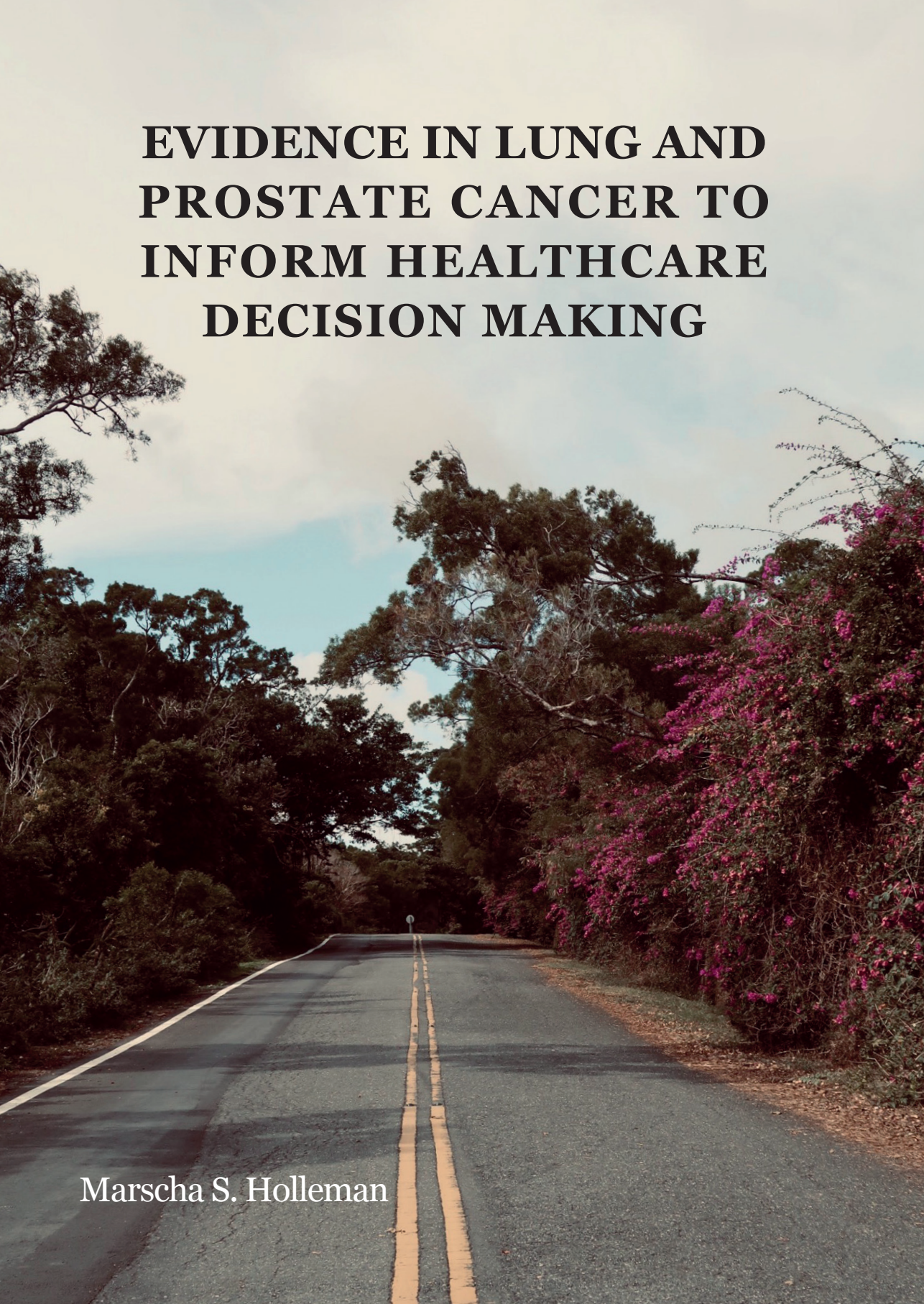
EVIDENCE IN LUNG AND PROSTATE CANCER TO INFORM HEALTHCARE DECISION MAKING



Marscha S. Holleman

Evidence in lung and prostate cancer to inform healthcare decision making

Informatie ten behoeve van besluitvorming in de gezondheidszorg op het gebied van long- en prostaatkanker

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Informatie ten behoeve van besluitvorming in de gezondheidszorg op het gebied van long- en prostaatkanker

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Chapter 1

General introduction

Background

Cancer is one of the most common diseases in developed countries with 3.91 million new cases and 1.93 million deaths in Europe in 2018.[1] It is the second leading cause of death in Europe with over 25% of all deaths.[2] Despite the high incidence and mortality rates, prognosis for patients with cancer has improved over the past years. This improvement is mainly caused by earlier diagnosis and the development of new anticancer therapies.[3]

However, the improvements in clinical outcomes induce substantial healthcare costs. A previous study showed that 56% of the cancer-related healthcare costs in Europe are inpatient care costs and 27% is due to cancer drugs. [4] In 2015, healthcare expenditures were around 86 billion Euros in the Netherlands. These expenditures are expected to increase to 174 billion Euros in 2040, which increases the healthcare expenditures as percentage of the Gross Domestic Product (GDP) from 12.7% to 16.4%. This increase is partly due to growing costs of cancer care, as these costs are expected to be four times higher in 2040 compared to 2015 (increase from 5.6 billion Euros in 2015 to 23.5 billion Euros in 2040).[5]

Since a vast majority of healthcare expenditures are publicly financed and financial resources are scarce, more spending on health may result into less budget for other public expenditures (e.g., education and environment). As a result, decision makers on the political level have to decide how to distribute the publicly financed budget over the different sectors. Since there is a limited healthcare budget, choices should also be made within healthcare. This means that spending on cancer care may result into less money for other patients. Cancer expenditures increase more than most other healthcare expenditures. [6] Consequently, the opportunity cost will increase as well (the benefits that could have been achieved when the same money was spent on an alternative treatment or programme), as less money can be spent on alternatives. [7]

Health technology assessment

Since policy decision-makers have to decide which healthcare programmes should be reimbursed, it is of utmost importance to base these decisions on transparent and high-quality information. Health technology assessment (HTA) could play a role in optimising the allocation of the healthcare budget, as HTA assesses the medical, social, economic, organisational, and ethical consequences of a health technology.[8,9] Health technologies can be drugs, medical devices, vaccines, procedures, and health programmes that are applied to solve health problems and to improve health related quality of life.[10] In an economic evaluation of a health technology, costs and consequences of a new technology are compared to the costs and consequences of its alternative. Cost-effectiveness analysis (CEA) and cost-utility analysis are

the most often used economic evaluations. In a CEA, the costs and effects of a new technology are compared to the standard of care.[11] The cost-effectiveness could be measured with the incremental cost-effectiveness ratio (ICER). The formula of the ICER is as follows:

$$ICER = \frac{(Costs\ new\ treatment - costs\ standard\ treatment)}{(Effects\ new\ treatment - effects\ standard\ treatment)}$$

Effects in CEAs are measured in natural units, for example life-years or quality-adjusted life-years (QALYs). In a QALY, both life-years and quality of life are considered by correcting life-years with the utility value of a certain health state. Expressing cost-effectiveness in terms of QALYs gained, is called a cost-utility analysis.[11]

To assess whether a technology could be regarded as cost-effective, an ICER threshold could be a distinctive tool. These thresholds may reflect the societal willingness to pay. In the Netherlands, threshold depends on the burden of disease, which means the higher the burden of a condition, the higher the ICER threshold (Table 1.1).[12] The iMTA Disease Burden Calculator (iDBC) could be used to assess the burden of disease.[13]

Table 1.1 ICER thresholds used in the Netherlands

Disease burden	Costs per QALY
0.1 - 0.4	Up to €20,000 per QALY
0.41 - 0.7	Up to €50,000 per QALY
0.71 – 1.0	Up to €80,000 per QALY

From the Dutch Healthcare Institute (ZiN)[12]

Considering the increasing incidence and prevalence of cancer cases, the high drug acquisition costs of new oncology treatments, and more often drugs are given until disease progression, the budget impact of cancer treatments is rising.[14] Therefore, a budget impact analysis (BIA) is also often required by healthcare decision makers to decide on the reimbursement of a new treatment. In a BIA, the financial consequences of when a new treatment is accepted versus the current situation without the new treatment are identified. Factors like incidence/prevalence, size of treated population, composition of healthcare interventions, and expenses should be considered in a BIA.[15]

Drug development process

Development of new drugs is a lengthy and thorough process that contains several phases (Figure 1.1). This process starts with drug discovery and development, followed by preclinical research, after which the drug will be extensively investigated in several clinical studies

(randomised controlled trials (RCTs)). If the efficacy and safety of a new drug is demonstrated in these RCTs, the clinical evidence is reviewed by the market licensing authority for market approval.[16] However, market approval of a new treatment does not directly mean that this new treatment is widely adopted and diffused in clinical practice, as the uptake and use in clinical practice may differ between countries and even between regions and hospitals within one country.[17] Thus, the uptake and use of new treatments could be quite heterogeneous. Moreover, since patients from RCTs could differ from patients in daily practice (i.e., younger and better condition),[18] the effectiveness and safety of a new treatment in clinical practice may differ from the clinical trial as well (e.g., less favourable overall survival (OS)). Therefore, there is increasing interest in real-world evidence in addition to evidence from clinical trials.

Figure 1.1 Drug development process

Different types of evidence

Since there is uncertainty around the real value of new treatments at the time they become available, it is of importance for healthcare decision makers to mitigate this uncertainty. Different approaches are available to obtain evidence on the value of a new medical treatment to inform healthcare decision making.

Prior to the decision whether or not to approve and reimburse a new treatment, several types of evidence are available. Figure 1.2 shows different levels of clinical evidence. RCTs are considered as the golden standard to demonstrate the efficacy and safety of a treatment. In an RCT, patients are randomly allocated to the treatment and are continuously monitored. These controlled conditions reduce bias and enables to test the efficacy of new treatments, which contribute to its internal validity.[19] It may be possible that more than one treatment option is already available for a certain disease area and therefore, the new treatment should be compared to multiple treatment options. However, in RCTs, head-to-head comparisons of these different treatment options are often missing and will not become available in the future. A network meta-analysis (NMA) could be used to gain insight into the relative effectiveness

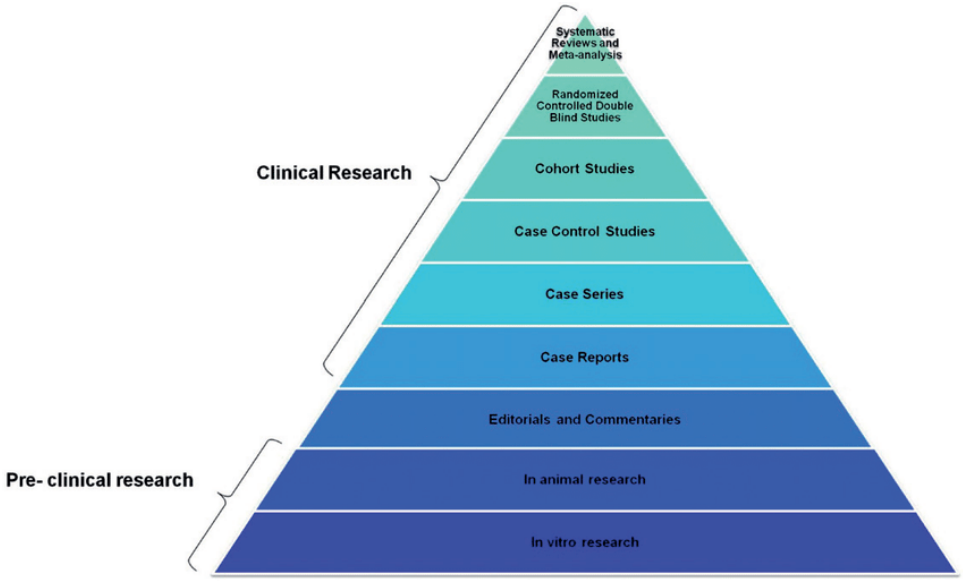
of a new treatment compared to multiple treatment options, as it enables to combine direct and indirect evidence from various RCTs to compare all available treatment options to each other.[20] To assess whether the additional benefits of a new treatment are worth the additional costs, a CEA based on evidence from clinical studies could be performed to inform healthcare decision makers on the reimbursement decision. Since patients are followed for a limited time period in RCTs and a lifetime perspective is preferred for CEAs, modelling techniques are required to extrapolate costs and effects beyond the study period.[11]

Although clinical evidence of a new treatment could be demonstrated in an RCT, it is unclear whether the outcomes are the same for patients in the real-world, as these patients are often older and have a less favourable condition.[18,21]So, there is still uncertainty around the costs and effects of a new treatment at the time it becomes available at the market. The uncertainty around the effectiveness and safety of a new treatment could be diminished by real-world data (RWD), as in RWD, data on the effectiveness, safety, use, resource use, and patient-reported outcomes are collected on patients in daily practice.[22] RWD on treatment patterns could provide insight into the uptake, access, and use of treatments in daily clinical practice. Moreover, RWD could provide insight into the effectiveness and safety of real-world treatment patterns, as nowadays, patients often receive multiple treatment lines. However, RCTs are often focussed on only one treatment line and its follow-up period is limited. Consequently, information on treatment sequences spanning multiple treatment lines is lacking. RWD with an adequate follow-up period allow studying the effectiveness and safety of treatment sequences. In addition, RWD could provide insight into the resource use and costs of real-world patients. Such studies on the real-world resource use and costs can be used in CEAs in real-world patients.[23,24]

Furthermore, uncertainty around the real value of a treatment could also be mitigated by sharing the financial risk between healthcare payer and pharmaceutical company. A wide range of such risk-sharing arrangements are available (e.g., money-back guarantee and discounted treatment initiation), which may reduce expenditures to the payer and may also have an impact on the benefits of a treatment.[25,26]

Since there are limited healthcare resources, evidence on the value of new treatments is of increasing interest. Such evidence could inform healthcare decision makers to make the most optimal allocation of the healthcare budget while the health of the entire population is maximised. In this thesis, different types of evidence in lung and prostate cancer are evaluated.

Figure 1.2 Levels of clinical evidence



From Varoni et al. 2014[27]

Case of lung cancer

Lung cancer is the number one diagnosed cancer (2.09 million cases in 2018) and the main cause of cancer-related mortality (1.76 million cases in 2018) worldwide.[28] Lung cancer incidence and mortality is also high in the Netherlands, with an incidence over 14,000 and a mortality over 10,000 in 2018. Incidence among men was about 7,600 and about 6,400 women. Mortality stratified by sex was almost 6,000 among men and over 4,200 among women.[29] Tobacco smoking is the main cause of lung cancer, 71% of all lung cancer deaths are caused by smoking. Most of the lung cancer cases are non-small cell lung cancer (NSCLC) (80-90%).[30] About 50% of all patients has stage IV lung cancer at time of diagnosis.[31] Lung cancer treatment depends on the disease stage and could consist of surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, or a combination of these options. Nowadays, therapies for NSCLC stage IV are more focussed on targeting specific cancer cells (targeted therapies). Biomarker testing is an important step during diagnosis, as several oncogenic drivers could be targeted with targeted therapies. These therapies could target for example EGFR or BRAF mutations or ALK or ROS1 rearrangements.[30] In a large study, more than half of all tumours tested had an oncogenic driver. This emphasises the importance of performing biomarker testing, as the treatment of choice could be driven by occurrence of oncogenic drivers.[32] Depending

on the biomarker test, a targeted therapy (e.g., osimertinib for EGFR or alectinib for ALK) is given as first-line treatment for NSCLC stage IV, followed by another targeted therapy or chemotherapy as second-line treatment. First-line treatment of NSCLC without oncogenic driver consists of platinum-based chemotherapy plus immunotherapy or immunotherapy alone (i.e., pembrolizumab). Immunotherapy with pembrolizumab is recommended as first-line treatment for patients with PD-L1 expression ≥ 50%. PD-L1-inhibitors are recommended as second-line treatment for PD-L1-naïve NSCLC.[30,33] Although, lung cancer is still the number one cause of cancer-related mortality, treatment and survival of NSCLC has improved within all disease stages in the last decades (five-year survival increased from 12 to 22% between 1961 and 2015 in the Netherlands). One-year survival of NSCLC stage IV increased from 10 to 23% in the period 1989-2010.[29,34] In patients treated with PD-L1 inhibitors (i.e., nivolumab or pembrolizumab), 16-25% of the patients had a long-term survival (≥ 5 years).[35,36]

Case of prostate cancer

Prostate cancer is the second most common type of cancer in men worldwide with 1.28 million cases in 2018.[37] In the Netherlands, prostate cancer is the most common type of cancer among men with an incidence of approximately 12,500 cases and a mortality of almost 2,900 patients in 2018. Of all patients with prostate cancer, 91% is 60 years or older.[29] Age and prostate cancer family history are important risk factors of prostate cancer.[38,39] Due to an ageing population, the incidence and prevalence is expected to increase.[38] Treatment options for prostate cancer are surgery, radiotherapy, androgen deprivation therapy (ADT), chemotherapy, hormone therapy (i.e., abiraterone and enzalutamide), and radium, but depends on the disease stage.[40] Treatment of metastatic prostate cancer is palliative and starts with ADT alone or in combination with chemotherapy, new androgen-receptor targeting agents or palliative radiotherapy.[38,41] After 14-20 months, prostate cancer will grow again despite ADT, this is called castration-resistant prostate cancer (CRPC).[38] Since 2004, new treatments (i.e., docetaxel, abiraterone, enzalutamide, cabazitaxel, and radium-223) with improved efficacy have been developed for patients with CRPC.[42-50] Partly due to early diagnosis (i.e., prostate-specific antigen (PSA) testing) of prostate cancer, survival has improved over the past decades.[51] In the Netherlands, five-year relative survival increased from 48 to 88% between 1961 and 2015.[29]

Objectives

The aim of this thesis is to provide evidence on the value of new treatments in lung and prostate cancer to inform healthcare decision making. The following research questions have been defined:

- What is the effectiveness of targeted therapies for patients with EGFR mutation-positive NSCLC?
- What is the cost-effectiveness of first-line EGFR-TKIs in patients with EGFR mutation-positive NSCLC?
- What is the value of pharmaceutical risk-sharing policies in NSCLC?
- What are the real-world costs of CRPC treatment in the Netherlands?
- What is the role and what are the outcomes of real-world data being used in a CRPC disease model?

These research questions will be illustrated from examples derived from NSCLC and CRPC.

Outline of the thesis

This thesis consists of two parts. The first part (chapter 2-4) contains several studies in lung cancer. In the second part (chapter 5-6), two studies in prostate cancer will be described.

Chapter 2 reports the results of an NMA of targeted therapies for patients with EGFR mutation-positive NSCLC. A systematic literature review was performed to obtain evidence of five different targeted therapies. Direct and indirect evidence was included in an NMA to assess the relative effectiveness and safety of these therapies. In Chapter 3, the evidence found in Chapter 2 was used to estimate the cost-effectiveness of four different targeted therapies for patients with EGFR mutation-positive NSCLC.

Chapter 4 discusses the impact of risk-sharing arrangements in NSCLC treatments, using 'what-if'-analyses to evaluate the costs and benefits associated with various risk-sharing arrangements.

Chapter 5 reports the real-world healthcare costs of patients with CRPC in the Netherlands. Chapter 6 describes the development of a disease model for CRPC using real-world data. The challenges regarding the development of a disease model will also be elaborately discussed in this chapter. In Chapters 5 and 6, real-world data of CRPC patients were obtained from the Castration-resistant Prostate Cancer Registry (CAPRI). CAPRI contains retrospectively collected data of CRPC patients from 20 hospitals in the Netherlands newly diagnosed between 2010 and 2015. In the CAPRI-registry, clinical outcomes, treatment outcomes, and resource use of CRPC patients in the Netherlands were registered.[18]

In Chapter 7, the main results of this thesis are described and discussed. Moreover, the limitations of this thesis are addressed.

Chapter 2

First-line tyrosine kinase inhibitors in EGFR mutation-positive non-small cell lung cancer: A network meta-analysis

M.S. Holleman, H. van Tinteren, H.J.M. Groen, M.J. Al, C.A. Uyl-de Groot

OncoTargets and Therapy 2019; 12:1413–1421.

Abstract

Introduction: Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) including afatinib, dacomitinib, erlotinib, gefitinib, and osimertinib have proven efficacy in terms of progression-free survival (PFS) in patients with non-small cell lung cancer (NSCLC) harbouring EGFR mutations. However, an overall view for comparing efficacy and toxicity on a meta-level is lacking. This study compared efficacy and toxicity of first-line treatment with five different EGFR-TKIs by conducting a network meta-analysis (NMA).

Methods: A systematic review was performed, aiming to find eligible literature. Data of PFS, overall survival (OS), objective response rate (ORR), and adverse events were extracted. An NMA based on Bayesian statistics was established to synthesise the efficacy and toxicity of all treatments.

Results: Thirteen RCTs, including data from 3,539 patients with EGFR-mutated NSCLC, were analysed. Rank probabilities showed that osimertinib had a potentially better efficacy in terms of PFS and OS compared to all other TKIs. For ORR, afatinib and osimertinib showed a trend of superiority compared to the other four TKIs. Furthermore, there was a high risk of diarrhoea and rash for patients treated with afatinib or dacomitinib as well as a moderate risk for erlotinib, gefitinib, and osimertinib.

Conclusion: Our study showed a favourable efficacy of osimertinib in terms of PFS and OS compared to all other EGFR-TKIs in patients with NSCLC harbouring activating EGFR mutations. Furthermore, gefitinib, erlotinib, and osimertinib were associated with fewer toxicities compared to the other TKIs. Therefore, osimertinib is indicated as a preferable first-line TKI in patients with activating EGFR-mutated NSCLC.

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide.[52] Of all lung cancer cases, 80-85% are non-small cell lung cancer (NSCLC) and the majority of these cases are in the advanced or metastatic stage (III or IV) at the time of diagnosis.[53,54] Among these patients with NSCLC, a substantial number are harbouring activating Epidermal Growth Factor Receptor (EGFR) mutations, ranging from 10% in Europe to 38.4% in Asia.[55,56] During the past years, targeted therapies including tyrosine kinase inhibitors (TKIs) have been developed and become standard first-line treatment for patients with EGFR mutation-positive NSCLC.[57-59] Various trials showed higher response rates and improved progression-free survival (PFS) of first-line treatment with afatinib, erlotinib, and gefitinib compared to platinum-based doublet therapy in patients with activating EGFR-mutated (exon 19 deletion or exon 21 L858R mutation) NSCLC.[60-69] Recently, in head-to-head trials, dacomatinib and osimertinib showed a significant longer PFS compared to standard EGFR-TKIs, while dacomitinib, a second-generation EGFR-TKI, had a better efficacy compared to gefitinib, and osimertinib showed a more favourable PFS compared to standard EGFR-TKI (gefitinib or erlotinib).[70,71] Different EGFR-TKIs are available for the treatment of patients with EGFR mutation-positive NSCLC. However, since sufficient data from head-to-head trials of all these EGFR-TKIs are lacking, evidence of relative efficacy and toxicity of these first-line TKIs is scarce. Therefore, a network meta-analysis (NMA) was performed to compare the efficacy and toxicity of these TKIs as first-line treatment for patients with EGFR mutation-positive NSCLC. In traditional meta-analyses, the same intervention is compared to the same comparator in all included studies. NMA combines direct comparisons of interventions within RCTs with indirect comparisons across RCTs in multiple pairwise comparisons across a range of interventions. A greater share of available evidence is synthesised in the NMA method compared to traditional meta-analysis. The NMA method enables judicious estimation of the relative treatment effect for comparative effectiveness purposes.[72] Previous published NMAs did not show significant differences between EGFR-TKIs.[73-77] New data of several (new) TKIs are available (ARCHER1050 and FLAURA trials),[70,71] which may lead to new insights into the relative efficacy and toxicity of the EGFR-TKIs.

This study aimed to compare the efficacy and toxicity of first-line gefitinib, erlotinib, afatinib, dacomitinib, and osimertinib for patients with activating EGFR-mutated (exon 19 deletion or exon 21 L858R mutation) NSCLC through conducting an NMA of all available evidence in the literature.

Material and methods

Search strategy and selection criteria

An electronic search of the PubMed, EMBASE, and Cochrane Library databases was conducted in order to find eligible studies for the NMA, following PRISMA guidelines.[78] Eligible studies were phase IIB/III RCTs that compared the efficacy and toxicity of a single TKI to another TKI or to standard chemotherapy as first-line treatments in patients with stage IIIB/IV NSCLC harbouring EGFR mutations and who were not eligible for surgery or radiotherapy. Standard chemotherapy was defined as platinum-based doublet therapy.

Papers published from 1 January 2010 up to and including 1 November 2016 were included. Literature was reviewed by two reviewers (MH and CU) and discrepancies were discussed. The selection of studies was based on inclusion and exclusion criteria. Details of the search strategy can be found in the Supplemental material. Reference lists of published systematic reviews and meta-analyses were checked to ensure that no studies were overlooked. In February 2018, the literature search was manually updated to ensure that no relevant studies were missing, as new trials have been published in the previous two years.

Data extraction and quality assessment

Information on study design, number of participants, patient characteristics, interventions, comparators, objective response rate (ORR) (complete or partial response according to RECIST v1.1), PFS (time from randomisation until disease progression according to RECIST v1.1 or death from any cause), overall survival (OS) (time from randomisation until death from any cause), and adverse events (AE) were extracted. Toxicity was scored according to the Common Toxicity Criteria (CTC).[79] Absolute numbers of AEs were extracted and odds ratios (ORs) were calculated. Diarrhoea and rash (CTC grade 3 or higher) were included in the analyses of this study because these are the most common TKI-related adverse events. Other AEs were not included in the final analysis because they are less impacting and are known to be relatively homogenous across all EGFR-TKIs.[80,81] Data extraction was verified by the second reviewer (CU). For studies with more than one publication, the data was compared between publications. The most updated results were included in this study. Extracted data can be found in the Supplemental material.

Quality and risk of bias of the RCTs were assessed by using the Cochrane Collaboration's tool for assessing risk of bias.[82]

Statistical analyses

We performed a Bayesian fixed-effects network meta-analysis in WinBUGS 1.4 by using an adapted version of WinBUGS code from Dias et al.[83] (see Supplemental material). Due to the limited number of trials in each specific TKI group, a fixed-effects framework was deemed appropriate for the NMA.[84-86] The outcomes of PFS, OS, ORR, and AEs within trials were linked in a network.

To obtain the hazard ratio (HR) of treatment a versus b, the following formula was used for all comparisons: $\widehat{HR_{a,b}} = (e^{(\partial_b - \partial_a)})$, and chemotherapy was used as the reference treatment in the network ($\partial\ chemo = 0$). All other's were calculated based on direct and indirect evidence from the RCTs. The NMA also enabled us to estimate the probability of being the best treatment and to rank the treatments based on these probabilities. Brooks-Gelman-Rubin diagnostics in WinBUGS were used to assess convergence, which enabled the determination of the number of burn-in simulations that should be discarded before calculating the converged results.[87]

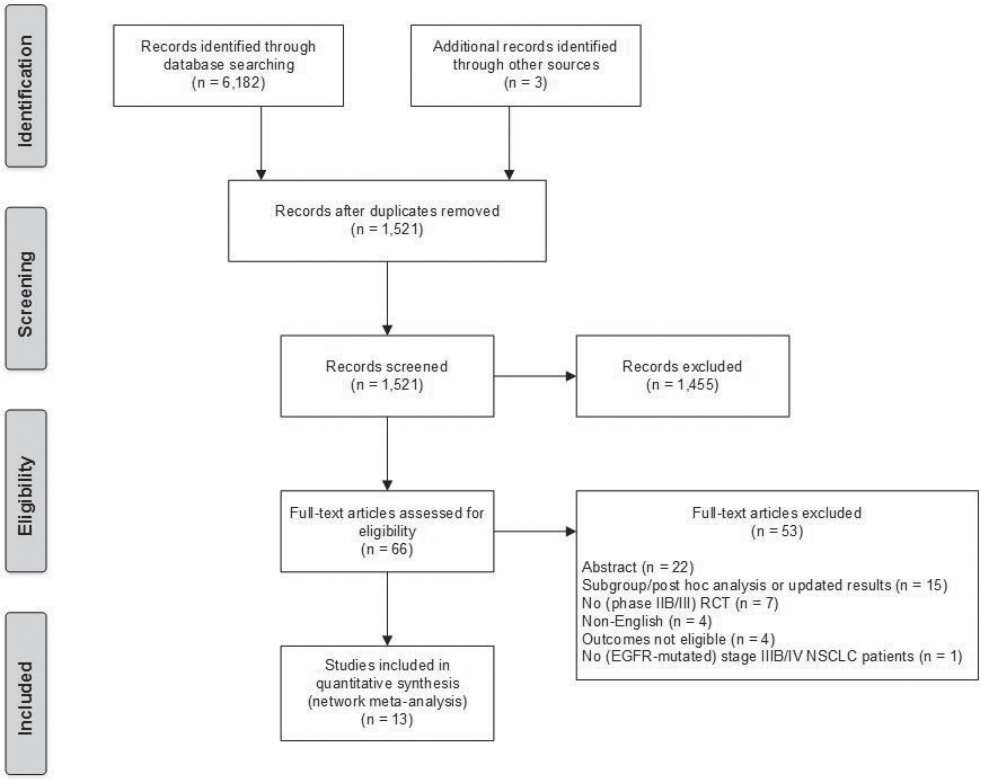
The FLAURA trial compared osimertinib to gefitinib or erlotinib. In this trial, no separate HRs of osimertinib versus gefitinib or osimertinib versus erlotinib, were reported. Therefore, we assumed that the HRs of PFS and OS were the same for osimertinib versus gefitinib as they were for osimertinib versus erlotinib.

Results

Identification of studies and study quality

Electronic search in the databases resulted in 6,182 records, from which 4,664 internal and external duplicates were excluded. Three additional records were included after a manual update of the literature search. After screening the titles and abstracts of the remaining 1,521 records, 66 abstracts and manuscripts were eligible for full-text reading. After this, 53 records were excluded and 13 unique RCTs were included in the analyses. The flow chart is presented in Figure 2.1.

Figure 2.1 Flow chart of the selection of studies



Abbreviations: NSCLC, non-small cell lung cancer; RCT, randomised controlled trial.

The patient characteristics of the 13 RCTs are summarised in Table 2.1. Eight of the 13 RCTs concerning gefitinib (NEJ002, WJTOG3405, IPASS, First-SIGNAL, Lux-Lung 6, CTONG0901, ARCHER1050, and FLAURA).[60-63,65,70,71,88-92] Four RCTs studied erlotinib (OPTIMAL, EURTAC, ENSURE, and CTONG0901),[64,66,69,91,93] three concerned afatinib (Lux-Lung 3, Lux-Lung 6, and Lux-Lung 7),[67,68,90,94,95] and one trial was included in the analyses for both dacomitinib and osimertinib, (the ARCHER1050 and FLAURA study, respectively).[70,71] Due to the heterogeneous study population of the IPASS and First-SIGNAL trials, we only included the results of the patients with activating EGFR-mutated (exon 19 deletion or exon 21 L858R mutation) NSCLC. A total of 3,539 patients with EGFR mutation-positive NSCLC were available for analyses, 2,691 of whom were randomly assigned to a TKI-arm, and 848 of whom received platinum-based doublet therapy. The HRs for PFS and OS, as reported in the trials, are presented in Table 2.2. All 13 RCTs were classified as having acceptable quality and low risk of bias, according to the Cochrane Collaboration's tool (see Supplemental material).

