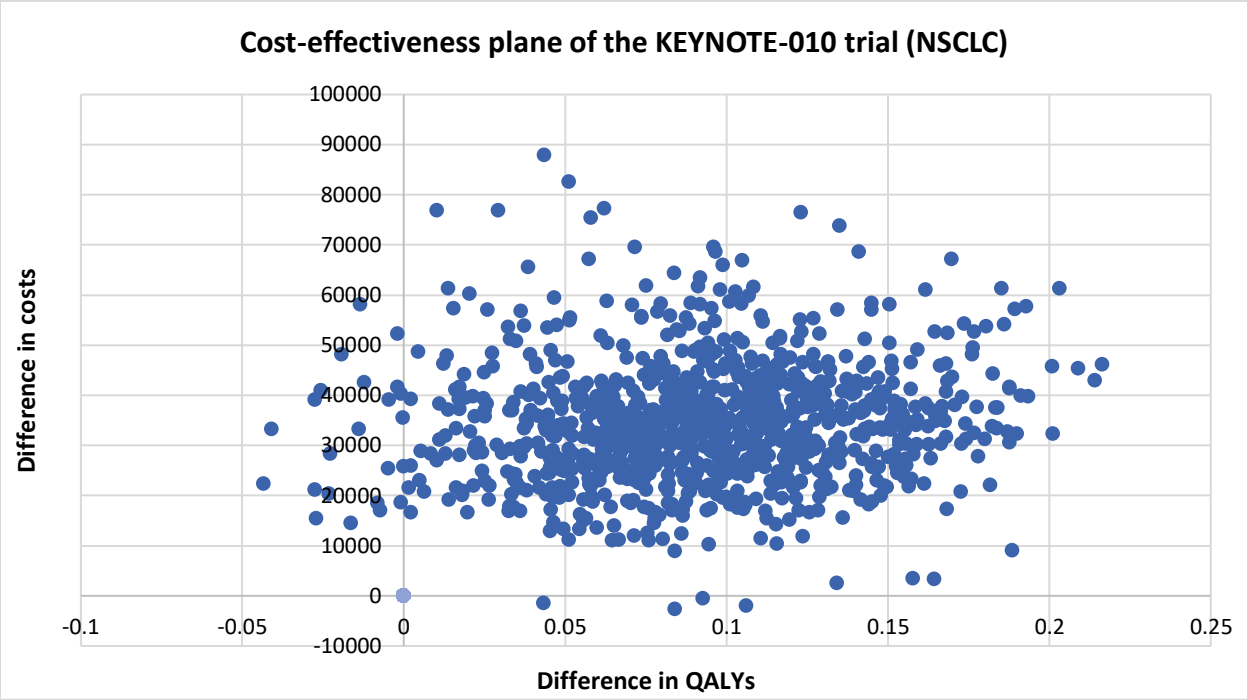


Figure S.16: The cost-effectiveness plane of pembrolizumab versus standard of care of the KEYNOTE-010 trial, depicting differences in QALYs over differences in cost (€).

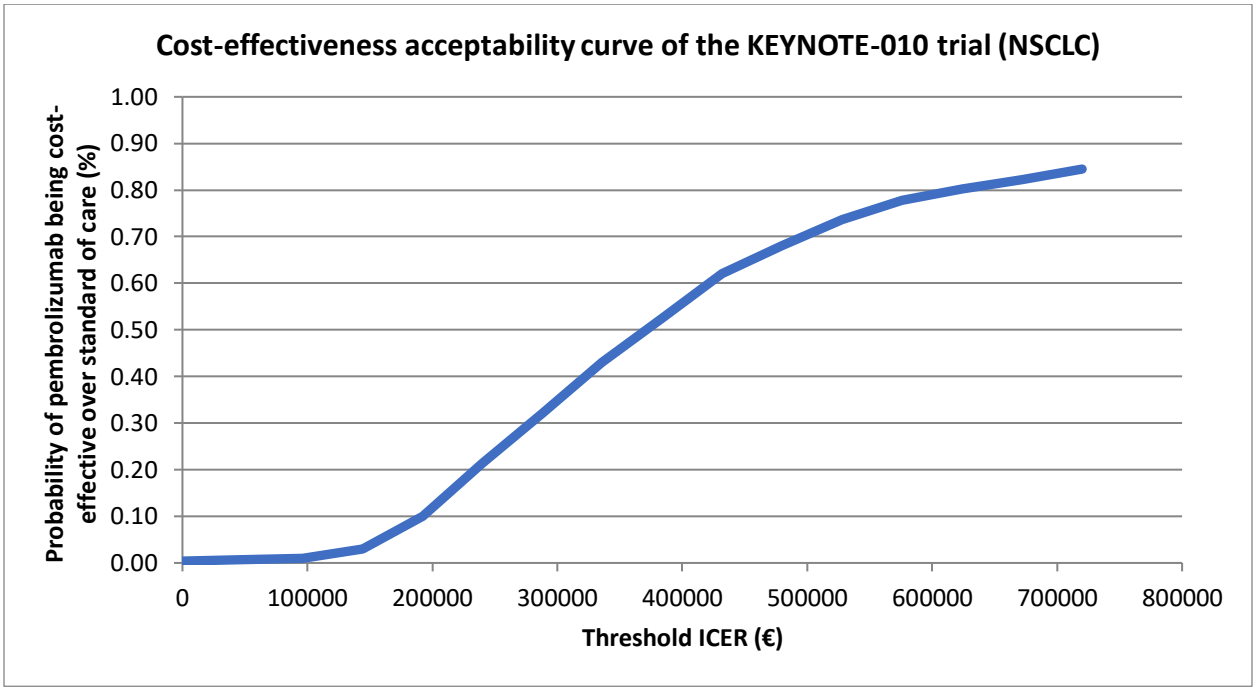


Figure S.17: The cost-effectiveness acceptability curve (CEAC) of pembrolizumab versus standard of care of the KEYNOTE-010 trial.

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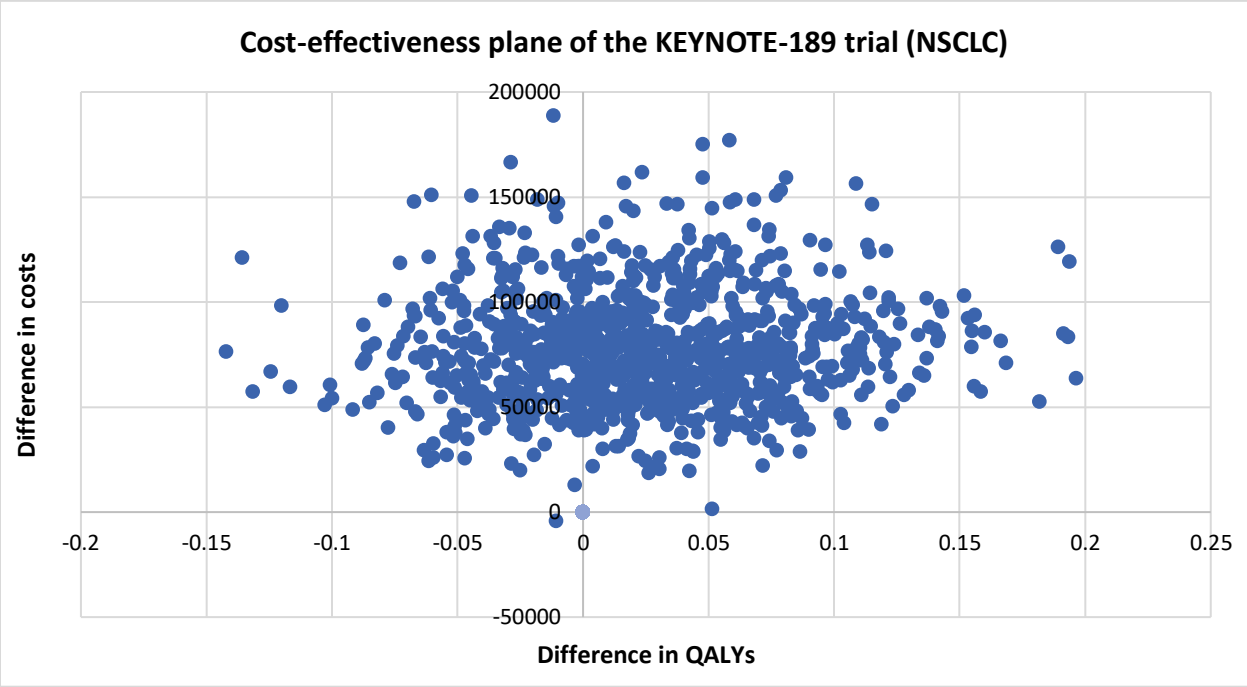