Table 2.1 Characteristics of included studies regarding TKIs

Trial	Treatment	EGFR patients	Male (%)	Age	Ethnicity	Never/ previous or current smoker (%)	Adeno-carcinoma histology (%)
NEJ002	Gefitinib	114	37	63.9[a]	Japanese	66/34	90
	TC	114	36	62.6[a]	Japanese	58/42	97
WJTOG3405	Gefitinib	86	31 30	64[b]	Japanese	71/29	97
	DP	86		64[b]	Japanese	66/34	98
IPASS	Gefitinib	132 129	21	57[b]	Asian	94/6	95
	TC		21	57[b]	Asian	94/6	97
First-SIGNAL	Gefitinib	26	12	57[b]	Korean	N/A	N/A
	GP	16	11	56.5[b]	Korean	N/A	N/A
OPTIMAL	Erlotinib	82	41	57[b]	Asian	72/28	88
	GC	72	40	59[b]	Asian	69/31	86
EURTAC	Erlotinib	86	33	65[b]	European	66/34	95
	CT	87	22	65[b]	European	72/28	90
ENSURE	Erlotinib	110	38	57.5[b]	Asian	72/28	95
	GC	107		56[b]	Asian	69/31	94
Lux-Lung 3	Afatinib	230	36	61.5[b]	Global	67/33	100
	AP	115	33	61[b]	Global	70/30	100
Lux-Lung 6	Afatinib	242	36	58[b]	Asian	75/25	100
	GP	122	32	58[b]	Asian	81/19	100
Lux-Lung 7	Afatinib	160	43	63[b]	Global	66/34	99
	Gefitinib	159	33	63[b]	Global	67/33	99
CTONG0901	Erlotinib	128	47	*	N/A	82/18	96
	Gefitinib	128	46		N/A	73/27	96
ARCHER1050	Dacomitinib	227	36	62[b]	Global	65/26	N/A
	Gefitinib	225	44	61[b]	Global	64/36	N/A
FLAURA	Osimertinib	279	36	64[b]	Global	65/35	99
	Standard TKI	277	38	64[b]	Global	63/37	98

Abbreviations: AP, cisplatin+pemetrexed; CT, chemotherapy (not specific); DP, cisplatin+docetaxel; GC, carboplatin+gemcitabine; GP, cisplatin+gemcitabine; TC, carboplatin+paclitaxel; N/A, not available.
[a]Mean
[b] Median
*In gefitinib arm, 72 patients (56.3%) ≤ 60 years and 56 patients (43.8%) ≥ 60 years old. In erlotinib arm, 71 patients

Table 2.2 Hazard ratios for PFS and OS of randomised studies in patients with EGFR-mutated advanced NSCLC treated with TKIs

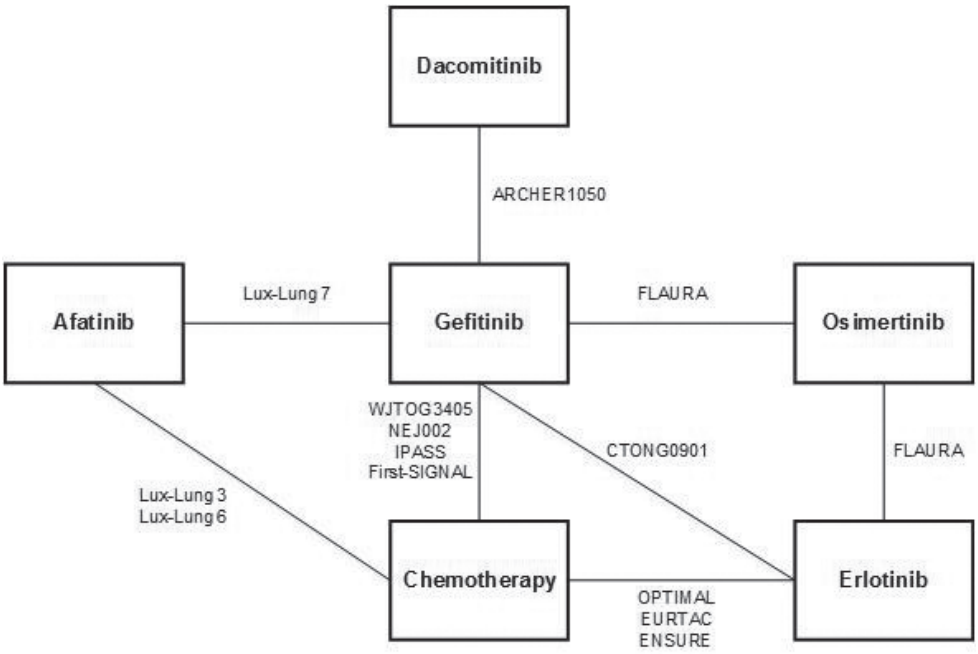
Trial	Treatment	Control	Primary end-point	Hazard ratio (95% CI) PFS	OS
NEJ002*	Gefitinib	TC	PFS	0.30 (0.22-0.41)	0.887 (0.634-1.241)
WJTOG3405*	Gefitinib	DP	PFS	0.489 (0.336-0.710)	1.252 (0.883-1.775)
IPASS*	Gefitinib	TC	OS	0.48 (0.36-0.64)	1.00 (0.76-1.33)
First-SIGNAL*	Gefitinib	GP	OS	0.544 (0.269-1.1)	1.043 (0.498-2.182)
OPTIMAL*	Erlotinib	GC	PFS	0.16 (0.10-0.26)	1.19 (0.83-1.71)
EURTAC*	Erlotinib	CT	PFS	0.37 (0.25-0.54)	1.04 (0.65-1.68)
ENSURE*	Erlotinib	GC	PFS	0.34 (0.22-0.51)	0.91 (0.63-1.31)
Lux-Lung 3*	Afatinib	AP	PFS	0.58 (0.43-0.78)	0.88 (0.66-1.17)
Lux-Lung 6*	Afatinib	GP	PFS	0.28 (0.20-0.39)	0.93 (0.72-1.22)
Lux-Lung 7*	Afatinib	Gefitinib	PFS, OS	0.73 (0.57-0.95)	0.86 (0.66-1.12)
CTONG0901	Erlotinib	Gefitinib	PFS	0.96 (0.69-1.35)	0.98 (0.67-1.42)
ARCHER1050	Dacomitinib	Gefitinib	PFS	0.59 (0.47-0.74)	0.76 (0.582-0.993)
FLAURA*	Osimertinib	Standard TKI	PFS	0.46 (0.37-0.57)	0.63 (0.45-0.88)

Abbreviations: AP, cisplatin+pemetrexed; CT, chemotherapy (not specific); DP, cisplatin+docetaxel; GC, carboplatin+gemcitabine; GP, cisplatin+gemcitabine; TC, carboplatin+paclitaxel; CI, confidence interval; N/A, not available.
*Crossover was allowed after progression on first-line treatment.

Network meta-analysis

Figure 2.2 shows the complete network, which comprised 13 RCTs that studied a TKI compared to another TKI or chemotherapy in patients with EGFR-mutated NSCLC. We simulated three different chains, which produced 60,000 iterations each. Due to a burn-in period, 30,000 iterations were discarded in each chain; the results were based on a total sample of 90,000 iterations. Brooks-Gelman-Rubin plots showed convergence of the parameters.

Figure 2.2 Complete network based on 13 RCTs



Abbreviations: RCT, randomised controlled trial.

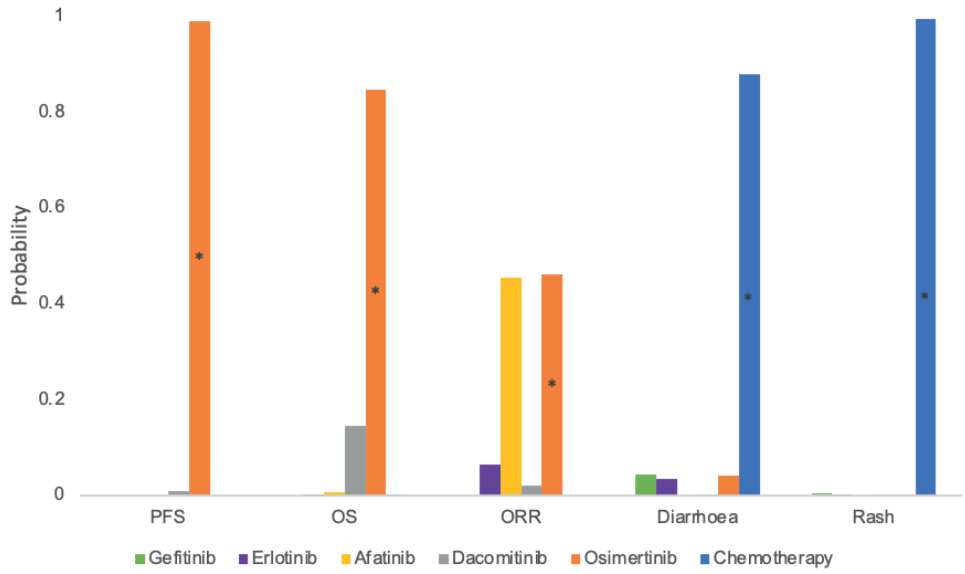
Table 2.3, Figure 2.3, and Figures S2.1-S2.6 in Supplemental material present the NMA results for PFS, OS, ORR, and AEs (diarrhoea and rash). Osimertinib showed a significantly better PFS and OS compared to all other treatments. It also had the highest probability of 99% and 85% showing the longest PFS and OS, respectively, as compared with other TKIs. Dacomitinib also showed a significantly improved PFS compared to gefitinib, erlotinib, and afatinib. Furthermore, afatinib and osimertinib performed best in terms of ORR compared to all other drugs with a probability of 46% for both drugs. However, the distribution of probabilities of being the best did not differ significantly on ORR (Figure 2.3).

Table 2.3 Treatment comparisons for PFS, OS (HRs [95% CI]), ORR, diarrhoea, and rash (ORs [95% CI])

PFS					
Chemotherapy	2.34 (2.03,2.71)	2.76 (2.3,3.34)	2.7 (2.27,3.24)	3.95 (3.05,5.21)	5.64 (4.58,7.02)
0.43 (0.37, 0.49)	Gefitinib	1.17 (0.98,1.41)	1.15 (0.96,1.39)	1.68 (1.35,2.13)	2.4 (2,2.91)
0.36 (0.30,0.43)	0.85 (0.71,1.02)	Erlotinib	0.97 (0.77,1.25)	1.42 (1.08,1.93)	2.04 (1.7,2.46)
0.37 (0.31,0.44)	0.87 (0.72,1.04)	1.03 (0.8,1.3)	Afatinib	1.45 (1.09,1.97)	2.07 (1.62,2.69)
0.25 (0.19,0.33)	0.59 (0.47,0.74)	0.7 (0.52,0.93)	0.69 (0.51,0.91)	Dacomitinib	1.41 (1.06,1.91)
0.18 (0.14,0.22)	0.42 (0.34,0.5)	0.49 (0.41,0.59)	0.48 (0.37,0.62)	0.71 (0.52,0.94)	Osimertinib
OS					
Chemotherapy	0.97 (0.84,1.12)	0.99 (0.83,1.19)	1.11 (0.94,1.31)	1.26 (0.94,1.73)	1.54 (1.19,2.04)
1.03 (0.89,1.19)	Gefitinib	1.02 (0.84,1.24)	1.14 (0.96,1.38)	1.3 (1.01,1.72)	1.59 (1.24,2.07)
1.01 (0.84,1.21)	0.98 (0.80,1.19)	Erlotinib	1.11 (0.89,1.42)	1.27 (0.93,1.8)	1.56 (1.22,2.03)
0.9 (0.76,1.06)	0.88 (0.73,1.05)	0.90 (0.71,1.13)	Afatinib	1.13 (0.83,1.59)	1.38 (1.04,1.89)
0.79 (0.58,1.06)	0.77 (0.58,0.99)	0.79 (0.56,1.08)	0.88 (0.63,1.21)	Dacomitinib	1.20 (0.84,1.77)
0.65 (0.49,0.84)	0.63 (0.48,0.81)	0.64 (0.49,0.82)	0.72 (0.53,0.96)	0.84 (0.57,1.19)	Osimertinib
ORR					
Chemotherapy	0.26 (0.2,0.34)	0.20 (0.14,0.27)	0.16 (0.12,0.22)	0.22 (0.16,0.31)	0.16 (0.10,0.27)
3.86 (2.94,5)	Gefitinib	0.75 (0.54,1.08)	0.63 (0.46,0.89)	0.84 (0.68,1.04)	0.62 (0.4,1.02)
5.09 (3.66,6.91)	1.33 (0.93,1.86)	Erlotinib	0.82 (0.55,1.27)	1.08 (0.74,1.66)	0.82 (0.53,1.34)
6.08 (4.45,8.1)	1.59 (1.13,2.17)	1.22 (0.79,1.81)	Afatinib	1.30 (0.9,1.96)	0.97 (0.58,1.73)
4.60 (3.23,6.37)	1.19 (0.96,1.46)	0.92 (0.6,1.35)	0.77 (0.51,1.12)	Dacomitinib	0.73 (0.45,1.26)
6.18 (3.65,9.8)	1.61 (0.98,2.49)	1.23 (0.75,1.9)	1.04 (0.58,1.72)	1.37 (0.79,2.2)	Osimertinib
Diarrhoea					
Chemotherapy	0.25 (0.08,1.36)	0.2 (0.06,1.32)	0.03 (0.01,0.15)	0.02 (0,0.25)	0.22 (0.06,1.45)
4 (0.74,12.81)	Gefitinib	0.65 (0.21,3.37)	0.08 (0.03,0.37)	0.07 (0.02,0.43)	0.79 (0.32,2.67)
5.11 (0.76,17.91)	1.55 (0.3,4.82)	Erlotinib	0.08 (0.02,0.73)	0.07 (0.02,0.91)	0.95 (0.38,3.21)
39.8 (6.71,131.4)	12.01 (2.7,35.35)	12.03 (1.38,46.74)	Afatinib	0.59 (0.14,6.84)	6.39 (1.82,43.4)
53.34 (3.96,239.4)	13.36 (2.33,44)	14.36 (1.1,64.27)	1.71 (0.15,7.28)	Dacomitinib	6.04 (1.52,58.31)
4.58 (0.69,15.86)	1.26 (0.37,3.16)	1.05 (0.31,2.63)	0.16 (0.02,0.55)	0.17 (0.02,0.66)	Osimertinib
Rash					
Chemotherapy	0.23 (0.1,0.71)	0.11 (0.04,0.42)	0.06 (0.02,0.22)	0 (0,0.05)	0.08 (0.03,0.35)
4.28 (1.4,10.23)	Gefitinib	0.41 (0.15,1.6)	0.22 (0.10,0.65)	0 (0,0.16)	0.31 (0.12,1.08)
9.18 (2.39,24.56)	2.46 (0.63,6.74)	Erlotinib	0.39 (0.12,2.21)	0.01 (0,0.43)	0.63 (0.25,2.18)
18.06 (4.51,49.39)	4.47 (1.54,10.17)	2.57 (0.45,8.35)	Afatinib	0.01 (0,0.77)	1.11 (0.35,5.86)
1170 (19.4,7267)	275.4 (6.1,1636)	162 (2.34,1009)	77.97 (1.31,477.4)	Dacomitinib	11.15 (1.82,740.19)
12.94 (2.87,37.81)	3.24 (0.92,8.28)	1.59 (0.46,4.03)	0.9 (0.17,2.83)	0.09 (0,0.55)	Osimertinib

Abbreviations: ORR, objective response rate; OS, overall survival; PFS, progression-free survival

Figure 2.3 Distribution of probabilities of being the best for outcomes and two major toxicities, classified by drugs



Abbreviations: ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
*P<0.0001

Diarrhoea occurred significantly more often in patients treated with afatinib or dacomtinib. Gefitinib, erlotinib, and osimertinib showed a mild risk of diarrhoea and chemotherapy had a low risk, with probabilities of being the best for diarrhoea, with 7%, 6%, 15%, and 72%, respectively. Regarding rash, occurrence was high among patients treated with afatinib or dacomitinib and moderate among patients treated with gefitinib, erlotinib, or osimertinib. The risk of rash was low for chemotherapy with a 99% probability of being the best treatment.

Discussion

In patients with EGFR-mutated NSCLC, TKIs have shown superior efficacy compared to platinum-based doublet therapy.[61-69] Now that we have at least five different EGFR-TKIs, the relative efficacy and toxicity of these TKIs becomes important to help physicians choose the optimal drug for treatment. In contrast to meta-analysis, which only estimates the relative effect of the same interventions with the same comparators, an NMA combines direct evidence within RCTs with indirect evidence across RCTs to estimate the relative effect of multiple pairwise comparisons. In this way, the relative efficacy of a whole set of treatments for a disease can be synthesised.[72] Previous NMAs tried to provide relative evidence on the efficacy

of EGFR-TKIs by using only three or four TKIs, or by including both first- and second-line TKIs in the network. These studies did not show significant differences between EGFR-TKIs in terms of efficacy and toxicity. Since a number of head-to-head trials between these drugs and data from new EGFR-TKIs are now available, we performed an NMA with five different TKIs (afatinib, dacomitinib, erlotinib, gefitinib, and osimertinib) to estimate their relative efficacy and toxicity as first-line treatment in patients with EGFR-mutated (exon 19 deletion or exon 21 L858R mutation) NSCLC. The results of the NMA indicated that osimertinib was significantly more effective on PFS compared to all other drugs. Dacomitinib proved to be the second best TKI on PFS with a significantly better PFS compared to gefitinib, erlotinib, and afatinib. Osimertinib also showed a significant better efficacy in terms of OS compared to all other TKIs. Furthermore, AEs (diarrhoea and rash) occurred more often in patients treated with afatinib or dacomitinib, compared to the other treatments. Due to the limited number of trials per treatment arm, a fixed-effect NMA was considered appropriate because heterogeneity could not be appropriately assessed.[84-86]

To our knowledge, this is the first study that performed an NMA to compare the results between five first-line EGFR-TKIs. Previous NMA studies failed to show significant differences between EGFR-TKIs.[73-77] By including additional evidence from new RCTs[70,71,91] and updating results in the network, new results were produced, namely significant efficacy differences between the TKIs.

An important assumption in our study was that all included studies were generally similar, both clinically and methodologically. All 13 studies only included patients with activating EGFR mutations, with the percentage of males ranging from 11-47%, the median age range being 56-65 years, and the percentage of adenocarcinoma histology type ranging between 90 and 100% across the studies, which contributed to the homogeneity of the study population. Additionally, efficacy of EGFR-TKIs could be different when it was provided as second- or third-line treatment. A previous study showed that chemotherapy might change the proportion of tumour cells with EGFR mutations within the primary tumor.[96] Treatment with a TKI after platinum-based doublet therapy would thus probably affect the efficacy by inducing resistance mechanisms. Therefore, only first-line TKI treatments were included in our analyses in order to avoid such bias and to improve homogeneity.

For our analysis, the most common NMA method was used and, consequently, proportional hazards were assumed.[83] Since in 11 of the 13 trials in which the proportional hazard assumption could be checked, the assumption was not violated.

The length of follow-up differs among the included studies. As HRs may depend on the follow-up period, findings may vary when HRs are estimated at a different follow-up period. Due to a lack of patient-level data, correction for the different length of follow-up in an NMA is not possible. Insight into the long-term direction of HRs can be obtained with a longer follow-up duration, although this will also induce selection bias.[97]

Although osimertinib showed a significant better OS compared to all drugs, gefitinib, erlotinib, and afatinib did not reveal a significant effect on OS compared to chemotherapy, which was similar to the individual studies. Some individual studies even showed OS results which were in favour of chemotherapy due to high proportions of crossover in the chemotherapy-arms.[60,62,64-66] The minimum proportion of crossover in the chemotherapy-arm was 59.3% in the WJTOG3405 study [62] and the maximum was 94.6% in the NEJ002 study.[61] A much smaller proportion of initiated TKI-patients received chemotherapy as subsequent treatment.[61,62,64-68] A recent study suggested that patients who received chemotherapy or TKI after first-line TKI or first-line chemotherapy had a longer OS than patients who only received first-line therapy.[93] The imbalanced subsequent treatments of the TKI- and chemotherapy-arms may have resulted in no significant OS differences between TKIs and chemotherapy. Therefore, it is questionable whether OS is an appropriate outcome measure in studies with substantial crossover.

Since final OS data was not available during our study period, the OS data of the FLAURA study were based on an interim analysis. Although this analysis did not show a formal statistical significance for OS, osimertinib seems to show a potential survival benefit compared to standard TKI.[71] An update of our NMA is desirable when final OS data of the FLAURA trial become available.

Conclusion

Our study showed that osimertinib is the most favourable EGFR-TKI in terms of PFS and OS. With regard to AEs, afatinib and dacomitinib had a higher risk of diarrhoea and rash. Gefitinib, erlotinib, and osimertinib showed a mild risk of AEs. Thus, regarding its high efficacy-mild toxicity pattern, osimertinib is indicated as the most favourable first-line TKI in patients with activating EGFR-mutated (exon 19 deletion or exon 21 L858R mutation) NSCLC.

Disclosure

One author (CU) reports grants from Boehringer-Ingelheim, Janssen-Cilag, Genzyme, Astellas, Sanofi, Roche, AstraZeneca, Amgen, Gilead, Merck, Bayer, outside the submitted work. All remaining authors declared no conflict of interest.

Supplemental material: Systematic review

Table S2.1 Search strategy PubMed

Database	**PubMed**
Date of search	**10 November 2016**
Date range	**1 January 2010 - 1 November 2016**

1	(("afatinib") AND "advanced non small cell lung cancer") AND "egfr mutations"
2	(("afatinib") AND "stage 4") AND "non small cell lung cancer") AND "egfr mutations"
3	(("afatinib") AND "versus") AND "chemotherapy"
4	((("afatinib") AND "versus") AND "chemotherapy") AND "first line therapy"
5	((((("afatinib") AND "versus") AND "chemotherapy") AND "advanced non small cell lung cancer") AND "egfr mutations"
6	(((((("afatinib") AND "versus") AND "chemotherapy") AND "stage 4") AND "non small cell lung cancer") AND "egfr mutations"
7	((("afatinib") AND "versus") AND "chemotherapy") AND "overall survival"
8	((("afatinib") AND "versus") AND "chemotherapy") AND "progression free survival"
9	(("erlotinib") AND "advanced non small cell lung cancer") AND "egfr mutations"
10	((("erlotinib") AND "stage 4") AND "non small cell lung cancer") AND "egfr mutations"
11	(("erlotinib") AND "versus") AND "chemotherapy"
12	((("erlotinib") AND "versus") AND "chemotherapy") AND "first line therapy"
13	((((("erlotinib") AND "versus") AND "chemotherapy") AND "advanced non small cell lung cancer") AND "egfr mutations"
14	(((((("erlotinib") AND "versus") AND "chemotherapy") AND "stage 4") AND "non small cell lung cancer") AND "egfr mutations"
15	((("erlotinib") AND "versus") AND "chemotherapy") AND "overall survival"
16	((("erlotinib") AND "versus") AND "chemotherapy") AND "progression free survival"
17	(("gefitinib") AND "advanced non small cell lung cancer") AND "egfr mutations"
18	((("gefitinib") AND "stage 4") AND "non small cell lung cancer") AND "egfr mutations"
19	(("gefitinib") AND "versus") AND "chemotherapy"
20	((("gefitinib") AND "versus") AND "chemotherapy") AND "first line therapy"
21	((((("gefitinib") AND "versus") AND "chemotherapy") AND "advanced non small cell lung cancer") AND "egfr mutations"
22	(((((("gefitinib") AND "versus") AND "chemotherapy") AND "stage 4") AND "non small cell lung cancer") AND "egfr mutations"
23	((("gefitinib") AND "versus") AND "chemotherapy") AND "overall survival"
24	((("gefitinib") AND "versus") AND "chemotherapy") AND "progression free survival"

Table S2.2 Search strategy Embase

Database	**Embase**
Date of search	**21 November 2016**
Date range	**1 January 2010 - 1 November 2016**

1	'afatinib'/exp OR 'afatinib' AND 'advanced non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
2	'afatinib'/exp OR 'afatinib' AND 'stage 4' AND 'non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
3	'afatinib'/exp OR 'afatinib' AND versus AND 'chemotherapy' AND [2010-2016]/py
4	'afatinib'/exp OR 'afatinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'first line therapy' AND [2010-2016]/py
5	afatinib'/exp OR 'afatinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'advanced non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
6	'afatinib'/exp OR 'afatinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'stage 4' AND 'non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
7	'afatinib'/exp OR 'afatinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'overall survival' AND [2010-2016]/py
8	'afatinib'/exp OR 'afatinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'progression free survival' AND [2010-2016]/py
9	'erlotinib'/exp OR 'erlotinib' AND 'advanced non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
10	'erlotinib'/exp OR 'erlotinib' AND 'stage 4' AND 'non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
11	erlotinib'/exp OR 'erlotinib' AND versus AND 'chemotherapy' AND [2010-2016]/py
12	erlotinib'/exp OR 'erlotinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'first line therapy' AND [2010-2016]/py
13	'erlotinib'/exp OR 'erlotinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'advanced non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
14	'erlotinib'/exp OR 'erlotinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'stage 4' AND 'non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
15	'erlotinib'/exp OR 'erlotinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'overall survival' AND [2010-2016]/py
16	'erlotinib'/exp OR 'erlotinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'progression free survival' AND [2010-2016]/py
17	'gefitinib' AND 'advanced non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
18	'gefitinib'/exp OR 'gefitinib' AND 'stage 4' AND ('non small cell lung cancer'/exp OR 'non small cell lung cancer') AND 'egfr mutation' AND [2010-2016]/py
19	'gefitinib' AND versus AND 'chemotherapy' AND [2010-2016]/py
20	'gefitinib'/exp OR 'gefitinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'first line therapy' AND [2010-2016]/py
21	'gefitinib'/exp OR 'gefitinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'advanced non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
22	gefitinib'/exp OR 'gefitinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'stage 4' AND 'non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
23	'gefitinib'/exp OR 'gefitinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND ('overall survival'/exp OR 'overall survival') AND [2010-2016]/py
24	'gefitinib'/exp OR 'gefitinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND ('progression free survival'/exp OR 'progression free survival') AND [2010-2016]/py

Table S2.3 Search strategy Cochrane Library

Database	**Cochrane library**
Date of search	**2 December 2016**
Date range	**1 January 2010 - 1 November 2016**

1	'"afatinib" and "advanced" and "non small cell lung cancer" and "egfr mutations" , Publication Year from 2010 to 2016 in Trials'
2	'"afatinib" and "non small cell lung cancer stage IV" and "egfr mutations" , Publication Year from 2010 to 2016'
3	'"afatinib" and "chemotherapy" , Publication Year from 2010 to 2016 in Trials'
4	'"afatinib" and "chemotherapy" and "first-line therapy" , Publication Year from 2010 to 2016 in Trials'
5	'"afatinib" and "chemotherapy" and "advanced" and "non small cell lung cancer" and "egfr mutations" , Publication Year from 2010 to 2016 in Trials'
6	'"afatinib" and "chemotherapy" and "non small cell lung cancer stage IV" and "egfr mutations" , Publication Year from 2010 to 2016'
7	'"afatinib" and "chemotherapy" and "overall survival" , Publication Year from 2010 to 2016 in Trials'
8	'"afatinib" and "chemotherapy" and "progression-free survival" , Publication Year from 2010 to 2016 in Trials
9	"erlotinib" and "advanced" and "non small cell lung cancer" and "egfr mutations" , Publication Year from 2010 to 2016 in Trials'
10	"erlotinib" and "non small cell lung cancer stage IV" and "egfr mutations" , Publication Year from 2010 to 2016 in Trials'
11	'"erlotinib" and "chemotherapy" , Publication Year from 2010 to 2016 in Trials'
12	'"erlotinib" and "chemotherapy" and "first-line therapy" , Publication Year from 2010 to 2016 in Trials'
13	"erlotinib" and "chemotherapy" and "advanced" and "non small cell lung cancer" and "egfr mutations" , Publication Year from 2010 to 2016 in Trials'
14	'"erlotinib" and "chemotherapy" and "non small cell lung cancer stage IV" and "egfr mutations" , Publication Year from 2010 to 2016'
15	"erlotinib" and "chemotherapy" and "overall survival" , Publication Year from 2010 to 2016 in Trials'
16	'"erlotinib" and "chemotherapy" and "progression-free survival" , Publication Year from 2010 to 2016 in Trials'
17	'"gefitinib" and "advanced" and "non small cell lung cancer" and "egfr mutations" , Publication Year from 2010 to 2016 in Trials'
18	'"gefitinib" and "non small cell lung cancer stage IV" and "egfr mutations" , Publication Year from 2010 to 2016'
19	'"gefitinib" and "chemotherapy" , Publication Year from 2010 to 2016 in Trials'
20	'"gefitinib" and "chemotherapy" and "first-line therapy" , Publication Year from 2010 to 2016 in Trials'
21	"gefitinib" and "chemotherapy" and "advanced" and "non small cell lung cancer" and "egfr mutations" , Publication Year from 2010 to 2016 in Trials'
22	"gefitinib" and "chemotherapy" and "non small cell lung cancer stage IV" and "egfr mutations" , Publication Year from 2010 to 2016'
23	'"gefitinib" and "chemotherapy" and "overall survival" , Publication Year from 2010 to 2016 in Trials'
24	'"gefitinib" and "chemotherapy" and "progression-free survival" , Publication Year from 2010 to 2016 in Trials'

Table S2.4 In- and exclusion criteria title/abstract and full-text screening

Title/abstract screening		
	Exclusion criteria	Total number excluded studies
1	No first-line therapy	298
2	No (EGFR-mutated) NSCLC study population	236
3	First-line gefitinib, erlotinib, afatinib, or osimertinib not compared to other single TKI or platinum-based doublet therapy	201
4	No (phase IIB/III) RCT	177
5	(Systematic) review/overview	151
6	TKI combination treatment	145
7	Study subject was biomarker/DNA/molecular assessment	114
8	(Network) meta-analysis	72
9	Outcomes not eligible	37
10	NSCLC stage I-IIIA	17
11	Abstract	7
Full-text screening		
1	Abstract	22
2	Subgroup/post hoc analysis/updated results	15
3	No (phase IIB/III) RCT	7
4	Non-English	4
5	Outcomes not eligible	4
6	No (EGFR-mutated) stage IIIB/IV NSCLC patients	1

Supplemental material: Data extraction

Table S2.5 Data extraction of all included RCTs

Study name	Trial number	Year	First author	Treatments		Number of patients	
				n[,1]	n[,2]	n[,1]	n[,2]
WJTOG3405	00000000539	2010	Tetsuya Mitsudomi	Gefitinib (250 mg/per day)	Docetaxel/Cisplatin	86	86
NEJ002	C000000376*	2010	Makato Maemondo	Gefitinib (250 mg/per day)	Paclitaxel/Carboplatin	114	114
IPASS	NCT00322452	2011	Masahiro Fukuoka	Gefitinib (250 mg/per day)	Paclitaxel/Carboplatin	132	129
First-SIGNAL	NCT00455936	2011	Ji-Youn Han	Gefitinib (250 mg/per day)	Gemcitabine/Cisplatin	26	16
OPTIMAL	NCT00874419	2011	Caicun Zhou	Erlotinib (150mg/per day)	Gemcitabine/Carboplatin	82	72
EURTAC	NCT00446225	2012	Rafael Rosell	Erlotinib (150mg/per day)	Docetaxel/Cisplatin or Gemcitabine/Cisplatin	86	87
ENSURE	NCT01342965	2015	Y.-L. Wu	Erlotinib (150mg/per day)	Gemcitabine/Cisplatin	110	107
Lux-Lung 3	NCT00949650	2013	Lecia V. Sequist	Afatinib (40 mg/per day)	Pemetrexed/Cisplatin	230	115
Lux-Lung 6	NCT01121393	2014	Yi-Long Wu	Afatinib (40 mg/per day)	Gemcitabine/Cisplatin	242	122
Lux-Lung 7	NCT01466660	2016	Keunchil Park	Afatinib (40 mg/per day)	Gefitinib (250 mg/per day)	160	159
CTONG0901	NCT01024413	2017	J J Yang	Erlotinib (150mg/per day)	Gefitinib (250 mg/per day)	128	128
ARCHER1050	NCT01774721	2017	Yi-Long Wu	Dacomitinib (45mg/per day)	Gefitinib (250mg/per day)	227	225
FLAURA	NCT02296125	2018	J.-C. Soria	Osimertinib (80mg/per day)	Gefitinib (250 mg/per day) or Erlotinib (150mg/per day)	279	277

Study name	Primary end-point	Secondary end-points**	Patient enrolment	Data cut-off OS analysis	Median PFS (months)		PFS	Median OS (months)		OS
					n[,1]	n[,2]	HR (95% CI)	n[,1]	n[,2]	HR (95% CI)
WJTOG3405	PFS	OS, ORR	N/A	September 2013	9.2	6.3	0.489 (0.336-0.71)	34.8	37.3	1.252 (0.883-1.775)
NEJ002	PFS	OS, ORR, toxicity	March 2006	December 2010	10.4	5.4	0.322 (0.236-0.438)	27.7	26.6	0.887 (0.634-1.241)
IPASS	PFS	OS, ORR, QoL, AE, safety	March 2006-October 2007	June 2010	N/A	N/A	0.48 (0.36-0.64)	21.6	21.9	1 (0.76-1.33)
First-SIGNAL	OS	PFS, ORR, QoL	October 2005-November 2007	November 2009	N/A	N/A	0.544 (0.269-1.1)	N/A	N/A	1.043 (0.498-2.182)
OPTIMAL	PFS	OS, ORR, TTP, safety, QoL	August 2008-July 2009	December 2012	13.1	4.6	0.16 (0.1-0.26)	22.8	27.2	1.19 (0.83-1.71)
EURTAC	PFS	OS, ORR	February 2007-January 2011	April 2012	9.7	5.2	0.37 (0.25-0.54)	22.9	19.6	0.92 (0.63-1.35)
ENSURE	PFS	ORR	March 2011-June 2012	April 2014	11	5.5	0.42 (0.27-0.66)	26.3	25.5	0.91 (0.63-1.31)
Lux-Lung 3	PFS	OS, ORR, AEs, PROMs	August 2009-February 2011	November 2013	11.1	6.9	0.58 (0.43-0.78)	33.3	21.1	0.88 (0.66-1.17)
Lux-Lung 6	PFS	OS, ORR	April 2010-November 2011	December 2013	11	5.6	0.28 (0.2-0.39)	31.4	18.4	0.93 (0.72-1.22)
Lux-Lung 7	PFS, OS	ORR, QoL	December 2011-August 2013	April 2016	11	10.9	0.73 (0.57-0.95)	27.9	24.5	0.86 (0.66-1.12)
CTONG0901	PFS	OS, ORR, safety	July 2009-2014	June 2015	13.2	11.1	0.96 (0.69-1.35)	22.4	20.7	0.98 (0.67-1.42)
ARCHER1050	PFS	OS at 30 months, ORR, safety, PROMs	May 2013-March 2015	N/A	14.7	9.2	0.59 (0.47-0.74)	34.1	26.8	0.76 (0.582-0.993)
FLAURA	PFS	OS, ORR, safety	December 2014-March 2016	N/A	18.9	10.2	0.45 (0.36-0.57)	N/A	N/A	0.46 (0.37-0.57)

Study name	ORR n[,1]		ORR n[,2]		ALT/AST increase ≥ grade 3		Diarrhoea ≥ grade 3		Rash or acne ≥ grade 3		Male (%)		Age (median)		Ethnicity	
	CR/PR	No response	CR/PR	No response	n[,1]	n[,2]	n[,1]	n[,2]	n[,1]	n[,2]	n[,1]	n[,2]	n[,1]	n[,2]	n[,1]	n[,2]
WJTOG3405	36	22	19	40	38	3	1	0	2	0	31	30	64	64	Japanese	Japanese
NEJ002	84	29	35	72	30	1	1	0	6	3	37	36	63.9***	62.6***	Japanese	Japanese
IPASS	94	37	61	66	N/A	N/A	N/A	N/A	N/A	N/A	21	21	57	57	Asian	Asian
First-SIGNAL	22	4	6	10	9	1	N/A	N/A	N/A	N/A	12	11	57	56.5	Korean	Korean
OPTIMAL	68	14	26	46	3	1	1	0	2	0	41	40	57	59	Asian	Asian
EURTAC	50	36	13	74	2	0	4	0	11	0	33	22	65	65	European	European
ENSURE	69	41	36	71	N/A	N/A	0	0	7	1	38	39	57.5	56	Asian	Asian
Lux-Lung 3	129	101	26	89	N/A	N/A	33	0	37	0	36	33	61.5	61	Global	Global
Lux-Lung 6	162	80	28	94	5	5	13	0	35	0	36	32	58	58	Asian	Asian
Lux-Lung 7	112	48	89	70	0	14	20	2	15	5	43	33	63	63	Global	Global
CTONG0901	47	34	44	40	0	0	0	0	3	0	47	46	****	****	N/A	N/A
ARCHER1050	170	57	161	64	2	28	19	2	41	0	36	44	62	61	Global	Global
FLAURA	223	56	210	72	3	37	6	6	3	19	36	38	64	64	Global	Global

Supplemental material: WinBUGS code

```
model{
for(i in 1:ns2) {                # LOOP THROUGH 2-ARM STUDIES
            # normal likelihood
            y[i,2] ~ dnorm(delta[i,2],prec[i,2])
            #Deviance contribution for trial i
            resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
 }

for(i in 1:(ns2)){                #   LOOP THROUGH ALL STUDIES
   for (k in 2:na[i]) {                        #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)   # calculate variances
      prec[i,k] <- 1/var[i,k]      # set precisions
      delta[i,k] <-  d[t[i,k]] - d[t[i,1]]
    }
 }
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0                           # treatment effect is zero for reference treatment

# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

# pairwise HRs and LHRs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
            for (k in (c+1):nt) {
            HR[c,k] <- exp(d[k] - d[c])
            lnHR[c,k] <- (d[k]-d[c])
            }
}

# ranking on relative scale
for (k in 1:nt) {
            # rk[k] <- nt+1-rank(d[],k) # assumes events are “good”
             rk[k] <- rank(d[],k) # assumes events are “bad”
            best[k] <- equals(rk[k],1) #calculate probability that treat k is best
            # calculates probability that treat k is h-th best
            for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) }
            }
}
# *** PROGRAM ENDS
```

```
##Data
list(ns2=14, nt=6)

t[,1]   t[,2]   y[,2]   se[,2]   na[]   #Study/Comparison
1       2       -0.71539279   0.190855564   2   # WJTOG3405 / Gef vs Chemo
1       2       -1.133203733  0.157751813   2   # NEJ002 / Gef vs Chemo
1       2       -0.733969175  0.146776568   2   # IPASS / Gef vs Chemo
1       3       -1.832581464  0.24375292    2   # OPTIMAL / Erl vs Chemo
1       2       -0.608806032  0.359274      2   # First-SIGNAL / Gef vs Chemo
1       3       -0.994252273  0.196456179   2   # EURTAC / Erl vs Chemo
1       4       -0.544727175  0.151915487   2   # Lux-Lung 3 / Afa vs Chemo
1       4       -1.272965676  0.170364636   2   # Lux-Lung 6 / Afa vs Chemo
1       3       -0.867500568  0.228014764   2   # ENSURE / Erl vs Chemo
2       4       -0.314710745  0.130312659   2   # Lux-Lung 7 / Afa vs Gef
2       3       -0.040821995  0.171216396   2   # CTONG0901 / Erl vs Gef
2       5       -0.527632742  0.115795278   2   # ARCHER1050 / Dac vs Gef
2       6       -0.798507696  0.117227635   2   # FLAURA / Osi vs Gef
3       6       -0.798507696  0.117227635   2   # FLAURA / Osi vs Erl
END

##Inits
#chain1
list(d=c( NA, 0,0,0,0,0))
#chain2
list(d=c( NA, 1,1,1,1,1))
#chain3
list(d=c( NA, 2,2,2,2,2))
```

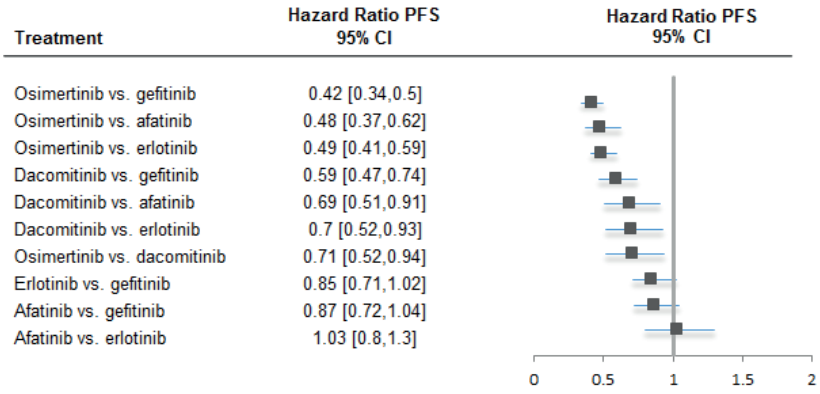
Supplemental material: Quality and risk of bias assessment

Table S2.6 Quality and risk of bias assessment

Trial	Sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome data	Incomplete outcome data	Selective reporting	Other sources of bias
NEJ002 (2010)	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
WJTOG3405 (2010)	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
IPASS (2009/2011)	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
First-SIGNAL (2012)	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	A maximum of 9 cycles of GP chemotherapy was recommended instead of 4-6 cycles. Crossover was recommended as second-line treatment
OPTIMAL (2011)	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
EURTAC (2012)	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
ENSURE (2015)	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
Lux-Lung 3 (2013)	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
Lux-Lung 6 (2014)	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
Lux-Lung 7 (2016)	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
CTONG0901 (2017)	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	
ARCHER1050 (2017)	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	
FLAURA (2018)	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment

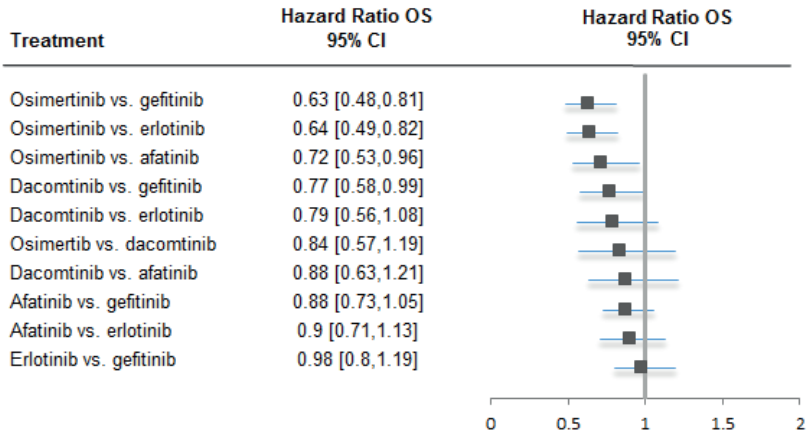
Supplemental material: Results NMA

Figure S2.1 Forest plot of PFS for all EGFR-TKIs



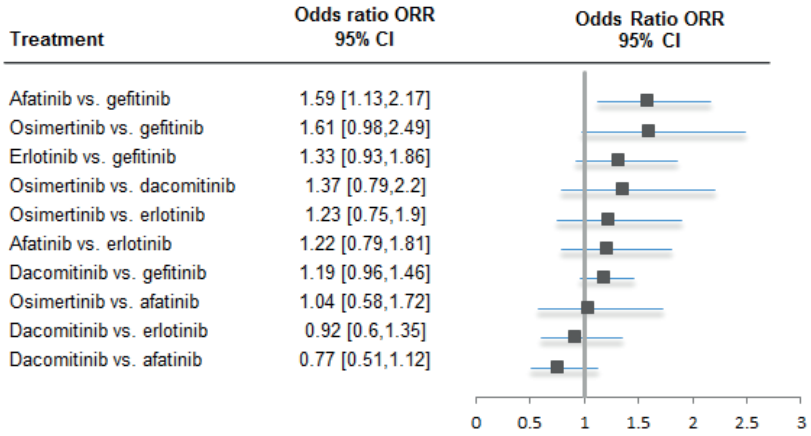
Abbreviations: CI, confidence interval; PFS, progression-free survival.

Figure S2.2 Forest plot of OS for all EGFR-TKIs



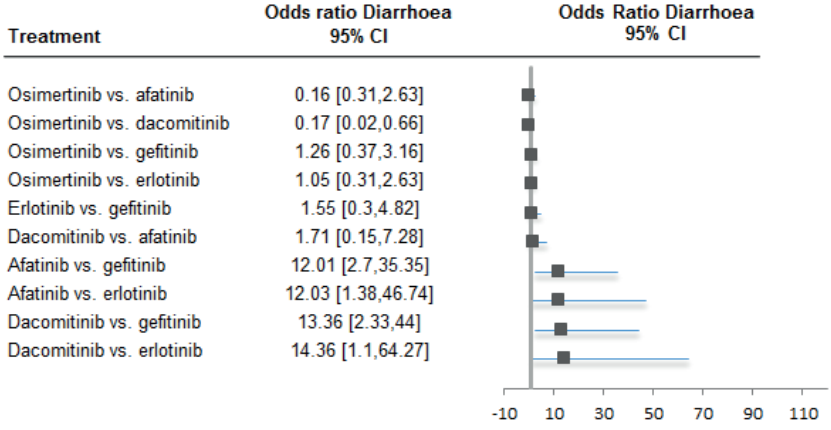
Abbreviations: CI, confidence interval; OS, overall survival.

Figure S2.3 Forest plot of ORR for all EGFR-TKIs.



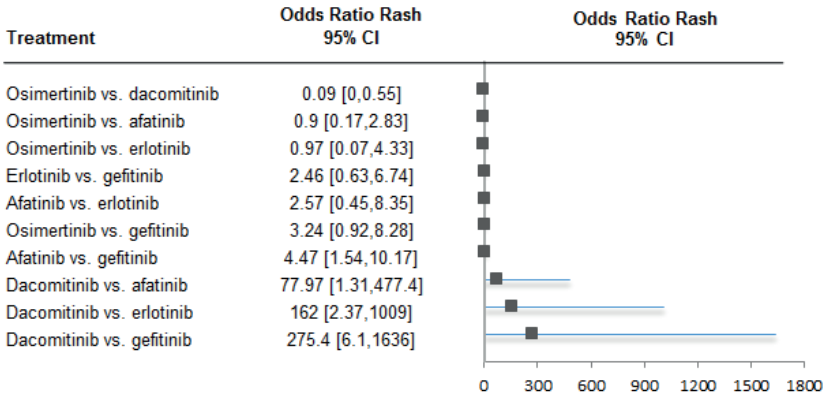
Abbreviations: CI, confidence interval; ORR, objective response rate.

Figure S2.4 Forest plot of diarrhoea for all EGFR-TKIs



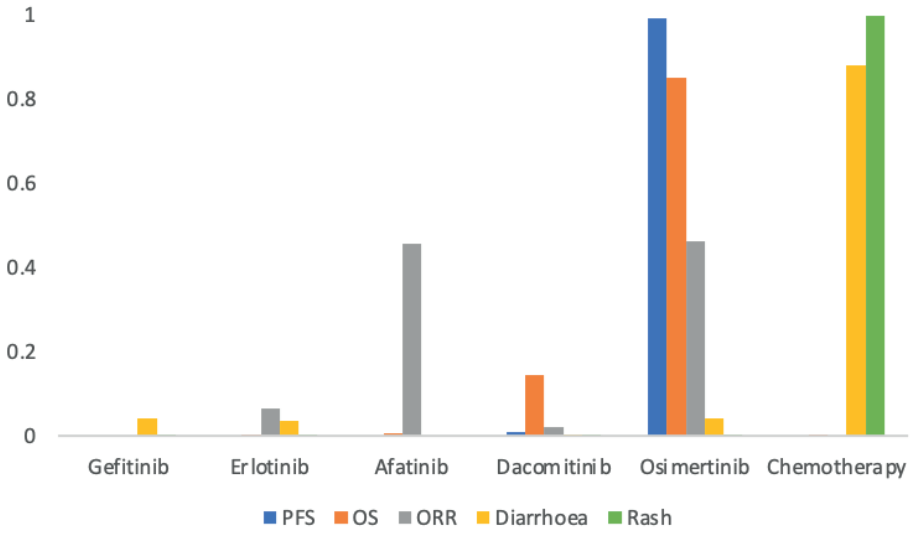
Abbreviations: CI, confidence interval.

Figure S2.5 Forest plot of rash for all EGFR-TKIs



Abbreviations: CI, confidence interval

Figure S2.6 Distribution of probabilities of being ranked best per treatment, classified by outcome



Abbreviations: ORR, objective response rate; OS, overall survival; PFS, progression-free survival

Chapter 3

Cost-effectiveness analysis of the first-line EGFR-TKIs in patients with non-small cell lung cancer harbouring EGFR mutations

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Eur J Health Econ 2020; 21:153-164.

Abstract

Objectives: To compare the cost-effectiveness of first-line gefitinib, erlotinib, afatinib, and osimertinib in patients with non-small cell lung cancer (NSCLC) harbouring epidermal growth factor receptor (EGFR) mutations.

Methods: A systematic review and network meta-analysis (NMA) were conducted to compare the relative efficacy of gefitinib, erlotinib, afatinib, and osimertinib in EGFR-mutated NSCLC. To assess the cost-effectiveness of these treatments, a Markov model was developed from Dutch societal perspective. The model was based on the clinical studies included in the NMA. Incremental costs per life-year (LY) and per quality-adjusted life-year (QALY) gained were estimated. Deterministic and probabilistic sensitivity analyses were conducted.

Results: Total discounted per patient costs for gefitinib, erlotinib, afatinib, and osimertinib were €65,889, €64,035, €69,418, and €131,997 and mean QALYs were 1.36, 1.39, 1.52, and 2.01 per patient, respectively. Erlotinib dominated gefitinib. Afatinib versus erlotinib yielded incremental costs of €27,058/LY and €41,504/QALY gained. Osimertinib resulted in €91,726 /LY and €128,343/QALY gained compared to afatinib. Gefitinib, erlotinib, afatinib, and osimertinib had 13%, 19%, 43%, and 26% probability to be cost-effective at a threshold of €80,000/QALY. A price reduction of osimertinib of 30% is required for osimertinib to be cost-effective at a threshold of €80,000/QALY.

Conclusions: Osimertinib had a better effectiveness compared to all other TKIs. However, at a Dutch threshold of €80,000/QALY, osimertinib appears not to be cost-effective.

Introduction

Lung cancer is the leading cause of cancer-related mortality in the Netherlands and worldwide, with 10,346 lung cancer deaths in the Netherlands in 2014.[98] Non-small cell lung cancer (NSCLC) is the most common type of lung cancer with 80-85% of all cases.[53] At diagnosis, many patients with NSCLC are already in an advanced disease stage (IIIB or IV) and thus ineligible for surgical resection.[99] Platinum-based therapy is the standard first-line treatment for advanced NSCLC, which provides a median overall survival (OS) of 7.9 months.[100] Nowadays, molecularly targeted agents are of high importance as treatment strategies for lung cancer patients.[101]For several cancer types, these targeted agents come with improved outcomes, but also increased costs.[102]

In NSCLC, mutations of the epidermal growth factor receptor (EGFR) play an important role in the growth and progression of tumour cells.[57] Prevalence of EGFR mutations is the highest in Asia with over 50% of all Asian patients with lung cancer type adenocarcinoma.[103] Among Dutch patients with NSCLC, the frequency of EGFR mutations is about 10.9%.[55,104] Currently, three first-line EGFR tyrosine kinase inhibitors (TKIs) are used in clinical practice: gefitinib, erlotinib, and afatinib. These drugs have shown significantly improved progression-free survival (PFS) as first-line treatment, compared to platinum-based therapy, in patients with EGFR mutation-positive (exon 19 deletion or exon 21 L858R mutation) NSCLC.[60-62,64-68] Osimertinib, a third-generation EGFR-TKI, is used as second-line treatment in clinical practice. Recently, a randomised controlled trial (RCT) showed a better efficacy of osimertinib compared to gefitinib and erlotinib as first-line treatment. Moreover, clinical studies showed the ability of osimertinib to penetrate the central nervous system (CNS). This may be an advantage over the standard treatment, as it could decrease the occurrence of CNS progression.[71] Therefore, osimertinib is expected to be used as first-line treatment in clinical practice in the near future. Clear direct evidence of the differences between gefitinib, erlotinib, afatinib, and osimertinib in terms of efficacy and toxicity is lacking as head-to-head comparisons are not available for all these TKIs. Thus, it is still uncertain whether one TKI is more favourable over the others in terms of efficacy and toxicity. Network meta-analysis (NMA) enables comparison of direct and indirect evidence across trials to synthesise the efficacy of different TKIs. Several NMAs on TKIs did not show significant differences between these drugs.[73-77] However, the outcomes of the NMAs differed from each other, which may be due to differences in the selection of studies and data.[86] Therefore, we built a new NMA of the efficacy of first-line gefitinib, erlotinib, afatinib, and osimertinib. Additionally, lung cancer has a substantial economic burden on the health care system, with total mean hospital costs of €33,143 per patient with NSCLC in the Netherlands.[105] For NSCLC, furthermore, TKIs are administered until disease progression or

unacceptable toxicity, which increases the drug acquisition costs. Nowadays, the comparative costs and effects are of growing importance for decision makers.[106] Therefore, information on the incremental value of new treatments in terms of effects and costs is needed for medical resource optimisation. However, not only the acquisition costs of the drugs should be taken into account in the assessment of the cost-effectiveness, but also for example costs of adverse event management, travelling, and productivity losses.[107] Hence, we aimed to assess the cost-effectiveness of first-line gefitinib, erlotinib, afatinib, and osimertinib in patients with stage IIIB/IV NSCLC harbouring EGFR mutations (exon 19 deletion or exon 21 L858R mutation) in the Netherlands from a Dutch societal perspective.

Methods

Systematic review and network meta-analysis

A systematic search of several databases (PubMed, EMBASE, and Cochrane Library) was conducted to identify phase IIB/III RCTs of first-line EGFR-TKI (including gefitinib, erlotinib, afatinib, or osimertinib) compared to another TKI or platinum-based therapy. Search strategy and in- and exclusion criteria can be found in the Supplemental material. Reference lists of published studies were also checked as additional information. The literature review was conducted by two reviewers (MH and CU). After screening titles and abstracts and then full-text reading of the records found by the systematic review, 12 unique RCTs were included in the NMA.[61-69,71,90,91] Quality and risk of bias of the included RCTs was assessed by using the Cochrane Collaboration's tool for assessing risk of bias. According to this assessment, all RCTs were classified as having acceptable quality and low risk of bias.[82] Data on patient characteristics, interventions, comparators, and treatment effects (PFS, OS, and adverse events (AEs)) were extracted. For the NMA, the outcomes of interest were PFS and OS. Since no separate HRs of osimertinib versus gefitinib or osimertinib versus erlotinib were reported in the FLAURA trial, the HRs of PFS and OS were assumed to be the same for both comparisons. A fixed-effects network meta-analysis in WinBUGS 1.4 was built within a Bayesian framework by use of an adapted version of WinBUGS code from Dias et al.[83] Due to the limited number of RCTs per treatment arm, heterogeneity could not be appropriately assessed. Therefore, a fixed-effect NMA was considered as appropriate. The methods of the NMA are described in more detail in the Supplemental material and in a previous study.[108] The results of the NMA are presented in Table 1. Osimertinib had a significantly better PFS and OS compared to gefitinib, erlotinib, and afatinib.

Table 3.1 NMA results of PFS and OS

PFS				
Chemotherapy	2.34 (2.04,2.71)	2.76 (2.3,3.34)	2.70 (2.27,3.24)	5.63 (4.58,7.01)
0.43 (0.37,0.49)	Gefitinib	1.17 (0.98,1.41)	1.15 (0.96,1.39)	2.40 (2,2.90)
0.36 (0.3,0.44)	0.85 (0.71,1.02)	Erlotinib	0.97 (0.77,1.24)	2.04 (1.7,2.46)
0.37 (0.31,0.44)	0.87 (0.72,1.04)	1.03 (0.8,1.3)	Afatinib	2.07 (1.62,2.69)
0.18 (0.14,0.22)	0.42 (0.34,0.5)	0.49 (0.41,0.59)	0.48 (0.37,0.62)	Osimertinib
OS				
Chemotherapy	0.97 (0.84,1.12)	0.99 (0.83,1.19)	1.11 (0.94,1.31)	1.54 (1.19,2.04)
1.03 (0.89,1.19)	Gefitinib	1.02 (0.84,1.24)	1.14 (0.96,1.38)	1.59 (1.24,2.07)
1.01 (0.84,1.21)	0.98 (0.80,1.19)	Erlotinib	1.11 (0.89,1.41)	1.56 (1.22,2.03)
0.90 (0.76,1.06)	0.88 (0.73,1.05)	0.90 (0.7,1.13)	Afatinib	1.38 (1.04,1.89)
0.65 (0.49,0.84)	0.63 (0.48,0.81)	0.64 (0.49,0.82)	0.72 (0.53,0.96)	Osimertinib

Abbreviations: PFS, progression-free survival; OS, overall survival.

Model construction

A Markov model was constructed simulating the transition between three health states: progression-free, progression, and death, in which death was an absorbing state. A cycle length of 30 days was used for the model, which is an appropriate length given the development of lung cancer. It was assumed that all changes in the disease were noticed within this cycle length. In this model, during each cycle, patients with EGFR-mutated NSCLC move between the health states according to the transition probabilities. In each cycle, patients could remain progression-free, may progress, or die. A lifetime time horizon was used, in line with the Dutch guidelines,[107] accounting for all relevant costs and effects of TKI-therapies for patients with EGFR mutations. Half-cycle correction was applied to both costs and effects. Effects are expressed in life-years (LYs) gained and in quality-adjusted life-years (QALYs) gained. Outcomes are presented as incremental cost-effectiveness ratios (ICERs), i.e., incremental costs per LY gained and incremental costs per QALY gained.

Clinical effectiveness

Estimates of the clinical effectiveness in terms of pooled HRs were derived from the NMA. Since HRs only convey information on comparative effectiveness, whereas a model requires absolute estimates of PFS and OS, we used an indirect approach to estimate the transitions of patients treated with TKIs in the model. The NMA did not only include the four TKIs, but also chemotherapy. Thus, we first explored the Kaplan-Meier (KM) curves of PFS and OS for patients with EGFR mutations treated with chemotherapy from the EURTAC trial of erlotinib versus chemotherapy. According to clinical experts, the data of the chemotherapy patients in

the EURTAC trial[66] were deemed as most representative for our study as patient characteristics of that trial are most similar to the Dutch patient population eligible for TKIs (i.e., Caucasian population, mainly adenocarcinoma histology, mainly stage IV NSCLC). However, as the time horizon of the model is life time, whereas the KM curves are truncated at 40 months, where 15% of the patients is still alive, it was necessary to extrapolate the KM curve using a parametric survival curve. Since we had no access to the individual patient data (IPD) of the EURTAC trial, the method of Hoyle and Henley [109] was used to recreate the IPD. Times and survival probabilities were read off from the published KM graph. Based on these survival probabilities and corresponding time and provided numbers at risk, the method of Hoyle and Henley estimated the underlying number of events and censorships in each time interval. By use of the statistical programme R, several survival distributions were fit to the recreated IPD. Based on the fit to the KM curve and the Akaike and Bayesian Information Criterion (AIC and BIC) estimates, a Weibull distribution was assessed as having the best goodness-of-fit for both PFS and OS (see Supplemental material). The general Weibull equation is as follows (in which 't' is time in months): $S(t) = e^{-\lambda t^{\gamma}}$ Lambda and gamma parameters of the patients treated with chemotherapy in the EURTAC trial were used to estimate the parameters for gefitinib, erlotinib, afatinib, and osimertinib, as previously described in published studies.[110,111] For example, the lambda parameter (scale parameter) for gefitinib was estimated by multiplying the lambda for chemotherapy by the pooled HR of gefitinib versus chemotherapy. The gamma parameter (shape parameter) was set equal to the gamma for chemotherapy. The same was done for erlotinib, afatinib, and osimertinib. These parameters were used as input to calculate the transitions of all TKIs.

For each TKI, the percentage of patients in progression-free state at each time is determined by the values of the PFS curve at that time. Similarly, the percentage of patients in the death state is determined as 1 minus the OS curve at that time. From this, the percentage of patients in the progressed state follows, as the three states together should always add up to 100%.

After progression on first-line gefitinib, erlotinib, or afatinib, patients were tested for T790 M mutations. Patients who were T790 M mutation-positive received second-line osimertinib (50% of all patients) and patients who were T790 M mutation-negative were treated with pemetrexed-cisplatin.[101,112] Patients who had progressive disease on first-line osimertinib received second-line pemetrexed-cisplatin treatment. Thus, the progressed health state is split into a 'progression-free second line' and 'progressed second line' health state for those patients receiving a second-line treatment. Clinical data of second-line osimertinib and pemetrexed-cisplatin were derived from the literature.[113,114] The KM curves of second-line osimertinib and pemetrexed-cisplatin were also extrapolated by fitting various parametric functions. For

both second-line PFS and OS, the exponential function was assessed as having the best fit to the KM curves of second-line osimertinib and pemetrexed-cisplatin. The survival curves of all treatment options and the estimation of the transition parameters can be found in the Supplemental material. After progression on second-line osimertinib or pemetrexed-cisplatin, it was assumed that patients were treated with best supportive care (BSC) until death.

Utility weights

Health utility values reflecting the health-related quality of life in each health state were obtained from the literature.[115] The progression-free health state had the highest possible utility value while receiving TKI, with an estimated value of 0.71. This utility value was the same for all three TKI treatments. Progressive disease led to disutility for all TKIs. After progression on first-line TKI treatment, the utility value was estimated at 0.67 (irrespective of post-progression treatment with osimertinib or pemetrexed-cisplatin) and after progression on second-line treatment at 0.62.[115]

Disutility scores of severe adverse events (SAEs) with grades 3 or higher for first-line gefitinib, erlotinib, afatinib, osimertinib, second-line osimertinib, and pemetrexed-cisplatin were also included in the analyses. Occurrence of SAEs was extracted from the RCTs[60-62,64-69,71,90,91] and were only included when at least 1.5% of the patients experienced a certain SAE. The disutility estimates were derived from the literature. The SAEs were assumed to all occur in the first simulation cycle of that specific treatment, since the adverse events commonly appear within the first weeks after starting these treatments.[116,117] For the future effects, a discount rate of 1.5% was applied, according to the Dutch guidelines.[107] All utility values are presented in Table 3.2.

Table 3.2 Input parameters for the model

	Base case	Input DSA	Distribution	Reference
Costs				
Gefitinib per cycle	€2,526[a]		Gamma	[106]
Erlotinib per cycle	€2,260[a]		Gamma	[106]
Afatinib per cycle	€2,414[a]		Gamma	[106]
Osimertinib per cycle	€6,106[a]		Gamma	[106]
Pemetrexed/cisplatin per cycle[b]	€3,029[a]		Gamma	[106]
Best supportive care per cycle	€1,775	1,377;2,065[l]	Gamma	[118]
Mutation test	€929	604;906[l]	Gamma	[119]
Tumour response assessment[c]	€405	157;236[l]	Gamma	[119]
Outpatient visit	€83	65;97[l]	Gamma	[120]
Laboratory tests[d]	€77	60;89[l]	Gamma	[105]
Drug administration	€271	210;315[l]	Gamma	[118]

	Base case	Input DSA	Distribution	Reference
CNS progression osimertinib	€535	428;642	Gamma	[121]
CNS progression standard-TKI	€1,250	1,000;1,500	Gamma	[121]
End-of-life	€2,196	1,703;2,555[l]	Gamma	[122]
Home care per hour	€11	9;13[l]	Gamma	[120]
Indirect medical costs	€10,602[m]	4,578;26,326	Gamma	[120]
Informal care per hour	€14	11;17[l]	Gamma	[120]
Travelling	€6[e]	5;7[l]	Gamma	[120]
Productivity loss	€4,068	3,155;4,733[l]	Gamma	[123]
ALT/AST increase[f]	€464	360;540[l]	Gamma	[106]
Anaemia	€1,953	1,514;2,272[l]	Gamma	[124]
Anorexia	€797	618;927[l]	Gamma	[125]
Asthenia	€813	631;946[g l]	Gamma	[124]
Decreased appetite	€826	640;961[l]	Gamma	[124]
Decreased white blood cells	€1,405	1,089;1,634[h l]	Gamma	[124]
Diarrhoea	€2,359	1,830;2,744[l]	Gamma	[124]
Dyspnoea	€467	362;543[l]	Gamma	[106]
Fatigue	€813	631;946[l]	Gamma	[124]
Febrile neutropenia	€3,033	2,353;3,529[l]	Gamma	[124]
Leukopenia	€1,942	1,507;2,260[l]	Gamma	[124]
Nausea	€728	565;847[l]	Gamma	[124]
Neuropathy	€795	616;924[l]	Gamma	[124]
Neutropenia	€1,405	1,089;1,634[l]	Gamma	[124]
Paronychia	€2,359[k]	1,830;2,744[l]	Gamma	[124]
Rash	€2,359	1,830;2,744[l]	Gamma	[124]
Stomatitis	€4,229	3,280;4,920[l]	Gamma	[126]
Vomiting	€728[j]	565;847[l]	Gamma	[124]
Utilities				
Progression-free	0.71	0.67;0.80	Beta	[115]
After progression	0.67	0.59;0.75	Beta	[115]
After progression on second-line	0.62	0.49;0.74	Beta	[115]
Disutilities				
ALT/AST increase	-0	0;0[l]	Beta	[127]
Anaemia	-0.125	-0.10;-0.15[l]	Beta	[124]
Anorexia	-0.142	-0.114;-0.170	Beta	[128]
Asthenia	-0.074[g]	-0.037;-0.110	Beta	[129]
Decreased appetite	-0.048	-0.016;-0.080	Beta	[124]
Decreased white blood cells	-0.090[h]	-0.060;-0.120	Beta	[129]
Diarrhoea	-0.047	-0.016;-0.078	Beta	[129]
Dyspnoea	-0.256	-0.204;-0.307[l]	Beta	[128]
Fatigue	-0.074	-0.037;-0.110	Beta	[129]
Febrile neutropenia	-0,090	-0.058;-0.122	Beta	[124]
Leukopenia	-0.090	-0.059;-0.120	Beta	[124]
Nausea	-0.048	-0.016;-0.080	Beta	[129]
Neuropathy	-0.048	-0.016;-0.080	Beta	[124]
Neutropenia	-0.090	-0.060;-0.120	Beta	[129]

	Base case	Input DSA	Distribution	Reference
Paronychia	-0.033[k]	-0.009;-0.056	Beta	[129]
Rash	-0.033	-0.009;-0.056	Beta	[129]
Stomatitis	-0.151	-0.121;-0.181[l]	Beta	[130]
Vomiting	-0.048	-0.016;-0.080	Beta	[124]
Body surface area	1.70	1.36;2.04	Normal	[128]
Parameters survival distribution				
Lambda OS chemotherapy	0.019		Normal	
Gamma OS chemotherapy	1.203		Normal	
Lambda OS gefitinib	0.020		Normal	
Gamma OS gefitinib	1.203		Normal	
Lambda OS erlotinib	0.019		Normal	
Gamma OS erlotinib	1.203		Normal	
Lambda OS afatinib	0.017		Normal	
Gamma OS afatinib	1.203		Normal	
Lambda OS osimertinib	0.012		Normal	
Gamma OS osimertinib	1.203		Normal	
Intercept OS 2nd-line osimertinib	4.069		Normal	
Intercept OS 2nd-line pemetrexed/cisplatin	2.861		Normal	
Lambda PFS chemotherapy	0.073		Normal	
Gamma PFS chemotherapy	1.478		Normal	
Lambda PFS gefitinib	0.031		Normal	
Gamma PFS gefitinib	1.478		Normal	
Lambda PFS erlotinib	0.026		Normal	
Gamma PFS erlotinib	1.478		Normal	
Lambda PFS afatinib	0.027		Normal	
Gamma PFS afatinib	1.478		Normal	
Lambda PFS osimertinib	0.013		Normal	
Gamma PFS osimertinib	1.478		Normal	
Intercept PFS 2nd-line osimertinib	2.985		Normal	
Intercept PFS 2nd-line pemetrexed/ cisplatin	1.885		Normal	

Abbreviations: CNS, central nervous system; DSA, deterministic sensitivity analysis; OS, overall survival; PFS, progression-free survival.
[a]Costs comprised of acquisition costs and pharmaceutical delivery costs; no drug wastage assumed.
[b]Volume pemetrexed/cisplatin based on a point estimate body surface of 1.70m². Administration of 500mg/m² pemetrexed and 75mg/m² cisplatin each cycle.
[c]Tumour response assessment comprised CT and MRI scans for tumour assessment.
[d]Laboratory costs comprised haematology, sputum, and biochemistry test, excluding mutation test.
[e]Based on 14 kilometres (€0.19/kilometre) plus parking costs (€3,-).
[f]ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[g]Assumed to be the same as fatigue.
[h]Assumed to be the same as neutropenia.
[i]Assumed to be the same rash.
[j]Assumed to be the same as nausea.
[k]Assumed to be the same as rash.
[l]Parameters were varied with ±20% of the mean.
[m]€10,602 are the average indirect medical costs over a lifetime horizon. Indirect medical costs ranged between €4,578 and €26,326.