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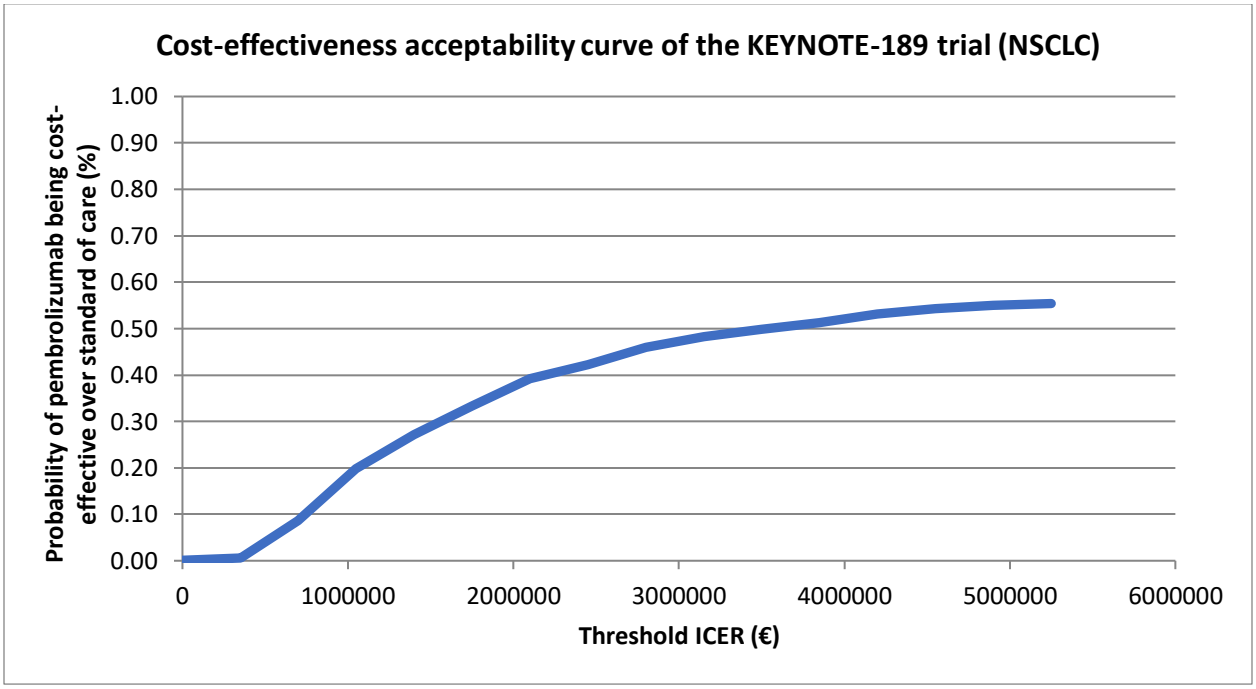