Costs

Following the Dutch guideline, a societal perspective was used for the model. Table 3.2 shows all unit costs of gefitinib, erlotinib, afatinib, and osimertinib treatment. Costs were based on the Dutch Costing manual, the Dutch Health Care Institute, Dutch Healthcare Authority, and the literature.[106,119,120] All costs are in Euros, based on the average consumer price index of 2018. Future costs were discounted by a rate of 4%, according to the Dutch guidelines.[107] More details on the costs can be found in the Supplemental material.

Sensitivity analyses

Since the cost-effectiveness model is based on a number of assumptions, several scenario analyses were performed to test the robustness of these assumptions. In the first scenario tested, a log-logistic function instead of the Weibull function was used to estimate the survival probabilities in the model. Secondly, the chemotherapy patient group from another clinical trial (Lux-Lung 6)[68] was used to estimate the survival probabilities of gefitinib, erlotinib, afatinib, and osimertinib. Thirdly, docetaxel instead of pemetrexed-cisplatin was included as second-line treatment.

Deterministic (DSA) and probabilistic sensitivity analysis (PSA) were performed to determine which parameters were most influential on the results of the model and to test the robustness of the model. The impact of varying single parameters on the cost-effectiveness ratio while holding the others constant, was assessed by univariate analyses. If available, the 95% confidence intervals (CI) were used for the DSA. If not, parameters were varied with ±20% of the mean. PSA was performed by simultaneously varying all the parameters in a Monte Carlo simulation according to prespecified distributions. Survival parameters lambda and gamma were assumed to be bivariate normal distributed, for utilities and probabilities, a beta distribution was applied and a gamma distribution was used for costs. Standard errors of utilities and probabilities were either obtained from the literature or calculated by 10% of the mean point estimate and 20% was used for the costs. In total, 1,000 simulation samples were randomly drawn from the distributions and each time the model results were recalculated. We constructed a cost-effectiveness plane that shows the base case ICER and the uncertainty surrounding the estimated costs and effects of the pairwise comparisons. Based on the cost-effectiveness plane, a cost-effectiveness acceptability curve was constructed, which shows the probability that a treatment is cost-effective compared to the alternative given a range of threshold ICERs.[131,132]

Results

Base case results

Table 3.3 shows the incremental base case results of the cost-effectiveness analyses. Gefitinib and erlotinib showed the lowest total discounted costs per patient and osimertinib had the highest estimated costs for patients with EGFR-mutated NSCLC. Osimertinib yielded the most effects, followed by afatinib, erlotinib, and gefitinib. Compared to gefitinib, erlotinib resulted in a QALY gain of 0.03 (and 0.03 LYs) and cost savings of €1,854 per patient, indicating that erlotinib dominates gefitinib. Afatinib compared to erlotinib yielded 0.13 QALYs (and 0.20 LYs) gained and a cost increase of €5,383 per patient, which resulted in an ICER of €27,058/LY and €41,504/QALY for afatinib versus erlotinib. Osimertinib yielded 0.49 QALYs (and 0.68 LYs) and €62,579 more costs relative to afatinib. Thus, an additional €91,726 per LY and €128,343 per QALY gained is spent on osimertinib compared to afatinib. The results of all other comparisons can be found in the Supplemental material.

Table 3.3 Base case results of cost-effectiveness analyses

Comparison	Costs (€)	Costs 1st-line (€)	LYs	QALYs	Δ Costs (€)	Δ Effects	ICER (€)
Gefitinib	65,889	39,467	2.01	1.36	-	-	-
Erlotinib	64,035	39,825	2.04	1.39			Dominates gefitinib
Afatinib	69,418	42,416	2.24	1.52	5,383	0.13	41,504
Osimertinib	131,997	124,149	2.92	2.01	62,579	0.49	128,343

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years; Δ, difference in costs/effects,

Scenario analysis

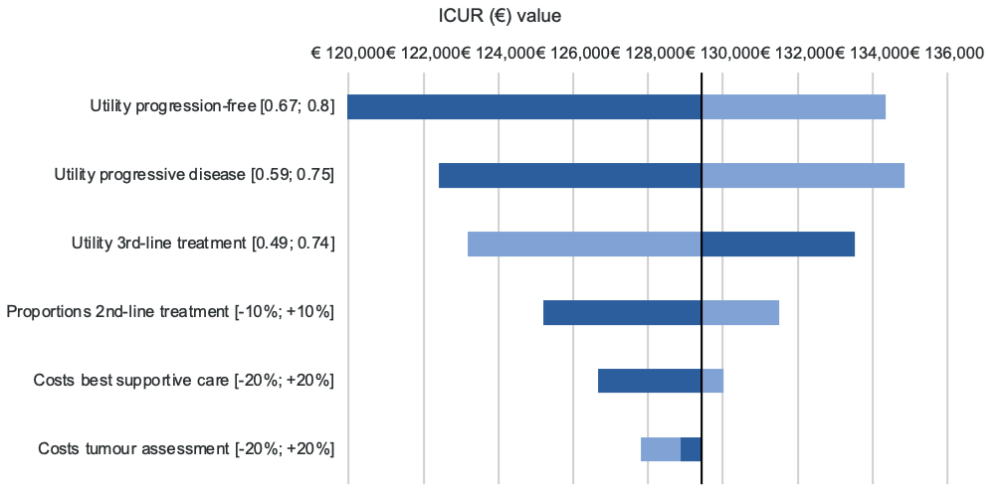
Considering a Dutch threshold of €80,000/QALY, osimertinib appears not to be cost-effective (ICER of osimertinib vs afatinib was €128,343/QALY). For osimertinib, a price reduction of 30% is required to be regarded as cost-effective (Supplemental material).

Sensitivity analyses

Based on visual inspection, the Log-Logistic distribution for PFS can be regarded as a plausible alternative for the Weibull distribution. Since the Log-Logistic distribution also scored second for AIC and BIC (see Supplemental material), we performed a scenario analysis by using the Log-Logistic distribution to estimate the survival probabilities, which were then included into the model. This mainly resulted into lower incremental costs and a lower ICER for osimertinib compared to afatinib. In another scenario, the chemotherapy patient group from the Lux-Lung 6 trial[68] was used instead of the EURTAC trial to estimate the survival probabilities of the TKIs. This scenario resulted in lower incremental costs and QALYs, especially for the comparison of osimertinib versus afatinib. Inclusion of another second-line treatment than pemetrexed-cisplatin hardly affected the results (see Supplemental material).

Since the comparison of osimertinib vs afatinib is most interesting (as gefitinib is dominated by erlotinib and afatinib is cost-effective compared to erlotinib), only the Tornado diagram of this comparison is presented here (Figure 3.1). DSA showed that utility value of the progression-free health state seemed to be the most influential drivers. The Tornado diagrams of erlotinib versus gefitinib and of afatinib versus erlotinib can be found in the Supplemental material.

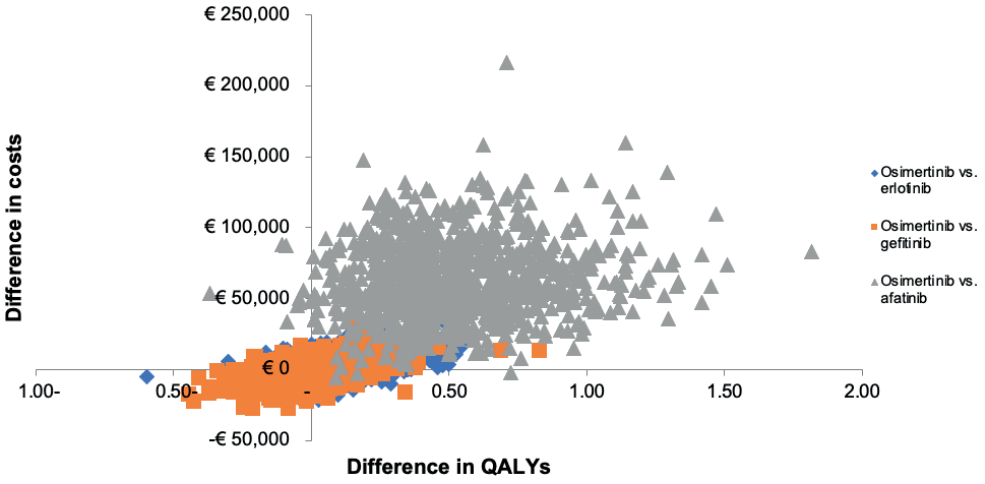
Figure 3.1 Base-case Tornado diagram of the ICER of osimertinib vs afatinib



Abbreviations: ICER, incremental cTst-effectiveness ratio.

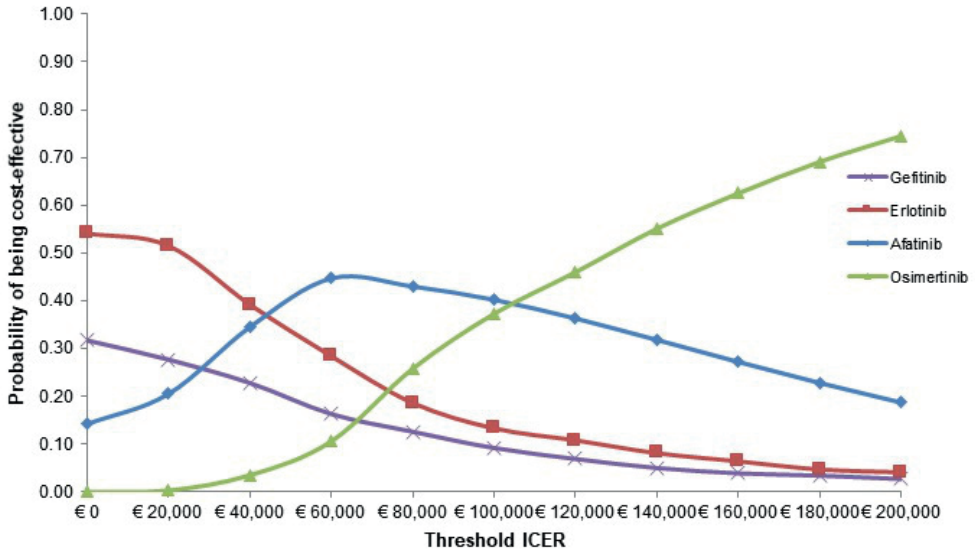
Figure 3.2 shows that almost 100% of the 1,000 PSA iterations were in the upper right quadrant, which means more QALYs gained at additional costs for osimertinib compared to afatinib. For afatinib versus erlotinib, about 60% of the PSA iterations were in the upper right quadrant, 20% fell within the lower right quadrant, 10% in the upper left, and another 10% was in the lower left quadrant. For erlotinib compared to gefitinib, about 30% of the iterations fell within both the lower left and upper right quadrant and about 20% fell within both the upper left and lower right quadrant. The cost-effectiveness acceptability curves (CEAC) of all TKIs are shown in Figure 3. At a Dutch threshold of €80,000/QALY, afatinib had the highest probability of being cost-effective (43%). Gefitinib, erlotinib, and osimertinib had a probability of 13%, 19%, and 26%, respectively, of being cost-effective at the Dutch threshold. At a threshold of €200,000/QALY, the probability of being cost-effective was 75% for osimertinib.

Figure 3.2 Cost-effectiveness plane of all comparisons



Abbreviations: QALYs, quality-adjusted life-years.

Figure 3.3 Cost-effectiveness acceptability curves



Abbreviations: ICER, incremental cost-effectiveness ratio.

Discussion

To the best of our knowledge, this was the first study in the Netherlands that compared the cost-effectiveness of first-line gefitinib, erlotinib, afatinib, and osimertinib for EGFR mutation-positive (exon 19 deletion or exon 21 L858R mutation) NSCLC patients. Our study found that erlotinib dominated gefitinib. Afatinib resulted in a cost per QALY of €41,504 compared to erlotinib. Compared to afatinib treatment, osimertinib had an ICER of €128,343 per QALY gained. Thus, osimertinib was the most efficacious treatment option, followed by afatinib, erlotinib, and gefitinib, but at a high cost.

Our results are similar to the results of Aguiar et al. with ICERs of $219,874/QALY of osimertinib vs afatinib in the US and $175,432/QALY in Brazil.[133] In a report from the Dutch Health Care Institute (ZIN), osimertinib yielded an ICER of €324,006/QALY compared to gefitinib, erlotinib, and afatinib. An ICER range from €70,847 to €324,006 was reported and the upper limit was used to calculate the required price reduction for osimerinib to be regarded as cost-effective (reduction of 55% at threshold of €80,000). The study submitted to ZIN used the effectiveness of only one trial (FLAURA trial), thus not all available evidence

was used to estimate the effectiveness of the drugs. Utility values for progression-free health state also differed: 0.829 in the report versus 0.71 in this study.[115,121] Since the utility values reported by the manufacturer were higher than previous reported utility values for this patient population, these values were not used in this study. When we take these aspects into account, our results would be in the order of the findings of the ZIN report. In other cost-effectiveness studies, only two TKIs were compared.[134-137] Lee et al.[135] showed incremental costs per QALY gained by erlotinib compared to gefitinib of $62,419 (incremental costs $14,061 and incremental QALY 0.23) and $41,494 per LY gained (incremental LY 0.34). These results are different from our study. This might be due to the fact that Lee et al.[135] simulated the survival probability for erlotinib based on the OS outcomes of the IPASS trial[60], because the OS results of erlotinib were still immature at that moment. Additionally, more studies were included in our analyses. Ting et al.[134] analysed the cost-effectiveness of erlotinib versus afatinib and found a mean ICER of $61,809/QALY, with incremental costs $6,417 and incremental QALY 0.17.[134] These outcomes are the opposite of our results. A plausible reason might be that only the EURTAC and Lux-Lung 3 trials were used for the data of erlotinib and afatinib, while we included various trials besides these two in our network.[61-69,71,90,91] Furthermore, Ting et al.[134] have corrected the survival probabilities of erlotinib for patients with more severe disease. However, survival estimates were not corrected for other prognostic factors that were unequally distributed among the two treatments (e.g., EGFR mutation type). Correcting for only one prognostic factor could result into biased corrections. When uncorrected survival probabilities were added in the study of Ting et al., erlotinib became less expensive and survival decreased. This yielded an ICER of $534,903 for afatinib versus erlotinib (incremental costs $7,494 and incremental QALY 0.014).[134]

Our results were similar to the cost-effectiveness ratios reported by Chouaid et al.[137] and the National Institute of Health and care Excellence (NICE).[136] Chouaid et al.[137] assessed the cost-effectiveness of afatinib compared to gefitinib by use of data from the Lux-Lung 7 trial, which resulted in incremental costs of €45,211 per QALY gained. The study by NICE yielded into a cost-effectiveness ratio of £10,076 per QALY gained of afatinib versus erlotinib.[136]

However, our study had several limitations. The first limitation was the use of a model-based approach (based on published RCT data), due to a lack of real-world data. Consequently, the results and conclusions of our study are dependent on the validity of the assumptions made in our model. However, various alternative assumptions were assessed through sensitivity analyses, which showed the robustness of our results.

Secondly, the survival probabilities of gefitinib, erlotinib, afatinib, and osimertinib were estimated by use of the EURTAC trial, which was a Caucasian trial. However, we also included Asian trials in the model, since trials with non-Asian patients for all four TKIs were not available during study period. Although Asian ethnicity is one of the risk factors for EGFR mutations,[103] two studies showed no significantly different risk of progression between Asian and non-Asian patients.[66,134] Thus, use of Asian studies are not expected to bias the efficacy of TKIs. Therefore, to our opinion, the results of our study could be generalised to the Dutch population.

Due to a lack of data on all TKIs, we were not able to perform subgroup analyses, e.g., patients with and without brain metastases. This could be regarded as a limitation, as these analyses might give more insight into the cost-effectiveness of EGFR-TKIs in subgroups.[138] Since brain metastases occur less frequent in patients treated with osimertinib compared to patients treated with gefitinib or erlotinib, it is expected that the QALY gain for osimertinib will increase. Thus, the ICER for this subgroup will be slightly lower compared to the outcomes for the total population. As the occurrence of brain metastases might have a substantial impact on the outcomes, further research on these subgroups is needed.

Furthermore, at the time of our study, the OS results of the FLAURA trial were still immature. Therefore, interim analysis of OS was used in our model. However, the use of final OS results would be more desirable because it reduces the uncertainty of the model outcomes.

Additionally, we assumed that patients treated with first-line gefitinib, erlotinib, or afatinib all received the same second-line treatments with the same proportions, namely osimertinib (50%) or pemetrexed-cisplatin (50%) and after progression on these second-line treatments, patients were treated with BSC. Though it may be reasonable that these proportions differ per TKI, we had no data to make such distinctions. Besides that, in reality, patients may also receive other second- or third-line treatments than those included in our model. In the ideal situation, we could fully account for the costs and effects of all second- and third-line treatments used in Dutch clinical practice. However, in the absence of any clear guidance on second- and third-line treatment strategy after TKI failure,[139,140] we considered our assumption a valid strategy. Scenario analysis also showed a marginal impact of different second-line treatments on the costs. In further research, it is recommended to use real-world data of the first-line and second- and third-line treatment strategy, when it is available.

Furthermore, treatment costs could be overestimated somewhat as we did not adjust for dose reductions. However, adjustment for dose reductions is expected not to have a large impact

on the cost-effectiveness results since the costs related to osimertinib are high anyway. The assumption of no drug wastage is justified because TKIs are pills and second-line pemetrexed-cisplatin was received by a relatively small proportion of patients, which is expected to have a small amount of drug wastage. The effect on the incremental differences would be negligible. However, it might be more precise when drug wastage is taken into account where relevant.

The clinical effectiveness of osimertinib for patients with EGFR-mutated NSCLC is promising, as it could improve PFS and OS. Moreover, central nervous system (CNS) progression occurred less frequent in patients treated with osimertinib compared to standard-TKI.[71] Besides the substantial clinical relevance, the costs of treating CNS metastases will also be lower for osimertinib versus standard-TKI. Despite these benefits, our results showed that osimertinib could not be regarded as cost-effective compared to all other TKIs. Therefore, it is of great importance to negotiate a lower price for osimertinib.

Conclusion

This study showed that the cost-effectiveness of afatinib compared to erlotinib is well below the Dutch threshold ratio of €80,000/QALY for treatments in this disease severity group. Osimertinib yielded a better effectiveness compared to afatinib. However, the ICER of osimertinib versus afatinib (€128,343 per QALY gained) appears to be too high given the Dutch threshold. The price of osimertinib should be reduced by 30% to become cost-effective.

Compliance with Ethical Standards

The authors declare that they have no conflict of interest.

Supplemental material: Systematic review and NMA

Search strategy

A systematic literature search was conducted in three electronic databases (PubMed, EMBASE, and Cochrane Library). Full details on the search strategy and key words can be found in Tables S3.1-S3.3. We included articles published from 1 January 2010 up to and including 1 November 2016. The literature search was manually updated in February 2018 to ensure that no relevant studies were missing, as new trials have been published since the last update of our systematic review. Phase IIB/III RCTs that compared the efficacy and toxicity of first-line single EGFR-TKI therapy (including gefitinib, erlotinib, afatinib, and osimertinib) compared to another TKI or standard chemotherapy (platinum-based doublet therapy) in patients with stage IIIB/IV NSCLC harbouring EGFR mutations who were ineligible for surgery or radiotherapy were included. Abstracts, systematic reviews, meta-analyses, and subgroup or post hoc analyses were excluded. We only include English language articles (see Table S3.4). Literature review and data extraction were conducted by two independent reviewers (MH and CU). Any discrepancies were discussed. Reference lists of published systematic reviews and meta-analyses were checked to ensure that no studies were missed. Quality and risk of bias of all included studies was assessed by using the Cochrane Collaboration's tool for assessing risk of bias. All included studies had an acceptable quality and low risk of bias (Table S3.5).

Table S3.1 Search strategy PubMed

Database	**PubMed**
Date of search	**10 November 2016**
Date range	**1 January 2010 - 1 November 2016**

1	(("afatinib") AND "advanced non small cell lung cancer") AND "egfr mutations"
2	((("afatinib") AND "stage 4") AND "non small cell lung cancer") AND "egfr mutations"
3	(("afatinib") AND "versus") AND "chemotherapy"
4	((("afatinib") AND "versus") AND "chemotherapy") AND "first line therapy"
5	(((("afatinib") AND "versus") AND "chemotherapy") AND "advanced non small cell lung cancer") AND "egfr mutations"
6	(((((afatinib") AND "versus") AND "chemotherapy") AND "stage 4") AND "non small cell lung cancer") AND "egfr mutations"
7	((("afatinib") AND "versus") AND "chemotherapy") AND "overall survival"
8	((("afatinib") AND "versus") AND "chemotherapy") AND "progression free survival"
9	(("erlotinib") AND "advanced non small cell lung cancer") AND "egfr mutations"
10	((("erlotinib") AND "stage 4") AND "non small cell lung cancer") AND "egfr mutations"
11	(("erlotinib") AND "versus") AND "chemotherapy"
12	((("erlotinib") AND "versus") AND "chemotherapy") AND "first line therapy"
13	(((("erlotinib") AND "versus") AND "chemotherapy") AND "advanced non small cell lung cancer") AND "egfr mutations"
14	(((((erlotinib") AND "versus") AND "chemotherapy") AND "stage 4") AND "non small cell lung cancer") AND "egfr mutations"
15	((("erlotinib") AND "versus") AND "chemotherapy") AND "overall survival"
16	((("erlotinib") AND "versus") AND "chemotherapy") AND "progression free survival"
17	(("gefitinib") AND "advanced non small cell lung cancer") AND "egfr mutations"
18	((("gefitinib") AND "stage 4") AND "non small cell lung cancer") AND "egfr mutations"
19	(("gefitinib") AND "versus") AND "chemotherapy"
20	((("gefitinib") AND "versus") AND "chemotherapy") AND "first line therapy"
21	(((("gefitinib") AND "versus") AND "chemotherapy") AND "advanced non small cell lung cancer") AND "egfr mutations"
22	(((((gefitinib") AND "versus") AND "chemotherapy") AND "stage 4") AND "non small cell lung cancer") AND "egfr mutations"
23	((("gefitinib") AND "versus") AND "chemotherapy") AND "overall survival"
24	((("gefitinib") AND "versus") AND "chemotherapy") AND "progression free survival"

Table S3.2 Search strategy Embase

Database	**Embase**
Date of search	**21 November 2016**
Date range	**1 January 2010 - 1 November 2016**

1	'afatinib'/exp OR 'afatinib' AND 'advanced non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
2	'afatinib'/exp OR 'afatinib' AND 'stage 4' AND 'non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
3	'afatinib'/exp OR 'afatinib' AND versus AND 'chemotherapy' AND [2010-2016]/py
4	'afatinib'/exp OR 'afatinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'first line therapy' AND [2010-2016]/py
5	afatinib'/exp OR 'afatinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'advanced non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
6	'afatinib'/exp OR 'afatinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'stage 4' AND 'non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
7	'afatinib'/exp OR 'afatinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'overall survival' AND [2010-2016]/py
8	'afatinib'/exp OR 'afatinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'progression free survival' AND [2010-2016]/py
9	'erlotinib'/exp OR 'erlotinib' AND 'advanced non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
10	'erlotinib'/exp OR 'erlotinib' AND 'stage 4' AND 'non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
11	erlotinib'/exp OR 'erlotinib' AND versus AND 'chemotherapy' AND [2010-2016]/py
12	erlotinib'/exp OR 'erlotinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'first line therapy' AND [2010-2016]/py
13	'erlotinib'/exp OR 'erlotinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'advanced non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
14	'erlotinib'/exp OR 'erlotinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'stage 4' AND 'non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
15	'erlotinib'/exp OR 'erlotinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'overall survival' AND [2010-2016]/py
16	'erlotinib'/exp OR 'erlotinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'progression free survival' AND [2010-2016]/py
17	'gefitinib' AND 'advanced non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
18	'gefitinib'/exp OR 'gefitinib' AND 'stage 4' AND ('non small cell lung cancer'/exp OR 'non small cell lung cancer') AND 'egfr mutation' AND [2010-2016]/py
19	'gefitinib' AND versus AND 'chemotherapy' AND [2010-2016]/py
20	'gefitinib'/exp OR 'gefitinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'first line therapy' AND [2010-2016]/py
21	'gefitinib'/exp OR 'gefitinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'advanced non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
22	gefitinib'/exp OR 'gefitinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND 'stage 4' AND 'non small cell lung cancer' AND 'egfr mutation' AND [2010-2016]/py
23	'gefitinib'/exp OR 'gefitinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND ('overall survival'/exp OR 'overall survival') AND [2010-2016]/py
24	'gefitinib'/exp OR 'gefitinib' AND versus AND ('chemotherapy'/exp OR 'chemotherapy') AND ('progression free survival'/exp OR 'progression free survival') AND [2010-2016]/py

Table S3.3 Search strategy Cochrane Library

Database	**Cochrane library**
Date of search	**2 December 2016**
Date range	**1 January 2010 - 1 November 2016**

1	'"afatinib" and "advanced" and "non small cell lung cancer" and "egfr mutations" , Publication Year from 2010 to 2016 in Trials'
2	'"afatinib" and "non small cell lung cancer stage IV" and "egfr mutations" , Publication Year from 2010 to 2016'
3	'"afatinib" and "chemotherapy" , Publication Year from 2010 to 2016 in Trials'
4	'"afatinib" and "chemotherapy" and "first-line therapy" , Publication Year from 2010 to 2016 in Trials'
5	'"afatinib" and "chemotherapy" and "advanced" and "non small cell lung cancer" and "egfr mutations" , Publication Year from 2010 to 2016 in Trials'
6	'"afatinib" and "chemotherapy" and "non small cell lung cancer stage IV" and "egfr mutations" , Publication Year from 2010 to 2016'
7	'"afatinib" and "chemotherapy" and "overall survival" , Publication Year from 2010 to 2016 in Trials'
8	'"afatinib" and "chemotherapy" and "progression-free survival" , Publication Year from 2010 to 2016 in Trials
9	"erlotinib" and "advanced" and "non small cell lung cancer" and "egfr mutations" , Publication Year from 2010 to 2016 in Trials'
10	"erlotinib" and "non small cell lung cancer stage IV" and "egfr mutations" , Publication Year from 2010 to 2016 in Trials'
11	'"erlotinib" and "chemotherapy" , Publication Year from 2010 to 2016 in Trials'
12	'"erlotinib" and "chemotherapy" and "first-line therapy" , Publication Year from 2010 to 2016 in Trials'
13	"erlotinib" and "chemotherapy" and "advanced" and "non small cell lung cancer" and "egfr mutations" , Publication Year from 2010 to 2016 in Trials'
14	'"erlotinib" and "chemotherapy" and "non small cell lung cancer stage IV" and "egfr mutations" , Publication Year from 2010 to 2016'
15	"erlotinib" and "chemotherapy" and "overall survival" , Publication Year from 2010 to 2016 in Trials'
16	'"erlotinib" and "chemotherapy" and "progression-free survival" , Publication Year from 2010 to 2016 in Trials'
17	'"gefitinib" and "advanced" and "non small cell lung cancer" and "egfr mutations" , Publication Year from 2010 to 2016 in Trials'
18	'"gefitinib" and "non small cell lung cancer stage IV" and "egfr mutations" , Publication Year from 2010 to 2016'
19	'"gefitinib" and "chemotherapy" , Publication Year from 2010 to 2016 in Trials'
20	'"gefitinib" and "chemotherapy" and "first-line therapy" , Publication Year from 2010 to 2016 in Trials'
21	"gefitinib" and "chemotherapy" and "advanced" and "non small cell lung cancer" and "egfr mutations" , Publication Year from 2010 to 2016 in Trials'
22	"gefitinib" and "chemotherapy" and "non small cell lung cancer stage IV" and "egfr mutations" , Publication Year from 2010 to 2016'
23	'"gefitinib" and "chemotherapy" and "overall survival" , Publication Year from 2010 to 2016 in Trials'
24	'"gefitinib" and "chemotherapy" and "progression-free survival" , Publication Year from 2010 to 2016 in Trials'

Figure S3.1 Flow diagram of literature review

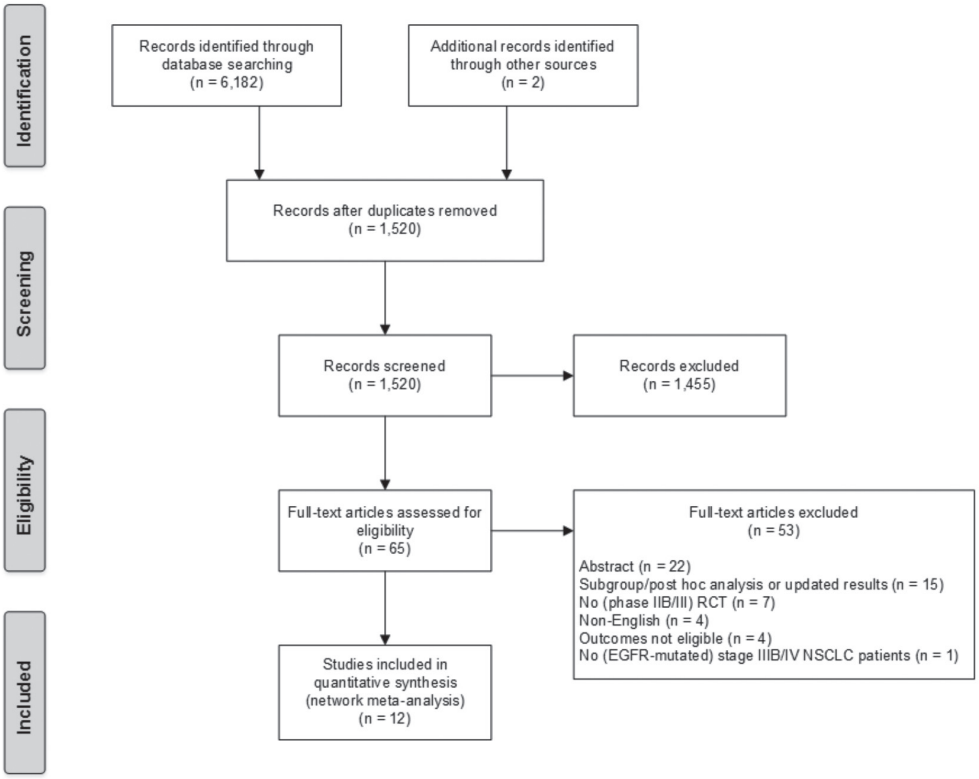


Table S3.4 In- and exclusion criteria title/abstract and full-text screening

Title/abstract screening		
	Exclusion criteria	Total number excluded studies
1	No first-line therapy	298
2	No (EGFR-mutated) NSCLC study population	236
3	First-line gefitinib, erlotinib, afatinib, or osimertinib not compared to other single TKI or platinum-based doublet therapy	201
4	No (phase IIB/III) RCT	177
5	(Systematic) review/overview	151
6	TKI combination treatment	145
7	Study subject was biomarker/DNA/molecular assessment	114
8	(Network) meta-analysis	72
9	Outcomes not eligible	37
10	NSCLC stage I-IIIA	17
11	Abstract	7
Full-text screening		
1	Abstract	22
2	Subgroup/post hoc analysis/updated results	15
3	No (phase IIB/III) RCT	7
4	Non-English	4
5	Outcomes not eligible	4
6	No (EGFR-mutated) stage IIIB/IV NSCLC patients	1

Table S3.5 Quality and risk of bias assessment of all included studies

Trial	Sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome data	Incomplete outcome data	Selective reporting	Other sources of bias
NEJ002 (2010)	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
WJTOG 3405 (2010)	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
IPASS (2009/2011)	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
First-SIGNAL (2012)	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	A maximum of 9 cycles of GP chemotherapy was recommended instead of 4-6 cycles. Crossover was recommended as second-line treatment
OPTIMAL (2011)	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
EURTAC (2012)	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
ENSURE (2015)	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
Lux-Lung 3 (2013)	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
Lux-Lung 6 (2014)	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
Lux-Lung 7 (2016)	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment
CTONG0901 (2017)	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	
FLAURA (2018)	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Crossover was recommended as second-line treatment

Methods network meta-analysis

The formula used to estimate the HR of treatment a versus b, is as follows: $\widehat{HR_{a,b}} = (e^{(\partial_b - \partial_a)})$. This formula was also used for all other comparisons. Chemotherapy was used as reference treatment in the network . Direct and indirect evidence from the RCTs was used to estimate all other's. Convergence was assessed by use of the Brooks-Gelman-Rubin diagnostics, which enabled to determine of the number of burn- $(\partial\ chemo = 0)$in simulations that should be discarded.

Since no separate HRs of osimertinib versus gefitinib and of osimertinib versus erlotinib were reported in the FLAURA trial, the HRs of PFS and OS were assumed to be the same for osimertinib versus gefitinib and for osimertinib versus erlotinib.

WinBUGS code

```
model{
for(i in 1:ns2) {               # LOOP THROUGH 2-ARM STUDIES
          # normal likelihood
          y[i,2] ~ dnorm(delta[i,2],prec[i,2])
          #Deviance contribution for trial i
          resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
 }

for(i in 1:(ns2)){              #   LOOP THROUGH ALL STUDIES
   for (k in 2:na[i]) {                  #  LOOP THROUGH ARMS
     var[i,k] <- pow(se[i,k],2)   # calculate variances
     prec[i,k] <- 1/var[i,k]      # set precisions
     delta[i,k] <-  d[t[i,k]] - d[t[i,1]]
    }
 }
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0                         # treatment effect is zero for reference treatment

# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
          for (k in (c+1):nt) {
          HR[c,k] <- exp(d[k] - d[c])
          lnHR[c,k] <- (d[k]-d[c])
          }
}
```

```
# ranking on relative scale
for (k in 1:nt) {
        # rk[k] <- nt+1-rank(d[],k) # assumes events are “good”
         rk[k] <- rank(d[],k) # assumes events are “bad”
        best[k] <- equals(rk[k],1) #calculate probability that treat k is best
        # calculates probability that treat k is h-th best
        for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) }
        }
}
# *** PROGRAM ENDS

##Data
list(ns2=13, nt=5)

t[,1]   t[,2]   y[,2]   se[,2]   na[]   #Study/Comparison
1       2       -0.71539279     0.190855564     2       # WJTOG3405 / Gef vs Chemo
1       2       -1.133203733    0.157751813     2       # NEJ002 / Gef vs Chemo
1       2       -0.733969175    0.146776568     2       # IPASS / Gef vs Chemo
1       3       -1.832581464    0.24375292      2       # OPTIMAL / Erl vs Chemo
1       2       -0.608806032    0.359274        2       # First-SIGNAL / Gef vs Chemo
1       3       -0.994252273    0.196456179     2       # EURTAC / Erl vs Chemo
1       4       -0.544727175    0.151915487     2       # Lux-Lung 3 / Afa vs Pem
1       4       -1.272965676    0.170364636     2       # Lux-Lung 6 / Afa vs Chemo
1       3       -0.867500568    0.228014764     2       # ENSURE / Erl vs Chemo
2       4       -0.314710745    0.130312659     2       # Lux-Lung 7 / Afa vs Gef
2       3       -0.040821995    0.171216396     2       # CTONG0901 / Erl vs Gef
2       5       -0.798507696    0.117227635     2       # FLAURA / Osi vs Gef
3       5       -0.798507696    0.117227635     2       # FLAURA / Osi vs Erl
END

##Inits
#chain1
list(d=c( NA, 0,0,0,0))
#chain2
list(d=c( NA, 1,1,1,1))
#chain3
list(d=c( NA, 2,2,2,2))
```

Results network meta-analysis

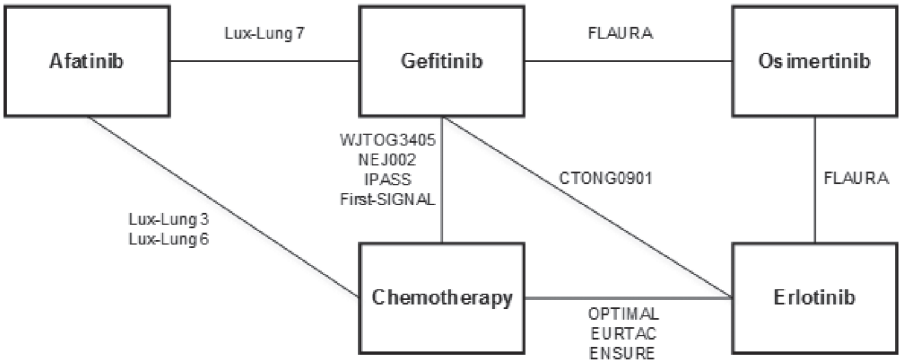
The characteristics of all included studies are presented in Table S3.6. Figure S3.2 shows the complete network of all included RCTs. Three different chains with 60,000 iterations each were simulated. In each chain, 30,000 iterations were discarded due to a burn-in period. Thus, the results were based on a total sample of 90,000 iterations. The results of the NMA are presented in Table S3.7.

Table S3.6 Characteristics of all included studies

	Trial	Treatment	EGFR patients	Primary end-point	Hazard ratio (95% CI) PFS	OS
1	***NEJ002***	Gefitinib TC	114 114	PFS	0.30 (0.22-0.41)	0.887 (0.634-1.241)
2	***WJTOG3405***	Gefitinib DP	86 86	PFS	0.489 (0.336-0.710)	1.252 (0.883-1.775)
3	***IPASS***	Gefitinib TC	132 129	OS	0.48 (0.36-0.64)	1.00 (0.76-1.33)
4	***First-SIGNAL***	Gefitinib GP	26 16	OS	0.544 (0.269-1.1)	1.043 (0.498-2.182)
5	***OPTIMAL***	Erlotinib GC	82 72	PFS	0.16 (0.10-0.26)	1.19 (0.83-1.71)
6	***EURTAC***	Erlotinib CT	86 87	PFS	0.37 (0.25-0.54)	1.04 (0.65-1.68)
7	***ENSURE***	Erlotinib GC	110 107	PFS	0.34 (0.22-0.51)	0.91 (0.63-1.31)
8	***Lux-Lung 3***	Afatinib AP	230 115	PFS	0.58 (0.43-0.78)	0.88 (0.66-1.17)
9	***Lux-Lung 6***	Afatinib GP	242 122	PFS	0.28 (0.20-0.39)	0.93 (0.72-1.22)
10	***Lux-Lung 7***	Afatinib Gefitinib	160 159	PFS, OS	0.73 (0.57-0.95)	0.86 (0.66-1.12)
11	***CTONG0901***	Erlotinib Gefitinib	128 128	PFS	0.96 (0.69-1.35)	0.98 (0.67-1.42)
12	***FLAURA***	Osimertinib Standard TKI	279 277	PFS	0.46 (0.37-0.57)	0.63 (0.45-0.88)

Abbreviations: AP, cisplatin+pemetrexed; CT, chemotherapy (not specific); DP, cisplatin+docetaxel; GC, carboplatin+gemcitabine; GP,cisplatin+gemcitabine; TC, carboplatin+paclitaxel; CI, confidence interval; N/A, not available.

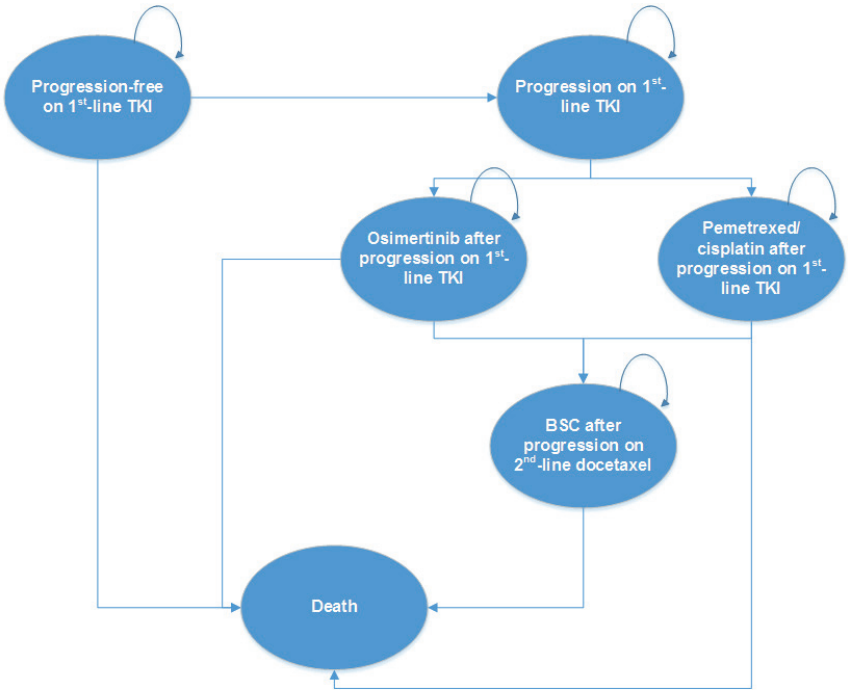
Figure S3.2 Complete network of all included RCTs



Supplemental material: Methods

Markov model

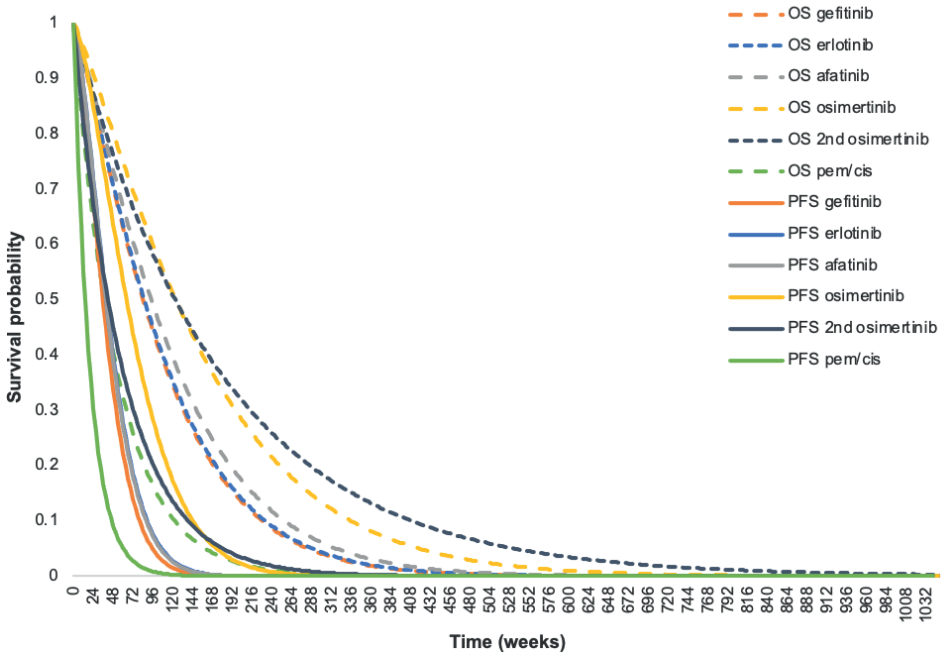
Figure S3.3 Schematic diagram of the Markov model



Abbreviations: BSC, best supportive care; TKI, tyrosine kinase inhibitor.

Survival curves

Figure S3.4 OS and PFS curves of first-line gefitinib, erlotinib, afatinib, osimertinib, second-line osimertinib, and pemetrexed/cisplatin



Abbreviations: OS, overall survival; pem/cis, pemetrexed/cisplatin; PFS, progression-free survival.

Survival probability

Figure S3.5 Distributions fitted to Kaplan-Meier curve for OS

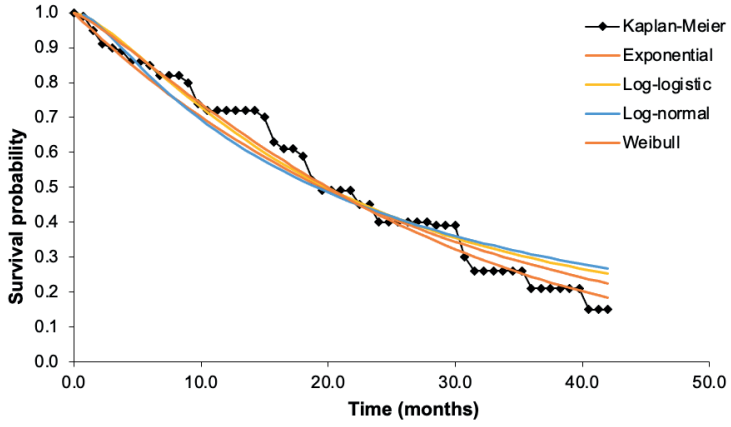


Figure S3.6 Distributions fitted to Kaplan-Meier curve for PFS

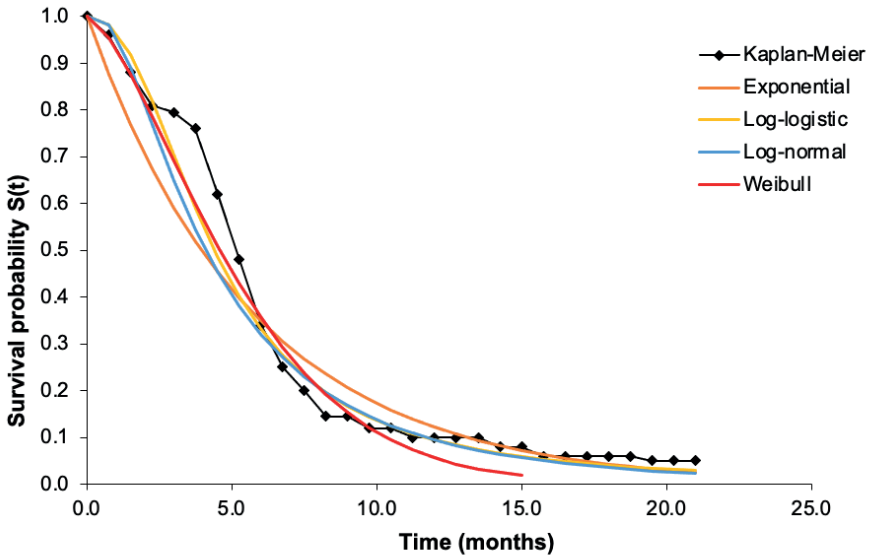


Table S3.7 Goodness of fit estimates for OS

	AIC	BIC
Weibull	510.4461	515.3779
Exponential	510.6748	513.1407
Log Logistic	515.0872	520.019
Log Normal	518.4373	523.3691

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table S3.8 Goodness of fit estimates for PFS

	AIC	BIC
Weibull	342.0324	346.8459
Log Logistic	344.0887	348.9021
Log Normal	348.5719	353.3853
Exponential	353.4994	355.9061

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure S3.7 Distributions fitted to Kaplan-Meier curve for OS for second-line osimertinib

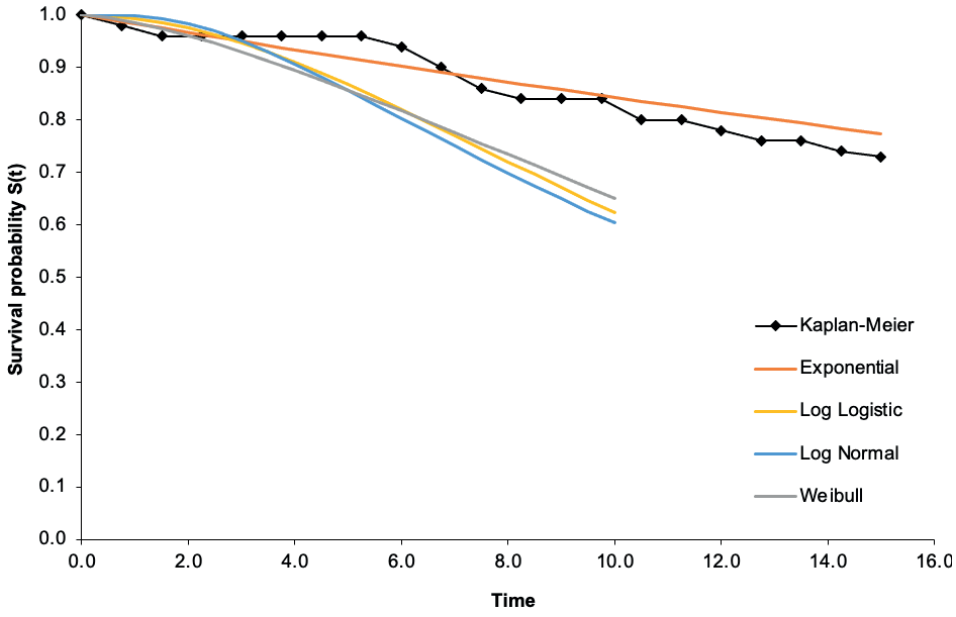


Figure S3.8 Distributions fitted to Kaplan-Meier curve for PFS for second-line osimertinib

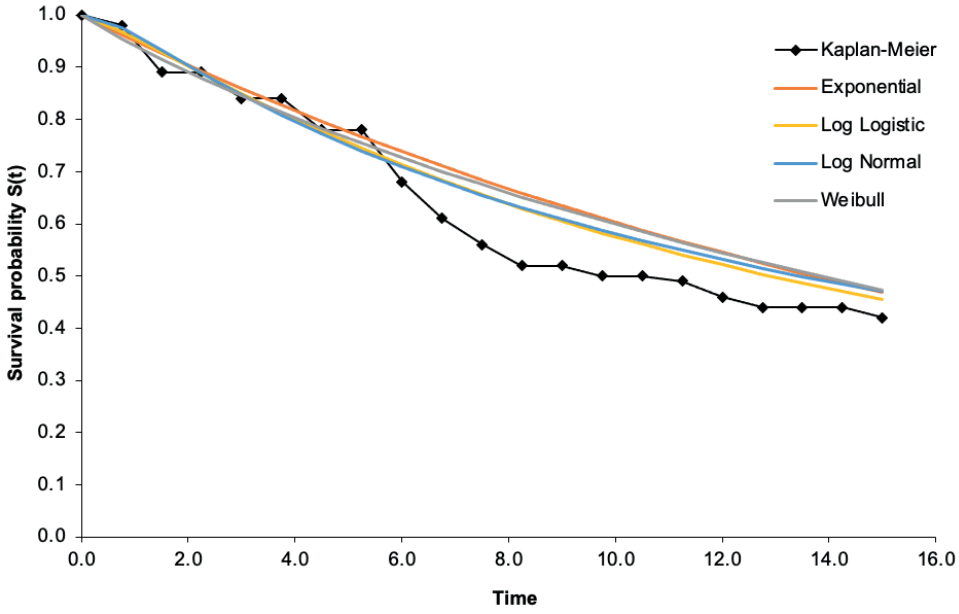


Table S3.9 Goodness of fit estimates for OS for second-line osimertinib

	AIC	BIC
Exponential	141.26	143.23
Weibull	143.23	147.17
Log Logistic	143.31	147.25
Log Normal	144.22	148.16

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table S3.10 Goodness of fit estimates for PFS for second-line osimertinib

	AIC	BIC
Log Normal	273.41	277.59
Log Logistic	274.08	278.27
Exponential	275.43	277.53
Weibull	277.19	281.38

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure S3.9 Distributions fitted to Kaplan-Meier curve for OS for second-line pemetrexed/ cisplatin

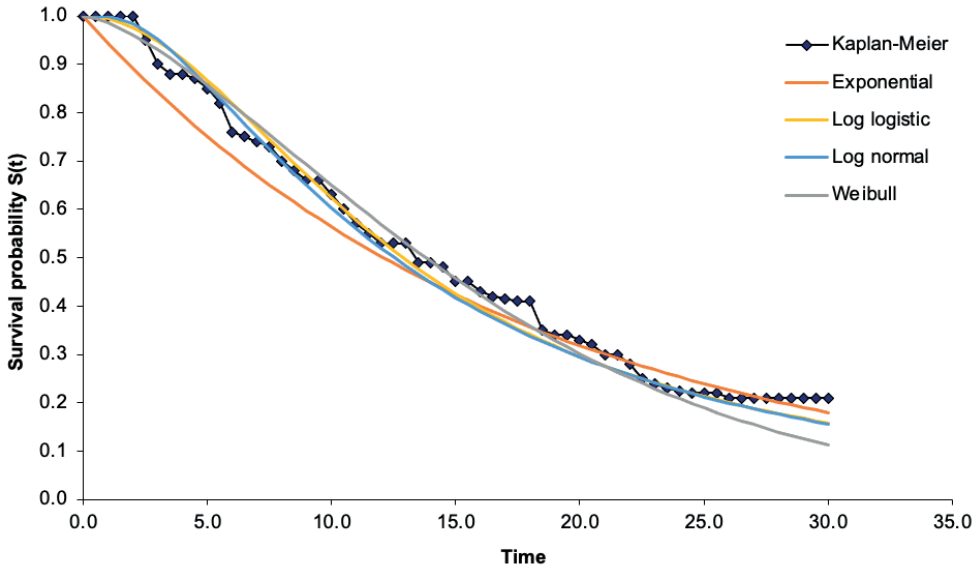


Figure S3.10 Distributions fitted to Kaplan-Meier curve for PFS for second-line pemetrexed/cisplatin

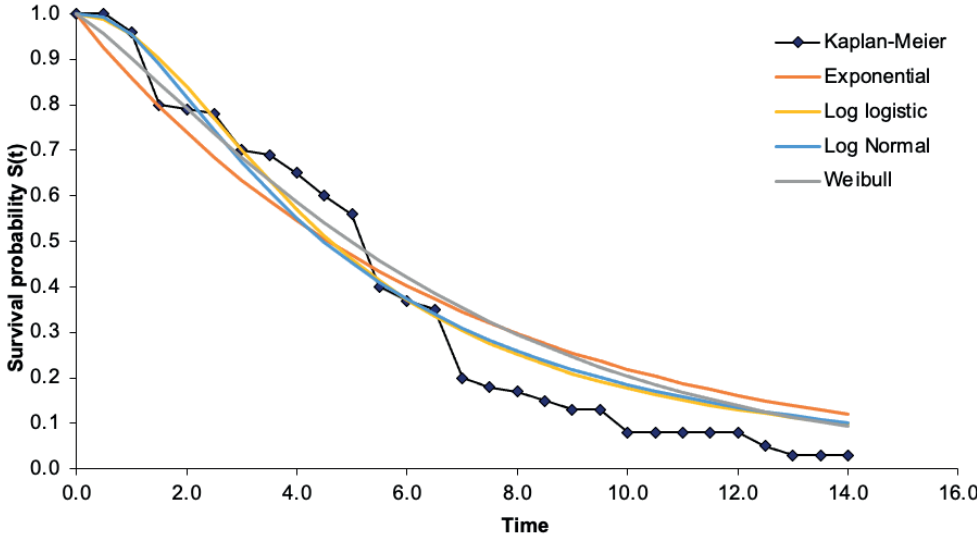


Table S3.11 Goodness of fit estimates for OS for second-line pemetrexed/cisplatin

	AIC	BIC
Log Normal	1028.74	1034.60
Weibull	1030.29	1036.16
Log Logistic	1030.99	1036.86
Exponential	1049.47	1052.40

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table S3.12 Goodness of fit estimates for PFS for second-line pemetrexed/cisplatin

	AIC	BIC
Log Logistic	743.14	748.83
Log Normal	745.13	750.82
Exponential	767.83	770.67
Weibull	764.32	770.01

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table S3.13 Parameter transition probabilities

	Value	Reference
Lambda OS chemotherapy	0.019	[66]
Gamma OS chemotherapy	1.203	[66]
Lambda OS gefitinib	0.020	
Gamma OS gefitinib	1.203	[66]
Lambda OS erlotinib	0.019	
Gamma OS erlotinib	1.203	[66]
Lambda OS afatinib	0.017	
Gamma OS afatinib	1.203	[66]
Lambda OS osimertinib	0.012	
Gamma OS osimertinib	1.203	[66]
Intercept OS 2nd-line osimertinib	4.069	[113]
Intercept OS 2nd-line pem/cis	2.861	[114]
Lambda PFS chemotherapy	0.073	[66]
Gamma PFS chemotherapy	1.478	[66]
Lambda PFS gefitnib	0.031	
Gamma PFS gefitinib	1.478	[66]
Lambda PFS erlotinib	0.026	
Gamma PFS erlotinib	1.478	[66]
Lambda PFS afatinib	0.027	
Gamma PFS afatinib	1.478	[66]
Lambda PFS osimertinib	0.013	
Gamma PFS osimertinib	1.478	[66]
Intercept PFS 2nd-line osimertinib [a]	2.985	[113]
Intercept PFS 2nd-line pem/cis	1.885	[114]

Abbreviations: OS, overall survival; pem/cis, pemetrexed/cisplatin; PFS, progression-free survival.
[a] Transition probability from progression-free to death was estimated by using the following formula: number of patients without progression in previous cycle of second-line treatment*(1 – survival probability OS).

Costs

Patients received oral gefitinib (250mg), erlotinib (150mg), afatinib (40mg), or osimertinib (80mg/day) daily until disease progression or unacceptable toxic effects. Before the start of TKI treatment, tumour tissue was assessed for EGFR-mutations. These testing costs were only applied to the first cycle of the model. Outpatient visits, including laboratory tests, took place every month, both in first-line TKI and second-line osimertinib and pemetrexed/cisplatin treatment.[66,113] Tumour response assessment took place, on average, after every 8 weeks and comprised CT and MRI scan.[60-62,64-69,90] For first-line TKI-treatment, it was assumed that only a very small proportion of patients would receive home care and informal care. These costs were not taken into account for TKIs, because the effect on the ICER will be negligible. Productivity

costs were based on a study of Louie et al.[123] In this study, productivity loss was measured by using the short form health and labour questionnaire (SF-HLQ) and patient's productivity costs were estimated by using the friction cost method.[123]

After progression on gefitinib, erlotinib, or afatinib, patients were tested for T790 M mutations. Patients with T790 M mutation-positive disease (50% of the patients) was treated with 80mg osimertinib on day one of a 30 day cycle. All other patients were treated with 500mg/m^2 pemetrexed plus 75mg/m^2 ciplatin after progression on TKI. Costs of pemetrexed/cisplatin were calculated by use of an estimated body surface area of 1.70m^2.[124] Second-line treatment was received until disease progression, unacceptable toxicity or death. Costs for pharmaceutical delivery were added to the drug costs. We assumed that gefitinib, erlotinib, afatinib, and osimertinib were delivered per 30 days each time. For second-line treatment, pharmaceutical costs were taken into account for each cycle.[120] Travel costs were based on a price per kilometre plus parking costs. According to the Dutch guidelines, a distance of 14 kilometre was used for travelling from a patient's home to the hospital and back to estimate patient's travel costs. These costs were applied to the model, both for first-line TKI and second-line treatment. Second-line patients received home care and informal care. Administration costs were added for pemetrexed/cisplatin treatment. We assumed that patients received BSC as third-line treatment after progression on second-line treatment. End-of-life costs comprised costs of the last month of life. These were one-off costs and were added to the health state progression. Severe adverse events were only applied to the first cycle of the model, for both first- and second-line treatment. Costs of adverse events comprised the total costs of the treatment of an adverse event per patient and were multiplied by the probability of each adverse event.

Table S3.14 Resource use progression-free and progressive disease health state

	Resource use PF (30 days)	Resource use PD (30 days)	Reference
Costs			
Gefitinib (250mg/day)	30.00	N/A	[106]
Erlotinib (150mg/day)	30.00	N/A	[106]
Afatinib (40mg/day)	30.00	N/A	[106]
Osimertinib (80mg/day)	30.00	N/a	[106]
Pemetrexed (500mg/m^2)	N/A	1.70 [a]	[106]
Cisplatin (10mg/m^2)	N/A	12.75 [b]	[106]
Best supportive care	N/A	-	[118]
Mutation test	1.00 [c]	N/A	[119]
Tumour response assessment	0.50	N/A	[119]
Outpatient visit	1.00	N/A	[120]

	Resource use PF (30 days)	Resource use PD (30 days)	Reference
Lab tests	1.00	1.00	[105]
Concomitant drugs	N/A	3.00	[106]
Administration pem/cis	N/A	1.00	[118]
Home care (per hour)	N/A	0.15	[124]
Informal care (per hour)	N/A	24.00	[124]
Traveling	1.00	1.00	[120]
Productivity loss	1.00*	N/A	[123]
End-of-life	N/A	1.00	[122,141]

Abbreviations: N/A, not applicable; pem/cis, pemetrexed/cisplatin; PF, progression-free; PD, progressive disease.
[a] Based on body surface area of 1.70m^2 and 500mg/m^2 pemetrexed
[b] Based on body surface area of 1.70m^2 and 75mg/m^2 cisplatin
[c] One-off costs; only applied to the first cycle of the model

Table S3.15 Input parameters for unit costs and probabilities adverse events

	Probability AE gefitinib	Probability AE erlotinib	Probability AE afatinib	Probability AE osimertinib	Probability AE 2nd-line osimertinib	Probability AE 2nd-line pem/cis
ALT/AST increase	0.103	N/A	N/A	N/A	N/A	0.015
Anaemia	N/A	N/A	N/A	N/A	0.035	0.038
Anorexia	0.022	N/A	N/A	N/A	N/A	N/A
Asthenia	N/A	N/A	N/A	N/A	0.025	0.030
Decreased appetite	N/A	N/A	0.018	0.025	N/A	0.023
Decreased white blood cells	N/A	N/A	N/A	N/A	N/A	0.091
Diarrhoea	0.026	N/A	0.105	0.022	N/A	N/A
Dyspnoea	N/A	N/A	N/A	N/A	0.025	0.023
Fatigue	0.016	N/A	0.021	N/A	N/A	N/A
Febrile neutropenia	N/A	N/A	N/A	N/A	N/A	N/A
Leukopenia	N/A	N/A	N/A	N/A	N/A	0.023
Nausea	N/A	N/A	N/A	N/A	N/A	0.045
Neuropathy	N/A	N/A	N/A	N/A	N/A	N/A
Neutropenia	0.018	N/A	N/A	N/A	N/A	0.053
Paronychia	N/A	N/A	0.046	N/A	N/A	N/A
Rash	0.061	0.057	0.139	N/A	N/A	N/A
Stomatitis	N/A	N/A	0.064	N/A	0.016	N/A
Vomiting	N/A	N/A	N/A	N/A	0.019	0.023

Abbreviations: N/A, not applicable; pem/cis, pemetrexed/cisplatin.[60-62,64-69,71,90,91,142]

Supplemental material: Results

Table S3.16 Cost-effectiveness estimates of all comparisons

Comparison	Incremental costs (€)	Incremental LYs	Incremental QALYs	ICER (€)
Erlotinib - gefitinib	-1,854	0.03	0.03	-68,542
Afatinib - gefitinib	3,529	0.23	0.16	22,514
Afatinib - erlotinib	5,383	0.20	0.13	41,504
Osimertinib – afatinib	62,936	0.68	0.49	129,075
Osimertinib – erlotinib	68,319	0.88	0.62	110,676
Osimertinib - gefitinib	66,465	0.91	0.64	103,152

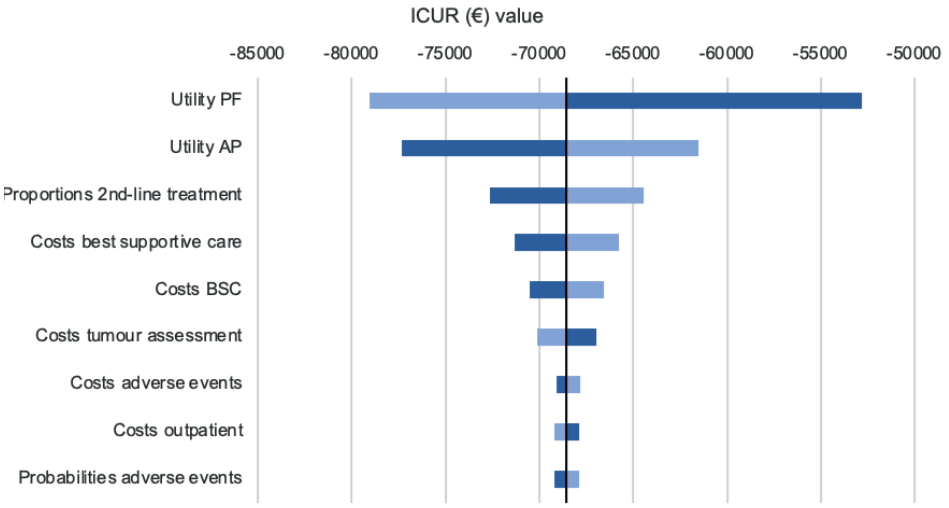
Abbreviations: ICER, incremental cost-effectiveness ratio.

Table S3.17 Results scenario analyses

	Incremental costs (€)	Incremental LYs	Incremental QALYs	ICER (€)
Log logistic function				
Erlotinib – gefitinib	-1,440	0.02	0.02	-94,805
Afatinib – erlotinib	2,607	0.12	0.08	33,847
Osimertinib – afatinib	22,372	0.40	0.28	81,158
Survival curves based on Lux-Lung 6	-1,955	0.03	0.02	-85,930
Erlotinib – gefitinib	4,296	0.18	0.12	37,289
Afatinib – erlotinib	37,531	0.59	0.42	90,013
Osimertinib – afatinib				
Second-line docetaxel treatment				
Erlotinib – gefitinib	-1,607	0.03	0.03	-59,411
Afatinib – erlotinib	5,149	0.20	0.13	39,650
Osimertinib – afatinib	62,045	0.68	0.49	126,900
Price reduction of 30% of osimertinib being cost-effective				
Osimertinib – afatinib	36,275	0.68	0.49	74,396

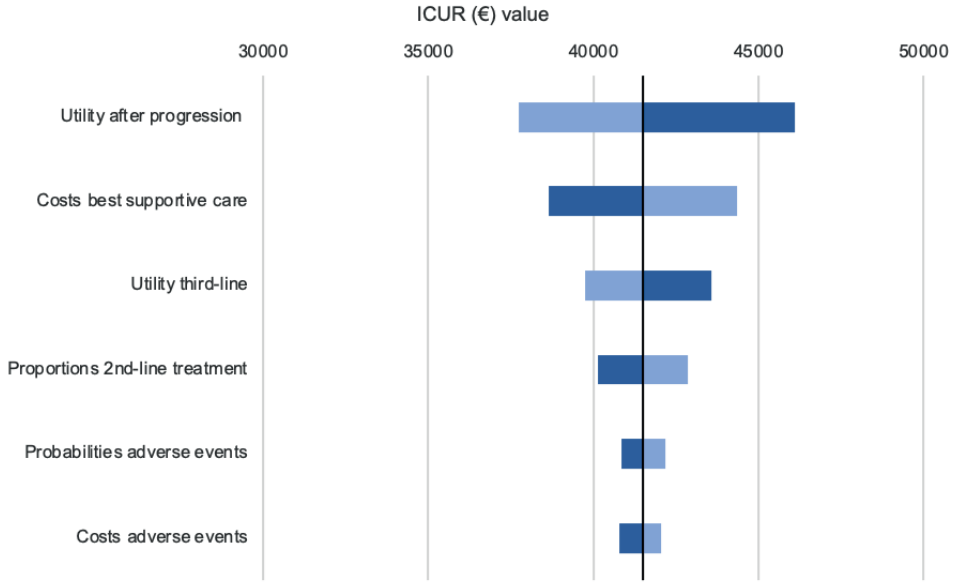
Abbreviations: ICER, incremental cost-effectiveness ratio.