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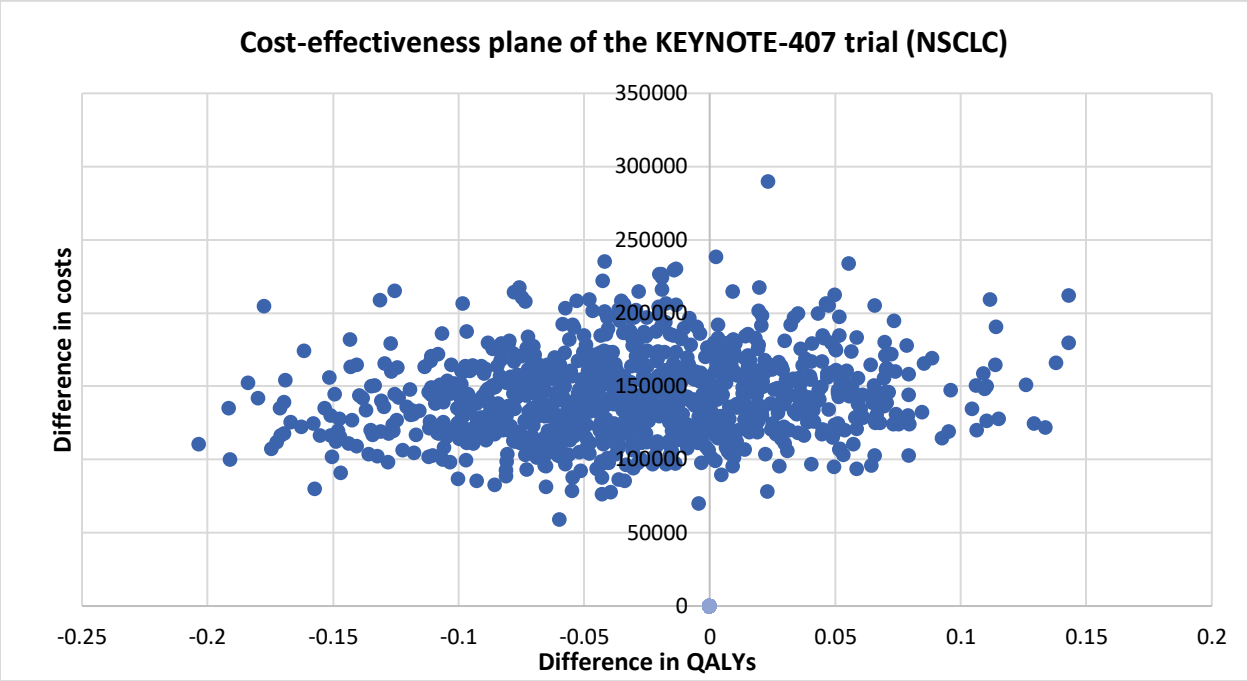

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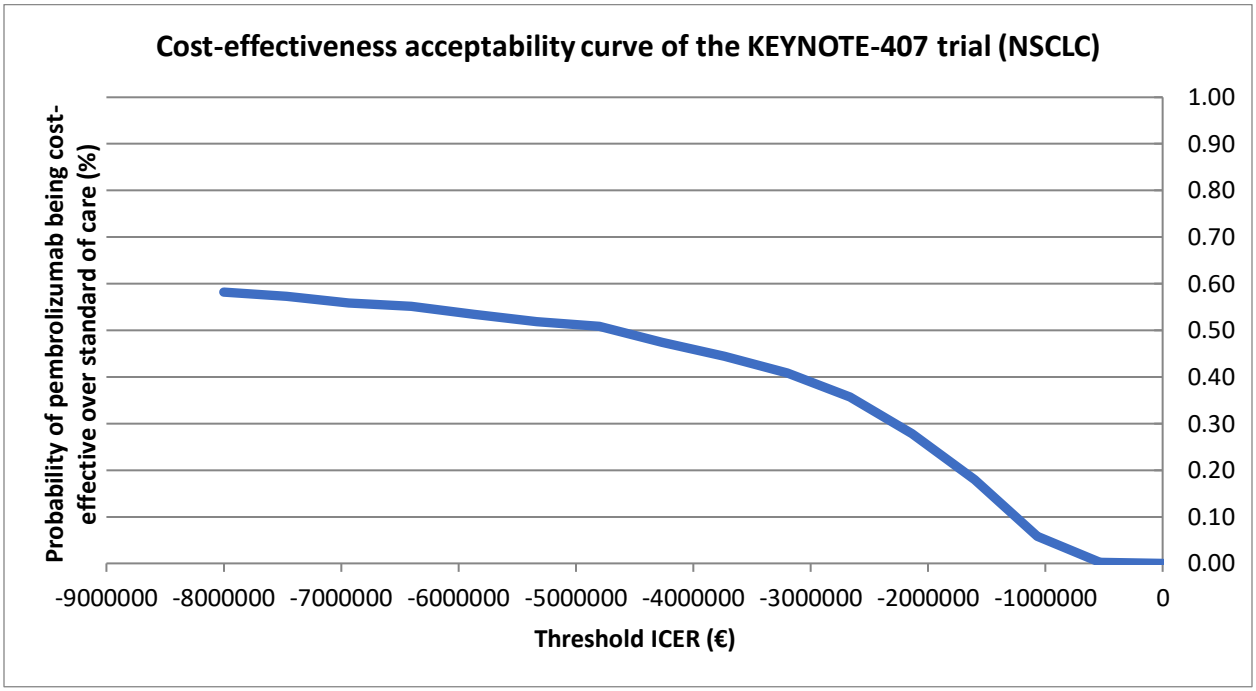