Figure S3.11 Tornado diagram of the ICER of gefitinib vs erlotinib



Abbreviations: ICUR, incremental cost-utility ratio.

Figure S3.12. Tornado diagram of the ICER of afatinib vs erlotinib



Abbreviations: ICUR, incremental cost-utility ratio.

Chapter 4

Determining the comparative value of pharmaceutical risk-sharing policies in non-small cell lung cancer using real-world data

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Abstract

Background: Risk-sharing arrangements (RSAs) can be used to mitigate uncertainty about the value of a drug by sharing the financial risk between payer and pharmaceutical company. We evaluated the projected impact of alternative RSAs for non-small cell lung cancer (NSCLC) therapies based on real-world data.

Methods: Data on treatment patterns of Dutch NSCLC patients from four different hospitals were used to perform "what if"-analyses, evaluating the costs and benefits likely associated with various RSAs. In the scenarios, drug costs or refunds were based on RECIST response, survival compared to the pivotal trial, treatment duration, or a fixed cost per patient. Analyses were done for erlotinib, gemcitabine/cisplatin, and pemetrexed/platinum for metastatic NSCLC, and gemcitabine/cisplatin, pemetrexed/cisplatin, and vinorelbine/cisplatin for non-metastatic NSCLC.

Results: Money-back guarantees led to moderate cost reductions to the payer. For conditional treatment continuation schemes, costs and outcomes associated with the different treatments were disperse. When price was linked to the outcome, the payer's drug costs reduced by 2.5-26.7%. Discounted treatment initiation schemes yielded large cost reductions. Utilisation caps mainly reduced the costs of erlotinib treatment, by 16%. Given a fixed cost per patient based on projected average use of the drug, risk-sharing was unfavourable to the payer due to lower than projected use. RSAs' impact on national scale was disperse.

Conclusion: For erlotinib and pemetrexed/platinum, large cost reductions were observed with risk-sharing. RSAs can mitigate uncertainty around the incremental cost-effectiveness or budget impact of drugs, but only when the type of arrangement matches the setting and type of uncertainty.

Introduction

At the time a reimbursement decision is made, the real value of a drug is often uncertain. Typically, there is efficacy evidence from a randomised controlled trial (RCT), but such trials are often conducted in highly selected patients and settings. In clinical practice a drug is likely to be used in a much broader range of patients and settings than in RCTs, and practices often change over time. This poses a risk for healthcare payers, since the real-world effectiveness of a drug may be lower than predicted, the costs may be higher, or both.[143]

Several types of policies have been designed to mitigate this uncertainty by sharing the financial risk between the payer and the pharmaceutical company. An example is the use of a money-back guarantee, where the payer (i.e., the government or health insurer) is refunded if patients do not achieve specified targets (i.e., tumour remission). Such agreements may allow drugs to be accepted for reimbursement relatively early, while preventing the waste of public resources on drugs that are ineffective or do not live up to expectations.[25,26]

Worldwide, hundreds of different risk-sharing agreements (RSAs) have been implemented over the last few years.[26,144,145] However, little is known about the relative merits of each type.

The results of some individual policies have been analysed,[144,145] but there has never been a study to quantify and compare the costs and benefits of alternative RSAs based on real-world data. There is little guidance for policy makers on when to use which type of risk-sharing policy, the feasibility of these schemes and potential adverse effects. This has resulted in inconsistencies; for example, similar drugs may have completely different RSAs for certain indications or in different countries. There is often a lack of transparency regarding the details of RSAs. A potential reason for this is that pharmaceutical companies may wish to keep the details of an RSA secret, not to give competitors an advantage.

While RSAs may reduce the drug expenditures to the payer, they may also influence the benefits a drug can realise for patients. Therefore, this study aims to evaluate and quantify the costs (from a payer's perspective) and benefits of alternative, theoretical risk-sharing policies. A real-world non-small cell lung cancer (NSCLC) database[105] was used to determine the expected total costs and benefits associated with different types of risk-sharing.

Methods

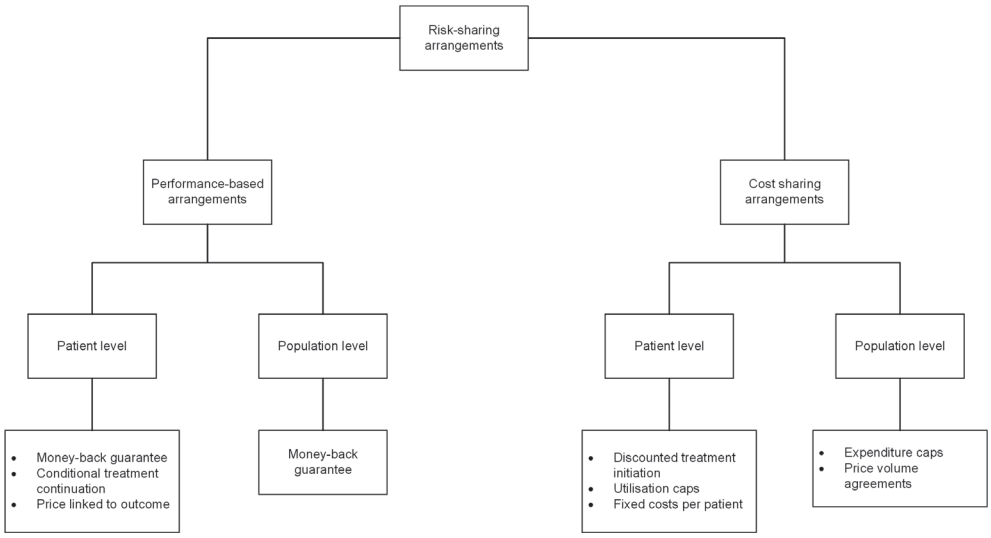
Data

Retrospectively collected data from the Dutch lung cancer database were used to inform the resource use, costs, and clinical outcomes associated with the selected drugs in the absence of risk-sharing.[105] The database contained a random sample of unselected patients with NSCLC who were identified through hospital databases of four hospitals (two academic and two non-academic hospitals). Data on 1,067 randomly selected patients newly diagnosed with stage I-IV NSCLC between 31 January 2009 and 31 January 2011 were collected. An earlier study showed that the distributions of patient characteristics in the four selected hospitals are similar to the total Dutch NSCLC population, except for clinical stage.[146] For the purposes of this paper, patients who received the following drug regimens were included in the analyses: erlotinib, gemcitabine/cisplatin, and pemetrexed/platinum (either carboplatin or cisplatin) for metastasised NSCLC (M+) and gemcitabine/cisplatin, pemetrexed/cisplatin, and vinorelbine/cisplatin for patients with non-metastasised disease (M0). These drugs were selected based on the high number of patients treated with these therapies in the database. The Dutch acquisition price of the included drugs is not based on risk-sharing or outcome-based pricing. Thus, the base case costs in this study are not inherently risk-sharing based.

Scenarios

Based on literature, a taxonomy of RSAs was determined and six different types of RSAs were included in the analyses[25,26] (Figure 4.1). Risk-sharing policies can be health outcome based ('performance-based arrangements' in Figure 4.1) and non-health outcome based ('cost-sharing arrangements' in Figure 4.1). For each type of patient-level arrangement, one or multiple different scenarios were defined, based on existing RSAs and to illustrate potential effects in 'what-if' analyses (Table 4.1). Selected scenarios did not include an 'expenditure cap' or 'price-volume agreement', since these arrangements require population-level utilisation data, which was not available in our database.

Figure 4.1 Taxonomy of included risk-sharing arrangements*



*Based on Garrison et al. and Walker et al. [25,26]

Table 4.1 Overview of the analysed scenarios

	Scenario
Money-back guarantee	Price of the drug to the payer was reduced to 0 for each patient with a recorded RECIST response to the drug that was never more favourable than 'progressive disease'. Full drug price was paid in all other cases. This is a patient-level RSA. Real-world median OS was compared to median OS in the pivotal trial. When the former was lower, the price of the drug (for all patients) was reduced proportionally.[147,148] This is a population-level RSA.
Conditional treatment continuation	Treatment was continued only in patients who had a complete or partial response after a maximum of three treatment cycles. Early treatment discontinuation was assumed not to have an effect on OS. Treatment was continued only in patients who had a complete or partial response after a maximum of three treatment cycles. Early treatment discontinuation was assumed to reduce OS, in line with the assumptions specified in the Supplemental material. The healthcare payer paid for the drug for up to three cycles. Only patients who demonstrated an adequate response (complete or partial) to the therapy continued with treatment. The pharmaceutical company subsequently provided free of charge drugs for these patients.[149,150]
Price linked to outcome	Full drug costs were reimbursed by the pharmaceutical company for patients who did not show a partial or complete response within four cycles.[151]

	Scenario
Discounted treatment initiation	The first cycle of the drug was offered for free. Thereafter, full drug price was paid. A drug price discount of 50% was applied to the first nine weeks of treatment.[145,152]
Utilisation caps	The healthcare payer paid for the drug for up to three cycles. The pharmaceutical company subsequently provided free of charge drugs for those patients who received more than three cycles.[145,153]
Fixed cost per patient	The drug was available at a single fixed cost per patient, irrespective of the duration of treatment.[a] The drug was available at a single fixed cost per patient irrespective of the duration of treatment.[154a] This single fixed cost is half of the cost used in RSA 6.1. The drug was available at a single fixed cost per patient per cycle.[a] Any excess (real-world cost per patient per cycle is higher than the fixed cost) led to proportional price reductions (real-world cost as percentage of the fixed cost) of the exceeded cost.[155]

Abbreviations: OS, overall survival; RECIST, response evaluation criteria in solid tumours; RSA, risk-sharing arrangement.
[a] Fixed costs for each treatment were based on Dutch drug assessment reports.[156-158]

Analyses

First, for each treatment, base case costs and outcomes were calculated per patient in the absence of risk-sharing. Second, it was estimated how these costs and outcomes would change when different risk-sharing scenarios would be introduced, provided all other things would remain equal (e.g., clinicians would not change their treatment decisions). Changes in costs were assessed from the payer's perspective only. Finally, differences in costs and differences in outcomes were determined for the risk-sharing scenarios compared to the base case. Risk-sharing associated incremental cost-effectiveness ratios (RSA ICERs) were calculated for scenarios that had an impact on both the costs and the outcomes, compared to the base case without risk-sharing. These RSA ICERs reflect the incremental cost-effectiveness of the RSA, as opposed to the incremental cost-effectiveness of the drug regimen. RSA ICERs were not calculated for scenarios that did not have an impact on the outcomes, as a ratio cannot be calculated when the incremental effects are zero.

The results of the RSAs were extrapolated to estimate the expected impact of the RSAs on national scale. In addition, several sensitivity analyses were done to test the uncertainty around the effects of the RSAs.

All outcomes were expressed in quality-adjusted life-years gained (QALYs). Based on literature, the following utility values were used: first-line progression-free (PF) NSCLC 0.71, first-line progressive disease (PD) 0.67, second-line PF 0.74, second-line PD 0.59, third- and further line PF 0.62, third- and further line PD 0.46. Definitive radiotherapy was assumed to be associated with the same utility value as the therapy from the previous episode. Palliative radiotherapy, radiotherapy aimed at distance metastases, and all types of surgery were assumed to be associated with a utility value of 0.62 (for PF) and 0.52 (for PD).[137,159]

Costs were estimated from a hospital perspective, based on Dutch prices and were converted to EUR 2017. Costs were reported as mean total costs per patient, including the costs of the drug treatment of interest and all subsequent treatments, diagnostics, follow-up visits, and hospitalisations. SPSS Statistics 23 was used for all analyses. More information on the assumptions underlying the risk-sharing scenarios can be found in the Supplemental material.

Results

For metastasised NSCLC, patients treated with erlotinib (n=47), gemcitabine/cisplatin (n=21), and pemetrexed/platinum (either carboplatin or cisplatin) (n=98) were included in the analyses. For non-metastasised NSCLC, patients treated with gemcitabine/cisplatin (n=69), pemetrexed/cisplatin (n=58), and vinorelbine/cisplatin (n=24) were included in the analyses. As a result, data from 317 patients was included. Table S4.3 in the Supplemental material shows the baseline characteristics of included patients.

Table 4.2 presents, among other things, the base case results as obtained by analysing the real-world data. Non-metastasised NSCLC treated with pemetrexed/cisplatin was associated with the highest mean total costs per patient. Erlotinib treatment for metastasised disease was associated with the lowest mean costs of all included regimens. The mean number of QALYs accrued by patients was highest in patients with non-metastasised disease treated with vinorelbine/cisplatin.

Money-back guarantee (scenarios 1.1 and 1.2)

Two different outcome-based money-back scenarios were tested (Table 4.2). If RSA 1.1 would have been implemented, savings for the payer would have been largest for pemetrexed/platinum and erlotinib for patients with metastasised disease, which showed the highest proportion of patients with progressive disease. For the vinorelbine/cisplatin combination treatment, all patients with non-metastasised disease responded or remained stable with

treatment, thus the costs were the same as the base case costs. In scenario 1.2, only the median OS of patients with metastasised NSCLC treated with gemcitabine/cisplatin was lower compared to the median OS in the pivotal trial (see Supplemental material).[160] As a result, this scenario yielded a small reduction of costs for patients treated with gemcitabine/cisplatin, *ceteris paribus*.

Conditional treatment continuation (scenarios 2.1, 2.2, and 2.3)

The accrued number of QALYs was lower in scenario 2.2 than in scenario 2.1, due to the assumed impact of treatment discontinuation on survival times. As a result, the RSA ICERs of scenario 2.1 compared to the base case ranged from €1,457 to €319,600, and the RSA ICERs of scenario 2.2 ranged from €1,150 to €106,533 per QALY gained. The RSA ICERs associated with scenario 2.3 ranged from €1,729 to €146,400 per QALY gained.

Price linked to outcome (scenario 3.1)

The price linked to outcome RSA resulted in large cost reductions, particularly for pemetrexed/platinum (€10,861 for M+ and €8,597 for M0 NSCLC). The reduction in payer costs was also substantial for erlotinib (€6,626), as a function of its high drug costs and relatively large proportion of non-responders.

Discounted treatment initiation (scenarios 4.1 and 4.2)

Offering the drug for free during the first 30 days substantially affected the costs associated with erlotinib treatment for patients with metastasised lung cancer. The effect of a drug price discount of 50% for the first nine weeks of treatment was relatively moderate for most treatment combinations, except for pemetrexed/platinum, which showed a cost reduction of €7,051 in patients with metastasised disease.

Utilisation caps (scenario 5.1)

When the pharmaceutical company provided free of charge drugs for patients who received more than three treatment cycles, the effect on the reduction of the costs was disperse ranging from a 0.3% to a 16% reduction in mean costs. This was due to different proportions of patients treated with chemotherapy who did not receive more than three treatment cycles (Table 4.2).

Fixed costs per patient (scenarios 6.1, 6.2, and 6.3)

In the scenarios where drug costs were based on the projected use prior to reimbursement, this resulted in an increase in the total costs per patient for all drugs compared to the base case results. This reflects the fact that real-world use for each of the drug regimens in daily practice was lower than projected. When projected drug costs were halved (scenario 6.2), the fixed price resulted in a cost reduction for four out of six treatments (Table 4.2). In scenario 6.3, a fixed cost per patient per cycle was applied. This RSA resulted in slight reductions in the cost per patient for all treatments (Table 4.2).

Table 4.2 Results base case and all analysed scenarios

	Mean total costs [a]	Δ mean total costs (%) [b]	Mean QALYs [b]	Δ mean QALYs	RSA ICER
Base case					
Erlotinib M+	27,463	N/A	0.46	0	N/A
Gemcitabine / cisplatin	31,401	N/A	0.65	0	N/A
M+	40,636	N/A	0.62	0	N/A
Pemetrexed / platinum M+	30,220	N/A	0.93	0	N/A
Gemcitabine / cisplatin	43,707	N/A	0.98	0	N/A
M0	30,519	N/A	1.11	0	N/A
Pemetrexed / cisplatin M0					
Vinorelbine / cisplatin M0					
Scenario 1.1					
Erlotinib M+	26,318	-1,145 (4.2)	0.46	0	N/A
Gemcitabine / cisplatin	31,172	-229 (0.7)	0.65	0	N/A
M+	36,021	-4,615 (11.4)	0.62	0	N/A
Pemetrexed / platinum M+	30,116	-104 (0.3)	0.93	0	N/A
Gemcitabine / cisplatin	42,860	-847 (1.9)	0.98	0	N/A
M0	30,519	0 (0)	1.11	0	N/A
Pemetrexed / cisplatin M0					
Vinorelbine / cisplatin M0					
Scenario 1.2					
Erlotinib M+	27,463	0 (0)	0.46	0	N/A
Gemcitabine / cisplatin	31,304	-97 (0.3)	0.65	0	N/A
M+	40,636	0 (0)	0.62	0	N/A
Pemetrexed / platinum M+	30,220	0 (0)	0.93	0	N/A
Gemcitabine / cisplatin	43,707	0 (0)	0.98	0	N/A
M0	30,519	0 (0)	1.11	0	N/A
Pemetrexed / cisplatin M0					
Vinorelbine / cisplatin M0					

	Mean total costs [a]	Δ mean total costs (%) [b]	Mean QALYs [b]	Δ mean QALYs	RSA ICER
Scenario 2.1					
Erlotinib M+	24,267	-3,196 (11.6)	0.45	-0.01	319,600
Gemcitabine / cisplatin	31,216	-185 (0.6)	0.64	-0.01	18,500
M+	38,285	-2,351 (5.8)	0.59	-0.03	78,367
Pemetrexed / platinum M+	30,151	-69 (0.2)	0.89	-0.04	1,725
Gemcitabine / cisplatin	42,500	-1,207 (2.8)	0.92	-0.06	20,167
M0	30,417	-102 (0.3)	1.04	-0.07	1,457
Pemetrexed / cisplatin M0					
Vinorelbine / cisplatin M0					
Scenario 2.2					
Erlotinib M+	24,267	-3,196 (11.6)	0.43	-0.03	106,533
Gemcitabine / cisplatin	31,216	-185 (0.6)	0.61	-0.04	4,625
M+	38,285	-2,351 (5.8)	0.56	-0.06	39,183
Pemetrexed / platinum M+	30,151	-69 (0.2)	0.87	-0.06	1,150
Gemcitabine / cisplatin	42,500	-1,207 (2.8)	0.89	-0.09	13,411
M0	30,417	-102 (0.3)	1.04	-0.07	1,457
Pemetrexed / cisplatin M0					
Vinorelbine / cisplatin M0					
Scenario 2.3					
Erlotinib M+	23,071	-4,392 (16)	0.43	-0.03	146,400
Gemcitabine / cisplatin	30,967	-434 (1.4)	0.61	-0.04	10,850
M+	35,911	-4,725 (11.6)	0.56	-0.06	78,750
Pemetrexed / platinum M+	30,115	-105 (0.3)	0.87	-0.06	1,750
Gemcitabine / cisplatin	42,323	-1,384 (3.2)	0.89	-0.09	15,378
M0	30,398	-121 (0.4)	1.04	-0.07	1,729
Pemetrexed / cisplatin M0					
Vinorelbine / cisplatin M0					
Scenario 3.1					
Erlotinib M+	20,837	-6,626 (24.1)	0.46	0	N/A
Gemcitabine / cisplatin	30,086	-1,315 (4.2)	0.65	0	N/A
M+	29,775	-10,861 (26.7)	0.62	0	N/A
Pemetrexed / platinum M+	28,930	-1,290 (4.3)	0.93	0	N/A
Gemcitabine / cisplatin	35,110	-8,597 (19.7)	0.98	0	N/A
M0	29,762	-757 (2.5)	1.11	0	N/A
Pemetrexed / cisplatin M0					
Vinorelbine / cisplatin M0					
Scenario 4.1					
Erlotinib M+	21,869	-5,594 (20.4)	0.46	0	N/A
Gemcitabine / cisplatin	30,797	-604 (1.9)	0.65	0	N/A
M+	36,283	-4,353 (10.7)	0.62	0	N/A
Pemetrexed / platinum M+	29,518	-702 (2.3)	0.93	0	N/A
Gemcitabine / cisplatin	39,708	-3,999 (9.1)	0.98	0	N/A
M0	29,918	-601 (2.0)	1.11	0	N/A
Pemetrexed / cisplatin M0					
Vinorelbine / cisplatin M0					

	Mean total costs [a]	Δ mean total costs (%) [b]	Mean QALYs [b]	Δ mean QALYs	RSA ICER
Scenario 4.2					
Erlotinib M+	25,923	-1,540 (5.6)	0.46	0	N/A
Gemcitabine / cisplatin	30,594	-807 (2.6)	0.65	0	N/A
M+	33,585	-7,051 (17.4)	0.62	0	N/A
Pemetrexed / platinum M+	29,480	-740 (2.4)	0.93	0	N/A
Gemcitabine / cisplatin	40,832	-2,875 (6.6)	0.98	0	N/A
M0	29,984	-535 (1.8)	1.11	0	N/A
Pemetrexed / cisplatin M0					
Vinorelbine / cisplatin M0					
Scenario 5.1					
Erlotinib M+	23,071	-4,392 (16)	0.46	0	N/A
Gemcitabine / cisplatin	30,967	-434 (1.4)	0.65	0	N/A
M+	35,911	-4,725 (11.6)	0.62	0	N/A
Pemetrexed / platinum M+	30,115	-105 (0.3)	0.93	0	N/A
Gemcitabine / cisplatin	42,323	-1,384 (3.2)	0.98	0	N/A
M0	30,398	-121 (0.4)	1.11	0	N/A
Pemetrexed / cisplatin M0					
Vinorelbine / cisplatin M0					
Scenario 6.1					
Erlotinib M+	27,545	+82 (100.3)	0.46	0	N/A
Gemcitabine / cisplatin	32,971	+1,570 (105)	0.65	0	N/A
M+	40,779	+143 (100.4)	0.62	0	N/A
Pemetrexed / platinum M+	32,263	+2,043 (106.8)	0.93	0	N/A
Gemcitabine / cisplatin	48,447	+4,740 (110.8)	0.98	0	N/A
M0	31,854	+1,335 (104.4)	1.11	0	N/A
Pemetrexed / cisplatin M0					
Vinorelbine / cisplatin M0					
Scenario 6.2					
Erlotinib M+	23,865	-3,598 (13.1)	0.46	0	N/A
Gemcitabine / cisplatin	31,134	-267 (0.9)	0.65	0	N/A
M+	33,433	-7,203 (17.7)	0.62	0	N/A
Pemetrexed / platinum M+	30,427	+207 (100.7)	0.93	0	N/A
Gemcitabine / cisplatin	41,102	-2,605 (6.0)	0.98	0	N/A
M0	30,577	+58 (100.2)	1.11	0	N/A
Pemetrexed / cisplatin M0					
Vinorelbine / cisplatin M0					
Scenario 6.3					
Erlotinib M+	26,425	-1,038 (3.8)	0.46	0	N/A
Gemcitabine / cisplatin	31,381	-20 (0.1)	0.65	0	N/A
M+	36,998	-3,638 (9.0)	0.62	0	N/A
Pemetrexed / platinum M+	30,160	-60 (0.2)	0.93	0	N/A
Gemcitabine / cisplatin	42,824	-883 (2.0)	0.98	0	N/A
M0	30,429	-90 (0.3)	1.11	0	N/A
Pemetrexed / cisplatin M0					
Vinorelbine / cisplatin M0					

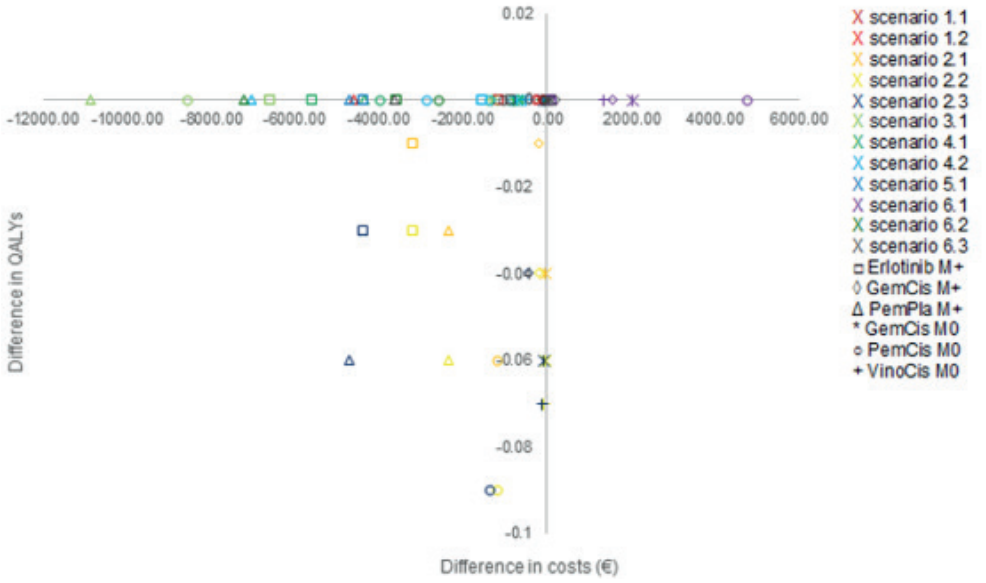
Abbreviations: M+, metastatic NSCLC; M0, non-metastatic NSCLC; RSA ICER, risk-sharing associated incremental cost effectiveness ratio.

[a] Costs in Euros

[b] Difference between the base case costs/outcomes and the costs/outcomes after applying the risk-sharing scenarios

Figure 4.2 shows the results of all scenarios for all treatments. Scenarios 3.1 and 4.1 led to the largest cost reduction for erlotinib and pemetrexed/platinum treatment in patients with metastasised NSCLC. Overall, large cost reductions were mainly observed for erlotinib and pemetrexed/platinum treatment (M+). However, for gemcitabine/cisplatin in patients with metastasised or non-metastasised disease and for vinorelbine/cisplatin (M0), the changes in costs were relatively small. In general, most RSAs resulted in a cost reduction, and some scenarios resulted in a loss of QALYs compared with a situation without RSA.

Figure 4.2 Overview of the results of all scenarios for all treatments



Abbreviations: Erlotinib M+, erlotinib for metastatic NSCLC; GemCis M+, gemcitabine/cisplatin for metastatic NSCLC; GemCis M0, gemcitabine/cisplatin for non-metastatic NSCLC; PemCis M0, pemetrexed/cisplatin for non-metastatic NSCLC; PemPla M+, pemetrexed/platinum for metastatic NSCLC; QALYs, quality-adjusted life-years; VinoCis M0, vinorelbine/cisplatin for non-metastatic NSCLC

Table 4.3 provides an overview of the different types of RSAs, including their potential effects on costs, outcomes, and managing uncertainty.

Table 4.3 Effects of different types of risk-sharing arrangements, from the perspective of the payer

Measure	Potential effect on measure	Money-back guarantee	Conditional treatment continuation	Price linked to outcome	Discounted treatment initiation	Utilisation caps	Fixed cost per patient
Δ total costs for the payer	**Increase?**	No.	Yes, when the costs of the design, implementation and execution of the RSA are higher than the cost savings due to the RSA.	Yes, when the costs of the design, implementation and execution of the RSA are higher than the cost savings due to the guarantee.	No.	No.	Yes, depending on the level of the fixed cost that is agreed upon. In the drugs discussed in this study, cost per patient were generally lower than originally projected, which results in potential losses to the payer if fixed costs are based on pre-listing projections.
	Equal?	Yes, when the savings equal the cost of the RSA.	Yes, when the savings equal the cost of the RSA.	Yes, when the savings equal the cost of the RSA.	No.	No.	Yes, depending on the level of the fixed cost that is agreed upon.
	Decrease?	Yes, when the prespecified endpoint was not reached, either by (a proportion) of patients (e.g. non-responders, scenario 1.1), or by the population (e.g. median OS, scenario 1.2), and this results	Yes, when the condition was not met for a proportion of patients (e.g. non-responders) and the resulting savings exceed the cost of the RSA.	Yes, when the prespecified endpoint was not reached, and this results in savings which exceed the cost of the RSA.	Yes, it is likely that this RSA reduces costs for the payer, since the initial part of a treatment is discounted. The cost of the RSA is likely limited, since it does not require real-world data collection.	Yes, it is likely that this RSA reduces costs for the payer, since only the initial part of a treatment must be paid for. The cost of the RSA is likely limited, since it does not require real-world data collection. It may be most	Yes, depending on the level of the fixed cost that is agreed upon.

Measure	Potential effect on measure	Money-back guarantee	Conditional treatment continuation	Price linked to outcome	Discounted treatment initiation	Utilisation caps	Fixed cost per patient
		in savings which exceed the cost of the RSA. Increase: when the costs of the design, implementation and execution of the RSA are higher than the cost savings due to the guarantee.				valuable in oncology, since treatment duration is highly variable in this area (e.g., patients are treated until disease progression).[4]	
Δ total outcomes for patients	**Increase?**	No.	No.	No.	No.	No.	No.
	Equal?	Yes, patient outcomes are not affected.	Yes, when the condition is met for all patients, or when early treatment discontinuation does not reduce patient outcomes.	Yes, patient outcomes are not affected.	Yes, patient outcomes are not affected.	Yes, patient outcomes are not affected, provided patients can continue treatment beyond the utilisation cap (i.e. sponsored by the pharmaceutical company).	Yes, patient outcomes are not affected.
	Decrease?	No.	Yes, when the condition is not met for all patients, and early treatment discontinuation reduces patient outcomes.	No.	No.	No.	No.

Measure	Potential effect on measure	Money-back guarantee	Conditional treatment continuation	Price linked to outcome	Discounted treatment initiation	Utilisation caps	Fixed cost per patient
Type of uncertainty it manages		Uncertainty around the benefits of a treatment, for example response rates, PFS, or OS. The less evidence available at the time a reimbursement decision is made, the higher the money-back value.[27] Hereby, it manages uncertainty around the incremental cost-effectiveness of the treatment.	Uncertainty around certain (intermediate) benefits of a treatment which can be measured during treatment, for example response rates. Hereby, it manages uncertainty around the incremental cost-effectiveness of the treatment.	Uncertainty around the benefits of a treatment, for example response rates, PFS, or OS. Hereby, it manages uncertainty around the incremental cost-effectiveness of the treatment.	Uncertainty around the benefits of a treatment, and especially when the benefits are expected to be highest for patients who continue treatment beyond an initial, prespecified period. It is also a way to reduce costs and therefore budget impact.	Uncertainty around the average duration of treatment: especially when the payer wants to facilitate that all patients can try the treatment, but wants to limit the costs associated with extended treatment durations. This RSA may be most beneficial in case there is limited evidence on whether longer treatment durations result in additional benefits.	Uncertainty around the average duration of treatment or the dosages patients will receive. It reduces uncertainty about the budget impact of a treatment.

Measure	Potential effect on measure	Money-back guarantee	Conditional treatment continuation	Price linked to outcome	Discounted treatment initiation	Utilisation caps	Fixed cost per patient
Potential adverse effects		- may substantially increase registration burden, since it is dependent on real-world outcomes. - is dependent on the widespread acceptance of a definition of the outcome of interest (e.g. response), the reproducibility of this endpoint, and the independence of adjudicators [4, 4, 28]. Moreover, the method of measuring outcomes should ideally be simple and outcomes should be clearly defined. - may not result in cost savings even when the drug performs worse than expected. For example: if the money-back guarantee was based on improving median OS and the	- may reduce patient outcomes when treatment is discontinued in patients who would have benefitted later. - may lead to undesirable effects, especially when an effective alternative treatment is not available for non-responders who must discontinue the treatment. - may substantially increase registration burden, since it is dependent on real-world outcomes. - is dependent on the widespread acceptance of a definition of the outcome of interest (e.g. response), the	- may substantially increase registration burden, since it is dependent on real-world outcomes. - is dependent on the widespread acceptance of a definition of the outcome of interest (e.g. response), the reproducibility of this endpoint, and the independence of adjudicators [4, 4, 28]. Moreover, the method of measuring outcomes should ideally be simple and outcomes should be clearly defined. - may not result in cost savings even when the drug performs.	- may not be acceptable to the pharmaceutical company, in case it renders the effective drug price too low or the financial uncertainty too high.	- may not be acceptable to the pharmaceutical company, in case it renders the effective drug price too low or the financial uncertainty too high. - is dependent on the availability of health outcomes data, since an agreed upon utilisation threshold should be established.[4]	- may result in higher costs for the payer than in a situation without an RSA. - may not be acceptable to the pharmaceutical company, in case it renders the effective drug price too low.

Measure	Potential effect on measure	Money-back guarantee	Conditional treatment continuation	Price linked to outcome	Discounted treatment initiation	Utilisation caps	Fixed cost per patient
		drug of interest did not improve median OS, this might not actually be obvious from real-world data. For example, OS might have been improved by another, later-line drug becoming available since the introduction of the RSA. - may not be acceptable to the pharmaceutical company, in case it renders the effective drug price too low or the financial uncertainty too high.	reproducibility of this endpoint, and the independence of adjudicators [4, 4, 28, 29, 29]. Any misclassification of responders may lead to unjust discontinuation of treatment. to treat their patients in a predefined way (i.e. stop treatment while there might still be benefit to gain from it). - may not result in cost savings even when the drug performs worse than expected, for example when other improvements in care processes (e.g., better supportive care) improve the intermediate outcome of interest.	worse than expected, similar to the example for the money-back guarantees. - may not be acceptable to the pharmaceutical company, in case it renders the effective drug price too low or the financial uncertainty too high			

Abbreviations: OS, overall survival; PFS, progression-free survival

Extrapolation of the results

We estimated the expected impact of RSAs on a national scale by multiplying the proportion of patients receiving one of the six selected treatments with the total Dutch population diagnosed with NSCLC between 2009 and 2011, which was based on previous study. Also based on this earlier study, it was assumed that 45% of all patients with NSCLC received systemic treatment.[146] Moreover, based on the data, it was assumed that the six systemic treatments that were included in this study accounted for approximately 40% of all prescribed systemic treatments in the Netherlands. The costs, effects, and impact of the RSAs in the study population were assumed to be generalizable to the national scale. The results of the extrapolation to the total Dutch population can be found in Table S4.4 in the Supplemental material. On a national scale, the differences in costs of one of the RSAs ranged from €2,178,860 (increased costs) to -€8,479,765 (cost savings).

Sensitivity analyses

To test the robustness of the effects of the RSAs, various sensitivity analyses were conducted (Table S4.5 in the Supplemental material). Scenario 2.1a and 2.1b showed cost savings and decreased QALYs for most treatments, which was in accordance with the main results, but for some treatments, the effects in terms of QALYs was the similar to the base case. For scenario 2.2a, the impact of the RSAs followed the same pattern as in the main results with RSA ICERs ranging from €1,957 to €82,325. However, in scenario 2.2b, incremental mean total costs were much lower than in scenario 2.2 (-€617 vs. -€3,196 per patient). In scenario 2.3a and 2.3b, the impact on costs and effects had the same direction as in the main results of scenario 2.3 with RSA ICERs ranging from €457 to €122,925. The impact of RSAs in scenario 3.1a and 3.1b had a similar pattern as in scenario 3.1 with cost savings ranging between -€817 and -€11,795 per patient. When the first two cycles were offered for free (scenario 4.1a), the cost savings were larger than when only the first treatment cycle was offered for free (scenario 4.1). Larger cost savings were also seen when a 75% discount was applied to the first nine weeks of treatment (scenario 4.2a) instead of a 50% discount (scenario 4.2). For scenario 5.1a and 5.1b, the cost savings followed the same pattern as in scenario 5.1. However, when we assumed that treatment was discontinued when the patient did not show an adequate response within a maximum four instead of three cycles, a few treatments in scenarios 2.1, 2.1, 2.3, and 5.1 showed no differences compared to the base case costs. This was due to the fact that most patients did not receive more than four treatment cycles, thus these patients discontinued treatment after four cycles anyway.

Discussion

This research shows the expected impact of a range of theoretical RSAs. It illustrates that the impact on mean total cost per patient can differ substantially between RSAs as well as between drug regimens within the same RSA. Furthermore, it illustrates that one type of RSA (a conditional treatment continuation scheme) can adversely affect patient outcomes, when treatment is discontinued prematurely and this results in reduced patient survival. The effect of early treatment discontinuation for non-responders may differ between drugs, depending on the probability of delayed response with continued treatment.

Looking at our results, RSAs show a larger cost impact in metastasised NSCLC than in non-metastasised NSCLC, despite shorter survival times in the metastasised setting. This is partially due to higher costs of some regimens in the metastasised setting, and partially due to lower proportions of responders with metastasised NSCLC, for example because patients were more heavily pre-treated. If the aim of RSAs is to reduce the risk to the payer, they are most favourable in clinical settings with considerable uncertainty regarding response rates, survival, patient numbers, or any other characteristics which affect budget impact. When these uncertainties do not exist, RSAs lose their value.

Based on the results of this study, the choice of whether and which type of RSA to use should depend on a careful analysis of the type of outcomes expected, and the type of uncertainty one aims to manage/reduce/share. This is also reflected in the RSA ICERs, which differ substantially for different drug regimens within the same RSA scenario.

Healthcare payers generally won't be able to force a pharmaceutical company into an RSA which the company considers unacceptable. Negotiations will be dependent on the perceived value of the drug, the willingness of the payer to reject the drug for reimbursement in case the company is not willing to accept the RSA, and the viable price range for the company.[161] Even when a performance-based RSA is agreed upon, and drug performance turns out to be limited, difficulties with the clinical evidence may cause discussions and delays in effectuating refunds or price cuts. In such instances, negotiating power from the payer may be limited since patients are already receiving the drug and it is difficult to remove from the market.

Interpretation of clinical evidence can be difficult and there is a lack of guidance for decision makers on how to quantify performance of drugs in the context of performance-based RSAs. Many pharmaceuticals are not prescribed as monotherapy (e.g., chemotherapy plus immunotherapy), which means improved clinical outcomes can be attributed to multiple compounds. Furthermore, patients may receive treatment sequences which may change over

time and may hamper the interpretation of clinical evidence. For example, in the context of an Australian managed entry scheme for ipilimumab in melanoma, it was found that the availability of post-ipilimumab treatments (e.g., dabrafenib, trametinib, pembrolizumab and nivolumab) via compassionate access programs might have impacted survival rates. Survival was higher than in the pivotal trial and refunds to Government were not required.[162]

It is important to note that the success of RSAs should not (solely) be measured by their impact on reducing costs to the payer. Even when an RSA does not result in effective price reductions compared to a situation without RSA, it may result in reduced uncertainty for a payer who aims to maximise value for money.

An additional benefit of RSAs is that when an RSA results in a reduction of the effective price of drugs without reducing the list price, this may prevent companies from having to offer a similarly low price in other countries which adopt less stringent cost-effectiveness requirements. Even though confidential price reductions are common independent of RSAs, RSAs may provide payers and companies with another tool to reduce effective prices without impacting the list price.

Limitations

It should be recognised that shifting part of the cost away from payers to pharmaceutical companies, may reduce incentives for (potentially risky) investment decisions by pharmaceutical companies. The potential impact on investments in Research & Development was not considered in this study. Also, the study did not consider the costs of designing, implementing, executing, and reviewing RSAs, or who would bear these costs. These costs may be substantial, especially in case real-world, patient level data collection is required, however, these costs are highly context-dependent and have not been published for the various types of RSAs.

Since we used a retrospectively collected dataset subtracted from medical records, data quality was determined by the information registered in the hospitals. While chemotherapy treatment information is generally carefully registered, sometimes information was missing in the medical record (e.g., dosage) and had to be estimated (e.g., based on body weight). Moreover, since some patients were treated in multiple hospitals and data of these patients could only be obtained for the study hospitals, patients were censored from the moment they were referred to a non-study hospital. Despite these limitations, the dataset was highly suitable to perform these analyses. As opposed to most real-world datasets (such as administrative datasets),

our data was specifically collected for pharmacoeconomic purposes and contained detailed information on resource use, costs, and also a large number of clinical outcomes including type and date of tumour response/progression. These data enabled us to do the 'what-if'-analyses.

The study population could be considered as representative of the Dutch NSCLC population with regard to the distributions of age, gender, and tumour histology, but a relatively high proportion of patients was classified with clinical stage I-III (61% vs. 47%). Therefore, the representativeness of the study population is not guaranteed. Depending on a hospital's patient population, the impact of RSAs may differ substantially. Amongst others, RSAs may have a larger impact in academic/specialised hospitals as expensive drugs are more often prescribed in these centres.

Results in this study were not corrected for censoring, therefore costs, QALYs, and RSA ICERs represent the study period only. Correction for censoring would increase the costs and QALYs, since it would incorporate (an estimate of) the costs and QALYs that were accrued after the study, by patients who were still alive at the end of the study period. It is unknown whether this would have an effect on the perceived relative benefits of RSAs.

The current analyses calculated the costs and outcomes associated with theoretical RSAs, assuming all other things would remain equal. It is not an experimental study, but a study based on a retrospective patient registry. Therefore, it does not consider potential changes in prescribing behaviour by clinicians in response to the RSA, or potential changes in price setting by pharmaceutical companies. However, the study does not claim to predict what would happen in case of implementing these RSAs for these selected drugs, but instead provides insight into the range of different effects RSAs might have on costs and outcomes of a drug. Potential "adverse effects" of RSAs were discussed in Table 4.3. The drugs that were chosen are merely used as case studies, and it is not suggested that any type of RSA should have been implemented for any of these drugs.

Note that the results presented in this study (Table 4.2) do not include the acceptability of a certain RSA for patients or their doctors. For example, in certain treatment areas it may be considered unethical to implement a conditional treatment continuation scheme which declines non-responders the option to continue a drug which might work for them in the future. While drug restrictions can result in similar situations without RSAs, RSAs may be more controversial in case of potential detrimental effects on the quality of life or survival of patients.

'Expenditure caps' and 'price volume agreements' were excluded from analyses in this study, since these types of RSA require population-level utilisation data. These RSAs aim to mitigate uncertainty around the budget impact and could be considered when there is uncertainty surrounding the average treatment duration and/or expected patient numbers.

This article did not discuss the option of implementing an RSA that combines aspects of different types of RSAs, such as an utilisation cap combined with discounted treatment initiation.[163] Furthermore, the article did not discuss the practical aspects of how RSAs are implemented, which can determine their benefit. For example, an RSA may be implemented as a cap on total budget impact, when there is uncertainty in the length of treatment, number of patients, or both. However, this could result in a situation where fewer patients receive the drug than predicted, but they take it for longer than expected. In this case the budget impact cap may not be reached, but the extended use per patient may render the drug cost-ineffective. As a result, RSAs which are implemented based on budget impact thresholds may form an incentive for drug companies to overestimate initial budget impact forecasts in reimbursement submissions, so that subsequently determined budget impact thresholds will not reduce their expected sales.

Lastly, the scope of this study was limited to the impact of RSAs on NSCLC treatments. However, the principles of RSAs are similar for other treatments within and beyond oncology. The value of RSAs in other populations depends on the uncertainty of the value of treatments in populations, the costs of these treatments, and the extent to which clearly defined outcomes (like tumour response and death) can be identified.[144]

Further research

Further research regarding the costs of designing, implementing, and executing RSAs (e.g., transaction costs, administrative burden, and data collection) is recommended. Also, attitudes of clinicians, pharmaceutical companies, and payers to different types of risk-sharing should be studied, to inform acceptable RSAs which are beneficial to society without being detrimental to patient health and care.

Conclusions

RSAs can mitigate uncertainty around the incremental cost-effectiveness or budget impact of drugs. However, the choice of whether and which type of RSA to use should depend on a careful analysis of the type of outcomes expected and the type of uncertainty one aims to reduce.

Supplemental material: Methods used to quantify costs and effects of the risk-sharing scenarios

Base case analysis

Base case costs were calculated from the selected treatment onwards. Costs of previous treatments were not included. Drug costs were based on Z-index prices and drug wastage was included for all drugs in each of the scenarios, based on available pack/vial sizes and dosing per individual patient. Scenario specific assumptions can be found in Table S4.1.

Calculation of the effects consisted of two steps. First, we calculated the duration of each episode, using the formulas specified below. Secondly, QALYs were calculated by multiplying episode durations with corresponding utility values.

- Without disease progression during episode x: start episode (x+1) – start episode x.
- With disease progression during episode x: progression date x – start episode x.
- When patient died/was censored without reported disease progression: last known date – start episode x.
- Time after progression in episode x till the start of episode (x+1): start episode (x+1) – progression date x.
- When patient died/was censored after progression in episode x: last known date – progression date x.

Scenario 1.1

First, for each included patient, we assessed whether RECIST response to the drug of interest was more favourable than 'progressive disease' (i.e., complete response, partial response, or stable disease). When response was never more favourable than 'progressive disease', the cost of the drug of interest was set to 0. In all other cases, the costs were equal to the base case costs.

Scenario 1.2

For each treatment regimen, the real-world median overall survival (OS) was compared to the median OS reported in the corresponding pivotal trial. When the former was lower, the drug price for all patients was reduced proportionally. For example, for gemcitabine/cisplatin treatment for patients with metastatic NSCLC, the real-world median OS was 0.4 months lower than the median OS from the pivotal trial (8.3 vs. 8.7 months). Therefore, the drug costs of gemcitabine/cisplatin were reduced with 4.6% (8.3/8.7).

Scenario 2.1

We assessed whether patients had a complete or partial response in the time between start of the episode until end of the third treatment cycle. When patients did not have the outcome of interest, costs of the drug of interest were set to 0 after three treatment cycles, as treatment was discontinued for these patients. Costs were equal to the base case costs in all other cases. In this scenario, early treatment discontinuation was assumed not to have an effect on OS. Assumptions underlying this risk-sharing scenario can be found in Table S4.1.

Scenario 2.2

Costs were calculated in the same way as in scenario 2.1. In contrast to the former scenario, in scenario 2.2, early treatment discontinuation was assumed to reduce OS. The effect on OS for each treatment is reported in Table S4.1. Therefore, to calculate the effects, the time of each episode was recalculated and multiplied by the corresponding utility values.

Scenario 2.3

Response to the treatment was assessed in the same way as in scenario 2.1. Treatment continuation was only allowed for patients who had a complete or partial response, all other patients were assumed to discontinue treatment. For patients with an adequate response, the drug was provided for free after three treatment cycles. Similar to scenario 2.2, early treatment discontinuation was assumed to affect OS. The methods to recalculate the effects were similar to the methods used in scenario 2.2.

Scenario 3.1

First, it was assessed whether patients had a complete or partial response in the period between start of the episode until end of the fourth treatment cycle. Subsequently, all costs related to the drug of interest were set to 0 when a patient did not have an adequate response. It was assumed that this scenario did not affect OS, as patients continued treatment despite not having an adequate response.

Scenario 4.1

Drug costs were recalculated by subtracting the costs of the first cycle from the total costs of the drug of interest.

Scenario 4.2

Drug costs for the first nine weeks were calculated. We applied a 50% discount to these costs. The costs of all subsequent weeks were assumed to be the same as in the base case analysis.

Scenario 5.1

Firstly, we checked which patients received more than three treatment cycles. The costs of these first three cycles were kept equal to the base case costs of these three cycles. Costs of subsequent treatment cycles were reduced to 0.

Scenario 6.1 and 6.2

The costs of the drug of interest were changed into a single fixed cost per patient for all patients regardless of the treatment duration or number of treatment cycles.

Scenario 6.3

The drug was available at a single fixed cost per patient per cycle. Higher real-world drug costs led to a proportional cost reduction (real-world cost as percentage of the fixed cost) of the exceeded costs.

For scenario 1.1, 2.1, 2.2, 2.3, and 3.1, base case costs (and effects) were used for patients whose tumour response was unknown. Accurate administration of a patient's clinical status is of great importance for a good implementation of these RSAs.

Table S4.1 Assumptions underlying the risk-sharing scenarios

Scenario	Assumption
Base case	Calculation of costs and QALYs started from the selected treatment onwards. Prior treatments were not costed, since they were not impacted by the treatment of interest. Carboplatin and cisplatin treatment were pooled into one group (platinum), because the mechanisms of action and costs of these drugs are similar.
Scenario 1.2	Median OS in the pivotal trial of gemcitabine/cisplatin for metastasised NSCLC was 8.7 months.[160] Median OS in the pivotal trial of gemcitabine/cisplatin for non-metastasised NSCLC was 9.1 months.[164] Median OS in the pivotal trial of pemetrexed/cisplatin was 10.3 months.[165] Median OS in the pivotal trial of erlotinib as second-line treatment was 6.7 months.[166] Median OS in the pivotal trial of vinorelbine/cisplatin was 8 months.[167]

Scenario	Assumption
Scenario 2.1	Since all included chemotherapy combination treatments were administered every 21 days (one cycle), three cycles were assumed to equal 63 days of treatment, for each of the drugs. Patients who had an adequate response (complete or partial response) after a maximum of three 21-days cycles (63 days) continued treatment. Patients who did not have a complete or partial response within 63 days, were assumed to progress after 63 days (without influencing OS), due to treatment discontinuation. For patients who did not have a complete or partial response within 63 days and who did not progress during this period, we assumed that the time till next treatment would be 77 days: 63 days for time till treatment discontinuation plus 14 days for time from treatment discontinuation till start of the next treatment episode.
Scenario 2.2	Since all included chemotherapy combination treatments were administered every 21 days (one cycle), three cycles were assumed to equal 63 days of treatment, for each of the drugs. Patients who had an adequate response (complete or partial response) after a maximum of three 21-days cycles (63 days) continued treatment. All other patients had to discontinue treatment, which was assumed to affect their survival as follows: Erlotinib: for patients who did not continue treatment after 63 days, the OS after these 63 days was reduced by a maximum of 61 days (2 months).[168] Gemcitabine/cisplatin metastatic NSCLC: for patients who did not continue treatment after three cycles, the OS after these three cycles was reduced by a maximum of 45 days (1.5 months).[160] Gemcitabine/cisplatin non-metastatic NSCLC: for patients who did not continue treatment after three cycles, the OS after these three cycles was reduced by a maximum of 45 days (1.5 months).[164] Pemetrexed/platinum and pemetexed/cisplatin: for patients who did not continue treatment after three cycles, the OS after these three cycles was reduced by a maximum of 45 days (1.5 months).[165] Vinorelbine/cisplatin: for patients who did not continue treatment after three cycles, the OS after these three cycles was reduced by a maximum of 61 days (2 months).[167]
Scenario 4.1	One cycle was assumed to take 21 days for chemotherapy and 30 days (or 30 pills) for erlotinib.
Scenario 6.1	The fixed drug costs were based on cost projections as reported in the Dutch National Health Care Institute (ZIN) reports: €6,943 for erlotinib,[156] €13,862 for pemetrexed combination therapy,[157] €2,411 for vinorelbine/cisplatin combination therapy,[158] and €3,466 for gemcitabine/cisplatin combination therapy.[169]
Scenario 6.2	The fixed drug costs were based on half of the costs as projected in the Dutch National Health Care Institute (ZIN) reports (see scenario 6.1): €3,471 for erlotinib,[156] €6,931 for pemetrexed combination therapy,[157] €1,205 for vinorelbine/cisplatin combination therapy,[158] and €1,733 for gemcitabine/cisplatin combination therapy.[169]
Scenario 6.3	The costs per patient per cycle were assumed to be 75% of the costs per cycle as projected in the Dutch National Health Care Institute (ZIN) reports (see scenario 6.1): €1,350 for erlotinib,[156] €2,600 for pemetrexed combination therapy,[157] €450 for vinorelbine/cisplatin combination therapy,[158] and €650 for gemcitabine/cisplatin combination therapy.[169]

Abbreviations: OS, overall survival; QALYs, quality-adjusted life-years.

Supplemental material: Overall survival results

Median OS in the real-world data was estimated by use of Kaplan-Meier analyses. These results as well as the median OS from the pivotal trial are presented in Table S4.2.

Table S4.2 Median OS in pivotal trial vs real world data

Metastasised disease	Median OS pivotal trial (95%CI)	Median OS real world data (95%CI)	Reduction of costs (%)	Reference
Erlotinib	6.7 (NR)	8.5 (4.7-12.4)	0	[166]
Gemcitabine/cisplatin	8.7 (7.7-10.2)	8.3 (5.6-10.9)	5.6	[160]
Pemetrexed/platinum	10.3 (9.8-11.2)	11.2 (9.7-12.7)	0	[165]
Non-metastasised disease				
Gemcitabine/cisplatin	9.1 (8.3-10.6)	28.7 (NR)	0	[164]
Pemetrexed/cisplatin	10.3 (9.8-11.2)	26.6 (17.9-35.4)	0	[165]
Vinorelbine/cisplatin	8 (NR)	24.7 (21.3-28.1)	0	[167]

Abbreviations: NR, not reported; OS, overall survival.

Table S4.3 Baseline characteristics of the study population

	Total	Erlotinib M+	Gemcitabine/ cisplatin M+	Pemetrexed/ platinum M+	Gemcitabine/ cisplatin M0	Pemetrexed/ cisplatin M0	Vinorelbine/ cisplatin M0
Number of patients	317	47	21	98	69	58	24
Mean age (SD)	60.1 (10.1)	59.1 (11.3)	60.3 (7.3)	58.5 (10.3)	62.9 (8.8)	59.9 (11.8)	60.8 (7.7)
Age, n (%)							
< 65 yr	208 (65.6)	31 (66)	13 (61.9)	70 (71.4)	38 (55.1)	37 (63.8)	19 (79.2)
≥ 65 yr	109 (34.4)	16 (34)	8 (38.1)	28 (28.6)	31 (44.9)	21 (36.2)	5 (20.8)
Gender, n (%)							
Male	208 (65.6)	30 (63.8)	15 (71.4)	59 (60.2)	56 (81.2)	29 (50)	19 (79.2)
Smoking status, n (%)							
Non-smoker	20 (6.3)	8 (17)	0	7 (7.1)	1 (1.4)	3 (5.2)	1 (4.2)
Smoker	125 (39.4)	13 (27.7)	9 (42.9)	39 (39.8)	34 (49.3)	23 (39.7)	7 (29.2)
Former smoker[1]	117 (36.9)	20 (42.6)	6 (28.6)	36 (36.7)	22 (31.9)	17 (29.3)	16 (66.7)
Not reported	55 (17.4)	6 (12.8)	6 (28.6)	16 (16.3)	12 (17.4)	15 (25.9)	0
Charlson comorbidity score							
0	157 (49.5)	27 (57.4)	9 (42.9)	58 (59.2)	27 (39.1)	28 (48.3)	8 (33.3)
1	78 (24.6)	8 (17)	7 (33.3)	21 (21.4)	16 (23.2)	14 (24.1)	12 (50)
2	57 (18)	11 (23.4)	4 (19)	15 (15.3)	17 (24.6)	7 (12.1)	3 (12.5)
≥3	25 (7.9)	1 (2.1)	1 (4.8)	4 (4.1)	9 (13)	9 (15.5)	1 (4.2)
Histology, n (%)							
Adenocarcinoma	185 (58.7)	34 (72.3)	2 (9.5)	81 (83.5)	8 (11.6)	44 (75.9)	16 (69.6)
Squamous cell carcinoma	73 (23.2)	4 (8.5)	13 (61.9)	2 (2.1)	46 (66.7)	2 (3.4)	6 (26.1)
Large cell carcinoma	28 (8.9)	5 (10.6)	2 (9.5)	9 (9.3)	5 (7.2)	6 (10.3)	1 (4.3)
Other histology	13 (4.1)	4 (8.5)	3 (14.3)	2 (2.1)	5 (7.2)	2 (3.4)	0
Unknown	16 (5.1)	3 (6.4)	1 (4.8)	3 (3.1)	5 (7.2)	4 (6.9)	0
Missing	2	0	0	1	0	0	1
Clinical stage, n (%)							
Stage I	24 (7.6)	0	0	0	9 (13)	10 (17.2)	5 (20.8)
Stage II	23 (7.3)	0	0	0	9 (13)	7 (12.1)	7 (29.2)
Stage III	92 (29)	0	0	0	46 (66.7)	35 (60.3)	11 (45.8)
Stage IV	166 (52.4)	47 (100)	21 (100)	98 (100)	0	0	0
Unknown	12 (3.8)	0	0	0	5 (7.2)	6 (10.3)	1 (4.2)

Abbreviations: M+, metastatic NSCLC; M0, non-metastatic NSCLC; SD, standard deviation; yr, years.
[1] Quit > 1 month ago

Table S4.4 Extrapolation of results to the total Dutch population

	Mean costs per patient [a]	Total costs Dutch population [a]	Δ costs Dutch population [ab]	Mean QALYs per patient	Total QALYs Dutch population	Δ QALYs Dutch population [b]
Base case						
Erlotinib M+	27,463	10,202,164	N/A	0.46	170.88	N/A
Gemcitabine / cisplatin M+	31,401	5,140,545	N/A	0.65	106.41	N/A
Pemetrexed / platinum M+	40,636	31,726,703	N/A	0.62	484.07	N/A
Gemcitabine / cisplatin M0	30,220	16,554,117	N/A	0.93	509.44	N/A
Pemetrexed / cisplatin M0	43,707	20,089,363	N/A	0.98	450.44	N/A
Vinorelbine / cisplatin M0	30,519	5,764,795	N/A	1.11	209.67	N/A
Scenario 1.1						
Erlotinib M+	26,318	9,776,811	-425,353	0.46	170.88	N/A
Gemcitabine / cisplatin M+	31,172	5,103,056	-37,489	0.65	106.41	N/A
Pemetrexed / platinum M+	36,021	28,123,525	-3,603,178	0.62	484.07	N/A
Gemcitabine / cisplatin M0	30,116	16,497,147	-56,970	0.93	509.44	N/A
Pemetrexed / cisplatin M0	42,860	19,700,050	-389,313	0.98	450.44	N/A
Vinorelbine / cisplatin M0	30,519	5,764,795	0.00	1.11	209.67	N/A
Scenario 1.2						
Erlotinib M+	27,463	10,202,164	0	0.46	170.88	N/A
Gemcitabine / cisplatin M+	31,304	5,124,665	-158,800	0.65	106.41	N/A
Pemetrexed / platinum M+	40,636	31,726,703	0	0.62	484.07	N/A
Gemcitabine / cisplatin M0	30,220	16,554,117	0	0.93	509.44	N/A
Pemetrexed / cisplatin M0	43,707	20,089,363	0	0.98	450.44	N/A
Vinorelbine / cisplatin M0	30,519	5,764,795		1.11	209.67	N/A
Scenario 2.1						
Erlotinib M+	24,267	9,014,890	-1,187,274	0.45	167.17	-3.71
Gemcitabine / cisplatin M+	31,216	5,110,259	-30,286	0.64	104.77	-1.64
Pemetrexed / platinum M+	38,285	29,891,152	-1,835,552	0.59	460.64	-23.42
Gemcitabine / cisplatin M0	30,151	16,516,320	-37,797	0.89	487.53	-21.91
Pemetrexed / cisplatin M0	42,500	19,534,581	-554,782	0.92	422.87	-27.58
Vinorelbine / cisplatin M0	30,417	5,745,528	-19,267	1.04	196.45	-13.22

	Mean costs per patient [a]	Total costs Dutch population [a]	Δ costs Dutch population [ab]	Mean QALYs per patient	Total QALYs Dutch population	Δ QALYs Dutch population [b]
Scenario 2.2						
Erlotinib M+	24,267	9,014,890	-1,187,274	0.43	159.74	-11.14
Gemcitabine / cisplatin M+	31,216	5,110,259	-30,286	0.61	99.86	-6.55
Pemetrexed / platinum M+	38,285	29,891,152	-1,835,552	0.56	437.22	-46.85
Gemcitabine / cisplatin Mo	30,151	16,516,320	-37,797	0.87	476.57	-32.87
Pemetrexed / cisplatin Mo	42,500	19,534,581	-554,782	0.89	409.08	-41.37
Vinorelbine / cisplatin Mo	30,417	5,745,528	-19,267	1.04	196.45	-13.22
Scenario 2.3						
Erlotinib M+	23,071	8,570,590	-1,631,574	0.43	159.74	-11.14
Gemcitabine / cisplatin M+	30,967	5,069,496	-710,49	0.61	99.86	-6.55
Pemetrexed / platinum M+	35,911	28,037,643	-3,689,061	0.56	437.22	-46.85
Gemcitabine / cisplatin Mo	30,115	16,496,599	-57,518	0.87	476.57	-32.87
Pemetrexed / cisplatin Mo	42,323	19,453,225	-636,138	0.89	409.08	-41.37
Vinorelbine / cisplatin Mo	30,398	5,741,939	-22,856	1.04	196.45	-13.22
Scenario 3.1						
Erlotinib M+	20,837	7,740,687	-2,461,477	0.46	170.88	N/A
Gemcitabine / cisplatin M+	30,086	4,925,271	-215,274	0.65	106.41	N/A
Pemetrexed / platinum M+	29,775	23,246,938	-8,479,765	0.62	484.07	N/A
Gemcitabine / cisplatin Mo	28,930	15,847,472	-70,6645	0.93	509.44	N/A
Pemetrexed / cisplatin Mo	35,110	16,137,862	-3,951,501	0.98	450.44	N/A
Vinorelbine / cisplatin Mo	29,762	5,621,804	-142,991	1.11	209.67	N/A
Scenario 4.1						
Erlotinib M+	21,869	8,124,062	-2,078,102	0.46	170.88	N/A
Gemcitabine / cisplatin M+	30,797	5,041,666	-98,879	0.65	106.41	N/A
Pemetrexed / platinum M+	36,283	28,328,083	-3,398,620	0.62	484.07	N/A
Gemcitabine / cisplatin Mo	29,518	16,169,571	-384,546	0.93	509.44	N/A
Pemetrexed / cisplatin Mo	39,708	18,251,274	-1,838,089	0.98	450.44	N/A
Vinorelbine / cisplatin Mo	29,918	5,651,271	-113,524	1.11	209.67	N/A
Scenario 4.2						
Erlotinib M+	25,923	9,630,073	-572,091	0.46	170.88	N/A
Gemcitabine / cisplatin M+	30,594	5,008,434	-132,111	0.65	106.41	N/A
Pemetrexed / platinum M+	33,585	26,221,610	-5,505,094	0.62	484.07	N/A
Gemcitabine / cisplatin Mo	29,480	16,148,755	-405,362	0.93	509.44	N/A
Pemetrexed / cisplatin Mo	40,832	18,767,906	-1,321,457	0.98	450.44	N/A
Vinorelbine / cisplatin Mo	29,984	5,663,738	-101,057	1.11	209.67	N/A

	Mean costs per patient [a]	Total costs Dutch population [a]	Δ costs Dutch population [ab]	Mean QALYs per patient	Total QALYs Dutch population	Δ QALYs Dutch population [b]
Scenario 5.1						
Erlotinib M+	23,071	8,570,590	-1,631,574	0.46	170.88	N/A
Gemcitabine / cisplatin M+	30,967	5,069,496	-71,049	0.65	106.41	N/A
Pemetrexed / platinum M+	35,911	28,037,643	-3,689,061	0.62	484.07	N/A
Gemcitabine / cisplatin M0	30,115	16,496,599	-57,518	0.93	509.44	N/A
Pemetrexed / cisplatin M0	42,323	19,453,225	-636,138	0.98	450.44	N/A
Vinorelbine / cisplatin M0	30,398	5,741,939	-22,856	1.11	209.67	N/A
Scenario 6.1						
Erlotinib M+	27,545	10,232,626	30,462	0.46	170.88	N/A
Gemcitabine / cisplatin M+	32,971	5,397,564	257,019	0.65	106.41	N/A
Pemetrexed / platinum M+	40,779	31,838,351	111,648	0.62	484.07	N/A
Gemcitabine / cisplatin M0	32,263	17,673,246	1,119,128	0.93	509.44	N/A
Pemetrexed / cisplatin M0	48,447	22,268,043	2,178,680	0.98	450.44	N/A
Vinorelbine / cisplatin M0	31,854	6,016,966	252,171	1.11	209.67	N/A
Scenario 6.2						
Erlotinib M+	23,865	8,865,552	-1,336,612	0.46	170.88	N/A
Gemcitabine / cisplatin M+	31,134	5,096,835	-43,710	0.65	106.41	N/A
Pemetrexed / platinum M+	33,433	26,102,935	-5,623,768	0.62	484.07	N/A
Gemcitabine / cisplatin M0	30,427	16,667,509	113,392	0.93	509.44	N/A
Pemetrexed / cisplatin M0	41,102	18,892,008	-1,197,355	0.98	450.44	N/A
Vinorelbine / cisplatin M0	30,577	5,775,751	10,956	1.11	209.67	N/A
Scenario 6.3						
Erlotinib M+	26,425	9,816,560	-385,604	0.46	170.88	N/A
Gemcitabine / cisplatin M+	31,381	5,137,271	-3,274	0.65	106.41	N/A
Pemetrexed / platinum M+	36,998	28,886,322	-2,840,382	0.62	484.07	N/A
Gemcitabine / cisplatin M0	30,160	16,521,250	-32,867	0.93	509.44	N/A
Pemetrexed / cisplatin M0	42,824	19,683,503	-405,860	0.98	450.44	N/A
Vinorelbine / cisplatin M0	30,429	5,747,795	-17,000	1.11	209.67	N/A

Abbreviations: M+, metastatic NSCLC; M0, non-metastatic NSCLC; N/A, not applicable.
[a] Costs in Euros
[b] Difference between the base case costs/outcomes and the costs/outcomes after applying the risk-sharing scenarios

Table S4.5 Results sensitivity analysis of variance in the scenarios

	Mean total costs [a]	Δ mean total costs [ab]	Mean QALYs	Δ mean QALYs [b]	RSA ICER
Scenario 2.1a: Adequate response within a maximum of 2 cycles					
Erl M+	24,170	-3,293	0.45	-0.01	329,300
Gem/cis M+	31,046	-355	0.65	0	N/A
Pem/pla M+	38,000	-2,636	0.54	-0.08	32,950
Gem/cis Mo	30,083	-137	0.93	0	N/A
Pem/cis Mo	42,054	-1,653	0.91	-0.07	23,614
Vino/cis Mo	30,323	-196	1.03	-0.08	2,450
Scenario 2.1b: Adequate response within a maximum of 4 cycles					
Erl M+	24,884	-617	0.46	0	N/A
Gem/cis M+	31,401	0	0.65	0	N/A
Pem/pla M+	40,636	0	0.56	-0.06	N/A
Gem/cis Mo	30,130	-90	0.93	0	N/A
Pem/cis Mo	43,707	0	0.93	-0.05	N/A
Vino/cis Mo	30,519	0	1.05	-0.06	N/A
Scenario 2.2a: Adequate response within a maximum of 2 cycles					
Erl M+	24,170	-3,293	0.42	-0.04	82,325
Gem/cis M+	31,046	-355	0.54	-0.11	3,227
Pem/pla M+	38,000	-2,636	0.53	-0.09	29,289
Gem/cis Mo	30,083	-137	0.86	-0.07	1,957
Pem/cis Mo	42,054	-1,653	0.87	-0.11	15,027
Vino/cis Mo	30,323	-196	1.01	-0.10	1,960
Scenario 2.2b: Adequate response within a maximum of 4 cycles					
Erl M+	24,884	-617	0.43	-0.03	20,567
Gem/cis M+	31,401	0	0.55	-0.10	N/A
Pem/pla M+	40,636	0	0.55	-0.07	N/A
Gem/cis Mo	30,130	-90	0.86	-0.07	2,250
Pem/cis Mo	43,707	0	0.90	-0.08	N/A
Vino/cis Mo	30,519	0	1.04	-0.07	N/A

	Mean total costs [a]	Δ mean total costs [ab]	Mean QALYs	Δ mean QALYs [b]	RSA ICER
Scenario 2.3a: Adequate response within a maximum of 2 cycles					
Erl M+	22,546	-4,917	0.42	-0.04	122,925
Gem/cis M+	30,607	-794	0.54	-0.11	7,218
Pem/pla M+	35,655	-4,981	0.53	-0.09	55,344
Gem/cis Mo	29,895	-325	0.86	-0.07	4,643
Pem/cis Mo	40,648	-3,059	0.87	-0.11	27,809
Vino/cis Mo	30,222	-297	1.01	-0.10	2,970
Scenario 2.3b: Adequate response within a maximum of 4 cycles					
Erl M+	23,846	-3,617	0.43	-0.03	120,567
Gem/cis M+	31,401	0	0.55	-0.10	N/A
Pem/pla M+	38,039	-2,597	0.55	-0.07	37,100
Gem/cis Mo	30,188	-32	0.86	-0.07	457
Pem/cis Mo	43,707	0	0.90	-0.08	N/A
Vino/cis Mo	30,519	0	1.04	-0.07	N/A
Scenario 3.1a: Adequate response within a maximum of 2 cycles					
Erl M+	20,785	-6,678	0.46	N/A	N/A
Gem/cis M+	30,030	-1,371	0.65	N/A	N/A
Pem/pla M+	28,841	-11,795	0.62	N/A	N/A
Gem/cis Mo	28,723	-1,497	0.93	N/A	N/A
Pem/cis Mo	34,417	-9,290	0.98	N/A	N/A
Vino/cis Mo	29,392	-1,127	1.11	N/A	N/A
Scenario 3.1b: Adequate response within a maximum of 3 cycles					
Erl M+	21,554	-5,909	0.46	N/A	N/A
Gem/cis M+	30,030	-1,371	0.65	N/A	N/A
Pem/pla M+	28,841	-11,795	0.62	N/A	N/A
Gem/cis Mo	28,768	-1,452	0.93	N/A	N/A
Pem/cis Mo	34,417	-9,290	0.98	N/A	N/A
Vino/cis Mo	29,702	-817	1.11	N/A	N/A

	Mean total costs [a]	Δ mean total costs [ab]	Mean QALYs	Δ mean QALYs [b]	RSA ICER
Scenario 4.1a: First two cycles offered for free					
Erl M+	21,052	-6,411	0.46	N/A	N/A
Gem/cis M+	30,181	-1,220	0.65	N/A	N/A
Pem/pla M+	31,608	-9,028	0.62	N/A	N/A
Gem/cis M0	29,030	-1,190	0.93	N/A	N/A
Pem/cis M0	37,723	-5,984	0.98	N/A	N/A
Vino/cis M0	29,647	-872	1.11	N/A	N/A
Scenario 4.2a: 75% discount applied to first nine weeks					
Erl M+	23,055	-4,408	0.46	N/A	N/A
Gem/cis M+	29,946	-1,455	0.65	N/A	N/A
Pem/pla M+	29,837	-10,799	0.62	N/A	N/A
Gem/cis M0	29,035	-1,185	0.93	N/A	N/A
Pem/cis M0	37,294	-6,413	0.98	N/A	N/A
Vino/cis M0	28,824	-1,695	1.11	N/A	N/A
Scenario 5.1a: Adequate response within a maximum of 2 cycles					
Erl M+	22,546	-4,917	0.46	N/A	N/A
Gem/cis M+	30,607	-794	0.65	N/A	N/A
Pem/pla M+	35,655	-4,981	0.62	N/A	N/A
Gem/cis M0	29,895	-325	0.93	N/A	N/A
Pem/cis M0	40,648	-3,059	0.98	N/A	N/A
Vino/cis M0	30,222	-297	1.11	N/A	N/A
Scenario 5.1b: Adequate response within a maximum of 4 cycles					
Erl M+	23,846	-3,617	0.46	N/A	N/A
Gem/cis M+	31,401	0	0.65	N/A	N/A
Pem/pla M+	38,039	-2,597	0.62	N/A	N/A
Gem/cis M0	30,188	-32	0.93	N/A	N/A
Pem/cis M0	43,707	0	0.98	N/A	N/A
Vino/cis M0	30,519	0	1.11	N/A	N/A

Abbreviations: M+, metastatic NSCLC; M0, non-metastatic NSCLC; N/A, not applicable; RSA ICER, risk-sharing associated incremental cost effectiveness ratio.