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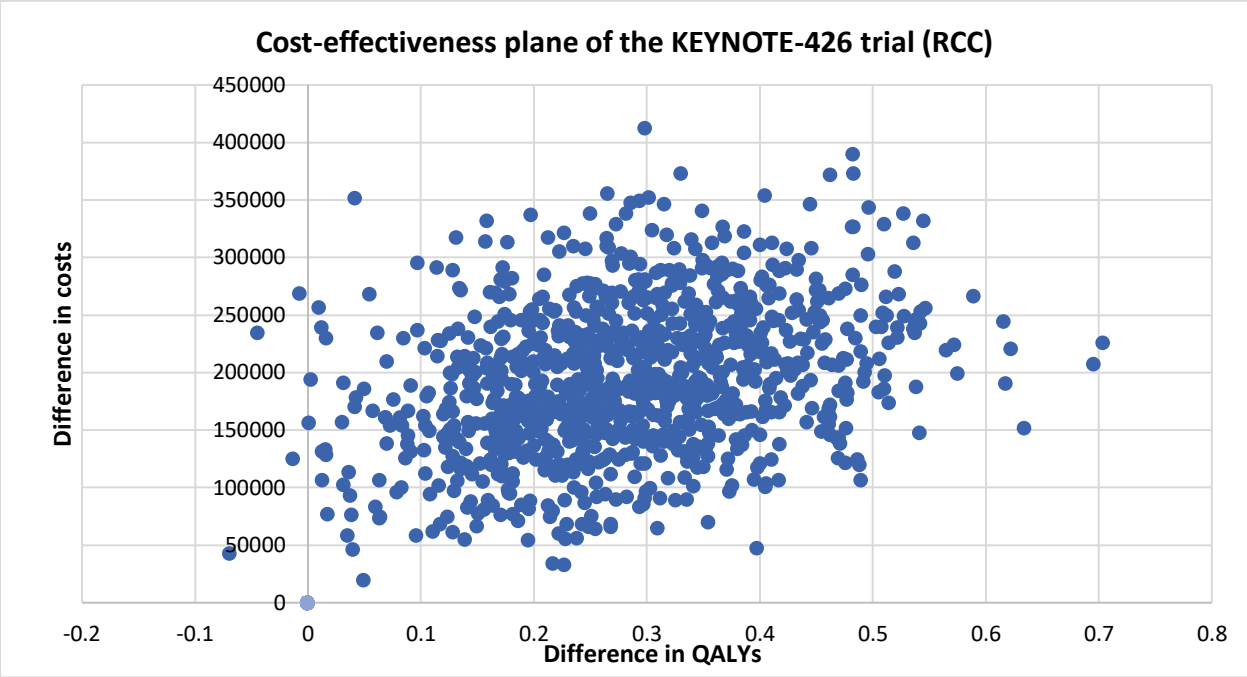

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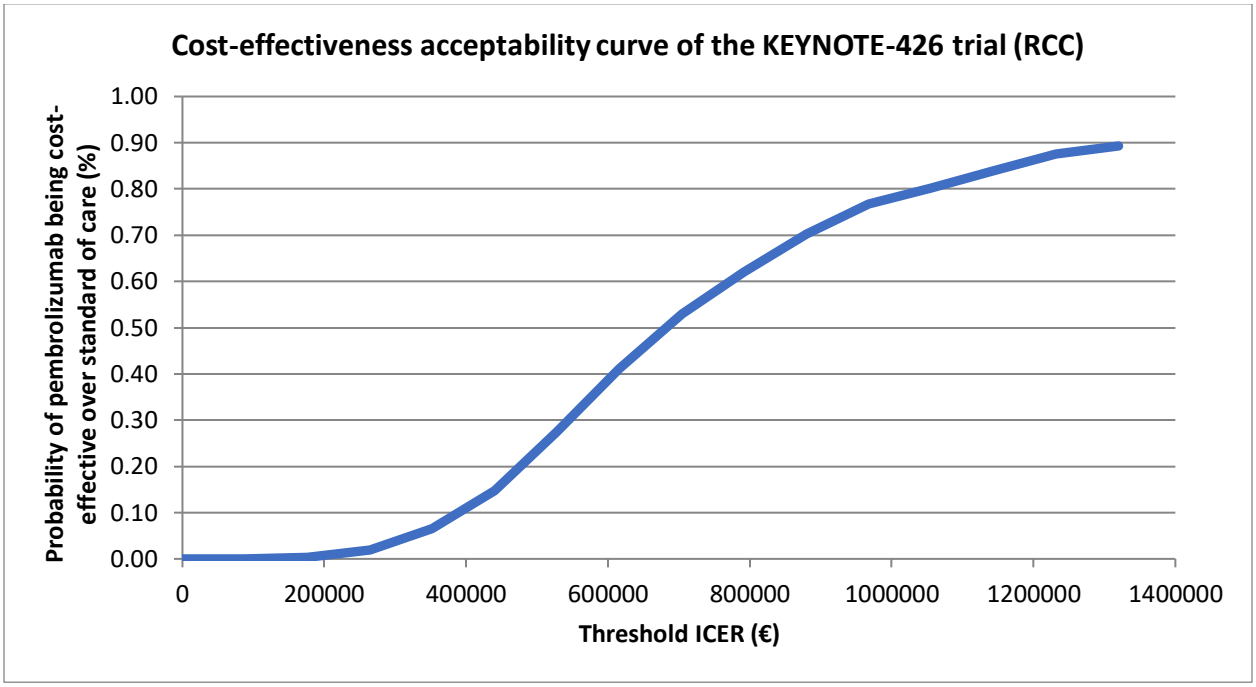

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Abbreviations

ACP	Adviescommissie Pakket
AIC	Aikake information criterion
ALK	anaplastic lymphoma kinase
BC	breast cancer
BIC	Bayesian information criterion
CBS	Centraal Bureau voor Statistiek
CC	cervical cancer
cHL	hodgkin lymphoma
cieBOM	Commissie ter Beoordeling van Oncologische Middelen / Oncology Appraisal Committee
CPS	combined positive score
CRC	colorectal cancer
dMMR	mismatch repair deficient
EC	endometrial cancer
EG	esophageal carcinoma
EGFR	epidermal growth factor receptor
EMA	European Market Authorization
EQ-5D	European Quality of Life Five Dimensions
HG	Horizonscan Geneesmiddelen
HNSCC	head and neck squamous cell carcinoma
HP	hepatocellular carcinoma
ICER	incremental cost-effectiveness ratio
KM	Kaplan-Meier
LY	life years
mCRPC	metastatic castration-resistant prostate cancer
MSI-H	microsatellite instability high
MTX	methotrexate
NSCLC	non-small cell lung cancer
NVALT	Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose
OS	overall survival
PD	progressed disease
PD-1	programmed death protein 1
PD-L1	programmed death-ligand 1
PF	progression-free
PFS	progression-free survival

PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life years
RCC	renal cell carcinoma
RCC	renall cell carcinoma
SD	stable disease
SoC	standard of care
TPS	tumor proportion score
UC	urothelial carcinoma
VWS	Ministerie van Volksgezondheid, Welzijn en Sport / Ministry of Health
WAR-CG	Wetenschappelijke Adviesraad – commissie geneesmiddelen / Scientific Advisory Board
WTP	willingness to pay
ZIN	Zorginstituut Nederland / Dutch National Health Care Institute

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