[a] Costs in Euros

[b] Difference between the base case costs/outcomes and the costs/outcomes after applying the risk-sharing scenario

Chapter 5

Real-world costs of castration-resistant prostate cancer in the Netherlands

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Submitted

Abstract

Background: New treatment options that impact survival have become available for patients with castration-resistant prostate cancer (CRPC). Insight in the real-world costs of CRPC-treatment is lacking.

Design, setting and participants: The CAPRI-registry retrospectively included patients diagnosed with CRPC between 2010-2015 in the Netherlands. Patients treated with at least one life-prolonging drug were included in this analysis.

Outcome measurements and statistical analysis: Patient characteristics were analysed using descriptive statistics. Total healthcare costs (only costs occurring within the healthcare system) of CRPC-patients were calculated from start of first-line treatment until death, lost-to-follow-up, or study end (December 2017). Costs were stratified by treatment line and by type of treatment.

Results and limitations: A total of 1,937 patients were included in this analysis. Mean total costs were €67,174 per patient. On average, patients received 2.7 lines of systemic treatment. Costs of systemic treatment accounted for 59% of the total costs. Mean total/monthly costs stratified by treatment line were €28,705/€3,421 in line 1, €34,452/€5,083 in line 2 and, €31,751/€6,841 in line 3.

Conclusions: Real-world healthcare costs of CRPC are substantial, which is mainly driven by costs of systemic treatment. Therefore, it is important to assess the additional costs in relation to the additional benefits of new treatments compared to existing treatment options.

Patient summary: We analysed the healthcare costs of patients with castration-resistant prostate cancer (CRPC) in daily practice. The total costs of CRPC are mainly driven by costs of systemic treatment.

Introduction

Prostate cancer is the second most common type of cancer in men worldwide.[37] In the Netherlands, over 13,000 new cases of prostate cancer were diagnosed and almost 3,000 patients died in 2019.[170] Treatment of metastatic prostate cancer is palliative. For these patients, treatment consists of androgen deprivation therapy (ADT) alone or in combination with chemotherapy, new androgen-receptor targeting agents or palliative radiotherapy.[38,41] Disease progression on ADT is called castration-resistant prostate cancer (CRPC).[41] Median overall survival (OS) of CRPC-patients with best supportive care without additional systemic life prolonging drugs is estimated to be 14 months.[171]

From 2004 onwards, various treatments for CRPC with improved OS were introduced in the Netherlands (year introduced in the Netherlands in parentheses): docetaxel (2005), cabazitaxel (post-docetaxel: 2011), abiraterone (post-docetaxel: 2012, docetaxel naive: 2013), enzalutamide (post-docetaxel: 2013, docetaxel naive: 2015), radium-223 (2014), apalutamide (2019), and olaparib (2020).[42-48,50,172-174] This has improved median OS to more than 30 months as was shown in a contemporary real-world cohort in the Netherlands.[175]

It is expected that the incidence and prevalence of prostate cancer will increase due to an ageing population and life-prolonging treatments.[38] Furthermore, prostate cancer has impact on the economic burden: the total costs of prostate cancer in the Netherlands were almost 386 million Euros in 2017. This accounted for 0.44% of the total healthcare expenditures in the Netherlands. Almost 85% of the total costs of prostate cancer are related to hospital care.[176] Due to increased length of survival, expensive new treatments, increased treatment duration, earlier treatment and rising prostate cancer incidence, the economic burden will remain or increase. It is relevant to gain insight into the real-world healthcare costs of CRPC. Reimbursement decisions of new treatments are usually based on data from clinical trials, but patients in daily practice differ from patients in a trial setting and off-label use of treatments often occurs, which might result into higher costs. [18,21,22] Moreover, it is important to evaluate clinical value of treatments in the real-world and accompanying costs. The objective of this study is to provide insight into the real-world healthcare costs of patients with CRPC in the Netherlands.

Material and methods

Data source and patient population

Data were obtained from the Castration resistant prostate cancer registry: an observational study in the Netherlands (CAPRI).[18,21] CAPRI is an observational multi-centre cohort study

that contains data on patient characteristics, treatment, and outcomes of patients from 20 hospitals in the Netherlands. Patients newly diagnosed with castration-resistant prostate cancer (CRPC) were retrospectively included from January 1, 2010 till December 31, 2015. Patients were followed until death, lost-to-follow-up, or December 31, 2017 (N=3,616). ADT in combination with chemotherapy for hormone-sensitive prostate cancer was only available at the end of the study period, therefore, these patients were excluded (N=16). It is estimated that 20% of all patients with CRPC in the Netherlands were included in the study population.[18,21]

Patients who were treated with at least one of the following life-prolonging drugs (LPDs) were included in this study: docetaxel (DOC), cabazitaxel (CAB), abiraterone acetate plus prednisone (ABI+P), enzalutamide (ENZ), or radium-223 (Ra-223), while patients treated with another treatment (N=458) or who received no treatment (N=1,205) were excluded.

Cost analysis

Costing was performed according to the methodology of the Dutch costing manual.[120]

A healthcare perspective was used: only costs occurring within the healthcare system were included. Cost components were determined by measuring patient level resource use and multiplying resource use with the unit cost (Table S5.1). Five main cost components were created.

1. treatment which encompasses systemic treatment (including radionuclides), surgery, radiotherapy, interventional radiology, bone health agents, growth factors, concomitant medication, and blood transfusion;
2. hospital visits which encompass outpatient visits, day care and emergency room stays (not all costs are necessarily CRPC-related);
3. hospital admissions including inpatient hospital stay and intensive care unit stay (not all costs are necessarily CRPC-related);
4. medical imaging including but not limited to bone scintigraphy, computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, positron emission tomography-computed tomography (PET/CT) scan (not all costs are necessarily CRPC-related);
5. drug administration costs (only for intravenous treatments).

In the instance of missing resource use data, conditional mean imputation was performed (the condition being the next event for the patient) insuring internality of total cost of care.

Unit cost for outpatient visits, inpatient stay, emergency room (ER) visits and blood transfusions were obtained from the Dutch Manual for costing.[120] All costs were based on EUR 2018 unit cost data or adjusted for inflation with the Consumer Price Index (CPI) to the reference year 2018. Prices for systematic treatment or other pharmaceuticals related to the CRPC-treatment were procured from the Dutch National Healthcare Institute.[177] Other unit costs were acquired from the Dutch Healthcare Authority.[119,178]

Data analysis

Patient and disease characteristics at the start of LPD treatment are summarised using descriptive statistics.

Costs were recorded until either death, lost-to-follow-up or the end of the study. Costs were stratified by line of treatment, from the beginning of systemic treatment until event (time to event), which could be either death, lost-to-follow-up or next treatment. Costs were also stratified by systemic treatment, which were divided into costs of systemic treatment and other costs (i.e., costs due to treatment (except systemic treatment), hospital visits, hospital admissions and medical imaging). A distinction was made between total costs and monthly costs (derived from the total cost divided by the time to event in months). Moreover, costs were classified in different categories: (drug) treatment, hospital visits, hospital admissions and medical imaging. Drug resource use accounted for full wastage. All aggregations of costs and descriptive statistics were performed in RStudio version 1.2.5019.[179]

Results

Patient and disease characteristics

Patient and disease characteristics at start life-prolonging drug 1 (LPD1) are shown in Table 5.1. In total, 1,937 patients were included in this study. Median age of the study population was 74 years (range: 46-99 years). Median PSA was 99 μg/L, median ALP 139 U/L, median LDH 231 U/L, and median haemoglobin 7.8 mmol/L. Most of the patients had a ECOG performance status of 1 (39%), had bone metastases (83%), and no known visceral metastases (42%).

Table 5.1 Patient characteristics

	All patients N = 1,937
Age, years	
Mean (SD)	73 (8)
Median (range)	74 (46-99)
Charlson Comorbidity Index, %	
6	64
7-8	30
9-10	5
>10	1
Gleason score, %	
£7	32
8-10	56
Unknown	13
Opioid analgesic use	
Yes	311 (16%)
No	732 (38%)
Missing	894 (46%)
PSA (µ/L)	
Median (IQR)	99 (41-239)
Missing	179 (9%)
ALP (U/L)	
Median (IQR)	139 (91-313)
Missing	270 (14%)
LDH (U/L)	
Median (IQR)	231 (192-308)
Missing	548 (28%)
Hb (mmol/L)	
Median (IQR)	7.8 (7-8.4)
Missing	297 (15%)
ECOG performance status, n (%)	
0	399 (21%)
1	760 (39%)
³2	243 (13%)
Missing	535 (28%)
Bone metastases, n (%)	
Yes	1,605 (83%)
No	152 (8%)
Missing	180 (9%)
Visceral metastases, n (%)	
Yes	213 (11%)
No	820 (42%)
Missing	904 (47%)

Abbreviations: ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; Hb, haemoglobin; IQR, interquartile range; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; SD, standard deviation.

Total costs of all patients

Healthcare costs of CRPC-patients are presented in Table 5.2. The median follow-up period was 16.4 months (mean: 18.6 months). At the end of the follow-up period, 67% of all patients died, 14% was alive, 18% lost to follow-up, and 1% unknown. Mean total costs amounted to €67,174. Patients received on average 2.7 lines of systemic treatment. Costs of systemic treatment were €39,638, which accounted for 59% of the total costs. Other cost drivers were hospital admissions (13%; €9,018), drug administration (11%; €7,173), radiotherapy (6%; €4,293), hospital visits (6%; €4,213), and medical imaging (4%; €2,493).

Table 5.2 Costs of all patients

	All patients n = 1,937	
Follow-up period, months		
Mean (SD)	18.6 (13.1)	
Median (IQR)	16.4 (8.7-25.1)	
Deceased patients, %	67%	
Patients alive at cutoff date, %	14%	
	Mean resource use (SD)	Mean costs (SD)
Treatment		
Systemic treatment	2.70 (1.24)*	€39,638 (€35,070)
Surgery	0.10 (0.30)	€763 (€2,950)
Radiotherapy	0.37 (0.48)	€4,293 (€4,293)
Interventional radiology	0.29 (0.45)	€380 (€819)
Bone resorption treatment	0.31 (0.46)	€673 (€1,403)
Growth factors	0.04 (0.19)	€308 (€4,557)
Concomitant medication	0.78 (0.41)	€257 (€314)
Blood transfusion	0.32 (0.47)	€1,015 (€2,208)
Drug administration		€7,173 (€6,260)
Hospital visits		
Outpatient visits	23.85 (18.12)	€3,104 (€2,340)
Daycare	1.49 (4.21)	€736 (€2,083)
Emergency room	1.39 (1.88)	€373 (€507)
Hospital admissions		
Inpatient hospital day	14.81 (19.31)	€8,740 (€11,076)
Intensive care unit day	0.23 (2.47)	€278 (€3,044)
Medical imaging		
Bone scan	1.17 (1.67)	€291 (€413)
CT scan	1.64 (2.18)	€318 (€423)
MRI scan	0.56 (1.06)	€178 (€336)
PET/CT scan	1.22 (1.75)	€1,308 (€1,873)
X-ray	2.51 (3.36)	€300 (€401)
Ultrasound	0.53 (1.11)	€62 (€129)
Other scan	0.36 (1.09)	€36 (€109)
Total costs		
Mean (SD)		€67,174 (€45,409)
Median (IQR)		€58,143 (€32,262-€92,674)

Abbreviations: CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; PET/CT, positron emission tomography-computed tomography; SD, standard deviation.
*Mean number of systemic treatment lines

Costs per treatment line

Table 5.3 presents the mean total and monthly costs of LPD1, LPD2 and LPD3. All included patients (N=1,937) received an LPD1, 1,186 patients (61%) received an LPD2, and 572 patients (30%) received an LPD3. The proportion of complete cases (i.e., starting a next treatment or death) was 85% for LPD1, 84% for LPD2 and 82% for LPD3. Median time to event was 9.2 months for LPD1, 7.1 months for LPD2, and 6 months for LDP3). Mean total and monthly costs were the lowest for LPD1 (€28,705 and €3,421, respectively). Mean total costs were the highest for LPD2 (€34,452; monthly costs: €5,083), but mean monthly costs were the highest for LPD3 (€6,841; total costs: €31,751). A total of 198 patients received further treatment line(s) after LPD3. Mean total costs of LPD4+ were €40,663.

Table 5.3 Costs per treatment line

	First-line treatment N = 1,937	**Second-line treatment N = 1,186**	**Third-line treatment N = 572**
Time to event, median (95%CI)	9.2 (8.9-9.5)	7.1 (6.5-7.6)	6.0 (5.6-6.4)
Complete cases*	85%	84%	82%
Drugs, n (%)			
Abiraterone	373 (19%)	453 (38%)	117 (20%)
Enzalutamide	407 (21%)	327 (28%)	118 (21%)
Docetaxel	1,131 (58%)	189 (16%)	60 (10%)
Cabazitaxel	NA	125 (11%)	198 (35%)
Radium-223	26 (1%)	92 (8%)	79 (14%)
Treatment			
Systemic treatment	€18,401 (€24,759)	€22,062 (€23,070)	€18,420 (€15,078)
Surgery	€434 (€2,313)	€319 (€1,603)	€321 (€1,651)
Radiotherapy	€1,212 (€2,887)	€1,532 (€3,327)	€1,468 (€2,961)
Interventional radiology	€172 (€518)	€205 (€491)	€186 (€418)
Bone resorption treatment	€279 (€976)	€361 (€997)	€386 (€943)
Growth factors	€72 (€706)	€262 (€4,720)	€161 (€1,069)
Concomitant medication	€142 (€185)	€124 (€194)	€91 (€136)
Blood transfusion	€343 (€1,134)	€491 (€1,343)	€754 (€1,535)
Drug administration	€4,045 (€3,852)	€2,588 (€3,320)	€3,694 (€3,443)

	First-line treatment N = 1,937	Second-line treatment N = 1,186	Third-line treatment N = 572
Hospital visits			
Outpatient visits	€1,763 (€1,347)	€1,419 (€1,182)	€1,162 (€1,028)
Daycare	€393 (€1,313)	€310 (€1,302)	€346 (€1,148)
Emergency room	€200 (€342)	€174 (€336)	€159 (€280)
Hospital admissions			
Inpatient hospital day	€4,408 (€8,559)	€3,941 (€6,196)	€4,218 (€6,251)
Intensive care unit day	€217 (€2,952)	€59 (€849)	€43 (€540)
Medical imaging			
Bone scan	€161 (€256)	€145 (€229)	€103 (€169)
CT scan	€173 (€263)	€148 (€233)	€139 (€225)
MRI scan	€86 (€212)	€90 (€211)	€87 (€200)
PET/CT scan	€680 (€1,184)	€648 (€1,142)	€589 (€1,011)
X-ray	€162 (€288)	€144 (€238)	€122 (€206)
Ultra sound	€33 (€86)	€34 (€92)	€22 (€61)
Other	€18 (€62)	€16 (€63)	€19 (€72)
Systemic treatment	€18,401 (€24,759) €10,304 (€11,975)	€22,062 (€23,070) €12,390 (€11,754)	€18,420 (€15,078) €13,331 (€10,452)
Other costs			
Total costs			
Mean (SD)	€28,705 (€28,682)	€34,452 (€26,740)	€31,751 (€19,840)
Median (IQR)	€17,785 (€10,876-€35,234)	€27,170 (€16,712-€44,119)	€28,657 (€17,783-€40,830)
Costs per month			
Mean (SD)	€3,421 (€4,766)	€5,083 (€3,660)	€6,841 (€9,258)
Median (IQR)	€2,702 (€1,383-€4,024)	€4,224 (€3,262-€5,881)	€5,447 (€3,757-€7,733)

Abbreviations: CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; PET/CT, positron emission tomography-computed tomography; SD, standard deviation.
*Patient died during treatment line or received a next treatment line

Figure 5.1 Mean total and monthly costs per treatment

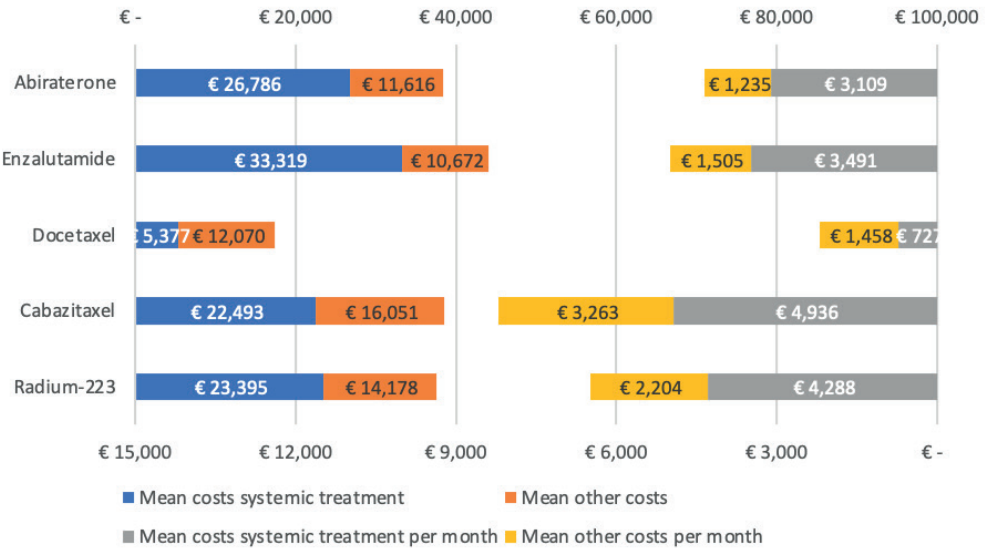
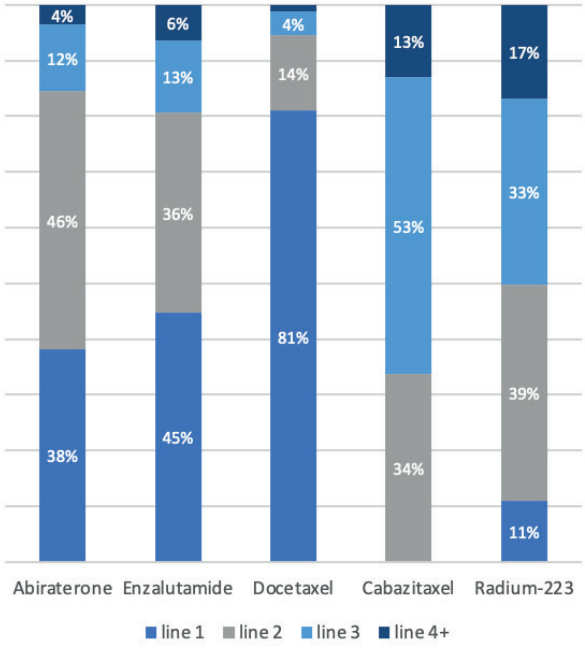


Figure 5.2 Systemic treatment per line (%)



Costs per treatment

Mean total and monthly costs per treatment are shown in Figure 5.1 and proportion of systemic treatment per line are presented in Figure 5.2. ENZ had the highest mean total costs (€43,945; SD: €33,542), followed by CAB (€38,545; SD: €19,982), ABI (€38,375; SD: €31,449), and Ra-223 (€37,572; SD €17,855). Mean monthly costs were the highest for CAB (€8,199; SD: €4,809), followed by Ra-223 (€6,491; SD: €3,329), ENZ (€4,996; SD: €4,180), and ABI (€4,344; SD: €2,282). DOC had the lowest mean total and monthly costs (€17,438; SD: €12,799; €2,186; SD: €2,289, respectively). For all treatments, costs of systemic treatment accounted for the largest part of the total costs (58-76%), except for DOC (31%).

Discussion

This study aimed to estimate the real-world costs of patients with CRPC in the Netherlands. Mean total treatment costs were €67,174 per patient. Total costs were mainly driven by the costs of systemic drugs (59%; €39,638). Monthly costs increased with each subsequent treatment line (LPD1: €3,421, LPD2: €5,083, LPD3: €6,841). The low monthly costs of LPD1 are driven by use of DOC in LPD1 (58%), which is relatively inexpensive compared to the other systemic treatments. Moreover, the share of systemic treatment costs is lower for LPD3 compared to LPD1 and LPD2. This is explained by the fact that more supportive care is given for LPD3. ENZ had the highest total costs of all treatments. CAB had the highest costs per month (€8,199). These costs are mainly driven by supportive care costs (e.g., day care costs). Moreover, CAB is only given in line 2 or higher and costs increase in subsequent treatment lines, which could explain the high monthly costs of CAB.

Systemic treatment costs are the main driver of the total costs. The only exception is DOC since DOC was the only systemic drug out of patent at time of the study. However, it is likely that the actual costs incurred for systemic therapy were lower, as a result of hospitals purchasing these pharmaceuticals from the manufacturers with confidential discounts.[180] Hospitals could also have incurred lower costs for systemic treatment due to parallel import of these pharmaceuticals.[181] It is expected that the total treatment costs will decrease: CAB is out of patent per April 2021 and ABI will follow in September 2022. Therefore, generics are expected to reach the market leading to a price reduction. In contrary, the use of LPDs earlier in the course of disease (non-metastatic CRPC or hormone sensitive prostate cancer (HSPC))[182,183] and new LPDs such as Olaparib, Darolutamide and Lutetium-177-PSMA-617 will likely increase diagnostic costs for molecular assays and total drug costs.[184-186] Moreover, in this study, drug wastage and no vial-sharing were assumed. However, costs will be lower

when no drug wastage and vial-sharing occurs in daily practice. Current drug costs might differ as well, as costs of this study were based on EUR 2018 unit costs.

The results of this study were comparable to the results of a German study that studied the treatment-related healthcare costs of metastasised CRPC (mCRPC).[187] Kreis et al. reported monthly healthcare costs of €7,631 for CAB, €2,392 for DOC, €5,226 for ABI, and €5,079 for ENZ. Monthly costs were comparable to our results, but there are small differences compared to our study. Differences could be due to differences in healthcare systems, unit costs, or treatment patterns. Since unit prices were not reported, a more detailed comparison of the studies was not possible. Another study reported healthcare costs per patient per year ranging from $27,549 (€22,708; estimated monthly cost: €1,892) for non-metastasised CRPC (nmCRPC) to $182,156 for mCRPC (€150,104; estimated monthly cost: €12,509). In the study by Wu et al., 85% of the mCRPC-patients was initially treated with an oral treatment (ABI+P or ENZ) compared to 40% in our study, which may explain the differences in costs.[188] Unit prices were also not reported in this study, therefore, a more detailed comparison was not possible. The total costs per CRPC-patient were higher compared to the costs of non-small cell lung cancer (€28,468), but lower compared to the costs of metastatic cutaneous melanoma (€105,078) in the Netherlands.[105,189]

This study has several limitations. First, all costs from CRPC-diagnosis until death, end of follow-up or last known date were measured, most of these costs are related to CRPC. As measured supportive care costs might also be related to other diseases than CRPC, reported costs may be overestimated. Second, 14% of all patients is still alive at the end of follow-up. These patients may use healthcare after follow-up, which will increase the total costs. Third, patients were included in the CAPRI-registry between 2010 and 2015. However, until 2013, only DOC was available as LPD1. Therefore, ENZ, ABI+P or Ra-223 as LPD1 is underrepresented in this analysis. The results should thus be regarded against the backdrop of the time period in which data were collected and may not be representative for the clinical practice nowadays. For further research, it is recommended to update this study to obtain faster insight into the real-world costs of CRPC. Up-to-date information is expected from the recently started CAPRI 3.0.

This study estimated the healthcare costs of CRPC in a real-world setting. Such data is of importance if one wants to estimate the cost-effectiveness of new treatments to inform healthcare decision-making. Costing data based on the real-world are preferable in cost-effectiveness models, as they reflect the clinical practice. In this study, the costs of CRPC management or treatments were not compared to its effectiveness (cost-effectiveness

analysis). As a result, this study could not provide information on how expenditures could be decreased or how resource use could be allocated in a more cost-effective way.

Conclusions

In this study, we studied the real-world healthcare costs of CRPC in the Netherlands. We concluded that the real-world healthcare costs of CRPC were considerably high, namely €67,174 on average. These costs are mainly driven by the costs of systemic treatments. To keep healthcare affordable, it is of utmost importance to weigh the clinical value of new treatments against their costs.

Patient summary

We analysed the healthcare costs of patients with castration-resistant prostate cancer (CRPC) in daily practice. The total costs of CRPC are mainly caused by costs of systemic treatment.

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Supplemental Material

Table S5.1 Unit costs

	Unit cost (€)	Source
Drug costs		
Abiraterone 250mg/120 pills	3,306	[177]
Cabazitaxel 40mg/ml 1,5ml vial	4,278	[177]
Docetaxel 20mg/ml 1ml vial	101	[177]
Enzalutamide 40mg/120 pills	4,734	[177]
Radium-223 1.1mq/ml 6ml vial	3,498	[177]
Other health care costs		
Administering general	585	[178]
Administering chemotherapy	780	[178]
Administering radium-223	880	[178]
Hospital admissions general	495	[120]
Hospital admissions IC	1,234	[120]
Hospital admissions oncology	662	[120]
Hospital admissions nursing home	175	[120]
Outpatient visits general	95	[120]
Outpatient visits physician	137	[120]
ER	269	[120]
Surgery	720 – 18,635	[178]
Prednisone	2	[177]
Blood transfusions	225 - 543	[120]
Radiotherapy general	3,890	[178]
Radiotherapy intensive	10,055	[178]
Bone resorption treatment	5 - 345	[177]
Growth factors	59 - 985	[177]
CT scan	194	[119]
MRI scan	317	[119]
Bone scan	248	[119]
PET scan	1,070	[119]
Ultrasound	117	[119]
X-ray	120	[119]
Other radiology costs	100	[119]
Interventional radiology	590	[119]

Chapter 6

Being transparent about brilliant failures: An attempt to use real-world data in a disease model for patients with castration-resistant prostate cancer

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Submitted

Abstract

Objectives: To explore whether a disease model based solely on real-world data (RWD) could be used to estimate cost-effectiveness of treatments for patients with castration-resistant prostate cancer (CRPC).

Methods: A patient-level simulation model was developed, in which patient-level data from the Dutch CAPRI-registry were used as input parameters. Time to event (TTE) and overall survival (OS) were estimated with multivariate regression models and type of event (i.e., next treatment or death) with multivariate logistic regression models. To test internal validity, TTE and OS from the simulation model were compared to the observed outcomes in the registry.

Results: Although, patient characteristics and survival outcomes of the simulated data were comparable to the observed data (median OS of 20.6 vs 19.8 months respectively), the disease model was less accurate in estimating differences between treatments (median OS simulated vs observed population: 18.6 vs 17.9 (abiraterone acetate plus prednisone); 24.0 vs 25.0 (enzalutamide); 20.2 vs 18.7 (docetaxel); 20.0 vs 23.8 months (radium-223)).

Conclusion: Overall, the developed disease model accurately approximated the observed data in the total CRPC-population. However, the disease model was not able to predict differences in survival between treatments due to unobserved differences. Therefore, the model is not suitable for cost-effectiveness analysis of CRPC treatment. Using a combination of RWD and RCTs to estimate treatment effectiveness may improve the model.

Introduction

With over 12,000 newly diagnosed patients per year, prostate cancer is the most common cancer in men in the Netherlands.[190] Patients with metastatic prostate cancer who have progressive disease on androgen deprivation therapy (ADT) (either ADT alone or in combination with chemotherapy, new androgen-receptor targeting agents, or palliative radiotherapy[38,191,192]) are considered as castration-resistant prostate cancer (CRPC).[193] Median overall survival (OS) of CRPC-patients treated with only best supportive care is 14 months.[171] Since 2004, multiple new treatments have become available that improved OS of these patients.[42-50]

There is an increasing interest in real-world data (RWD) complementary to randomised controlled trials (RCTs). Traditionally, RCTs are designed to show the efficacy of treatments in precisely defined groups under controlled circumstances. However, patients included in RCTs are not a good representation of patients in clinical practice. Previous studies showed that real-world patients with CRPC differ from trial patients, as a result of patient selection (i.e., patients in real-world practice are older and have more comorbidities).[18,21] Furthermore, information on the full disease course is lacking in RCTs as efficacy is estimated during a limited time period often considering only one treatment line. Moreover, RCTs usually compare a new treatment with standard of care (or placebo). If different drugs have positive trial results compared to standard of care or placebo, direct comparisons between these drugs are often lacking. Consequently, the effectiveness of different treatment sequences is thus unknown. Real-world disease models spanning multiple sequential treatment lines can provide insight in the (cost-)effectiveness of treatment sequences in clinical practice.

Models are needed to enable lifetime cost-effectiveness analyses (CEAs), among others due to extrapolation, combination of data sources, and correction for differences between patients. A well-performing model should be able to simulate reality, i.e., replicate observed outcomes. Using the same baseline characteristics, simulated outcomes should be similar to the observed outcomes. Moreover, relative differences on survival outcomes between treatments in the simulated data should be similar to the observed differences between treatments. In this article, we describe our experiences in developing a disease model based on RWD of CRPC-patients.

Methods

Data and patients

Data were derived from the Castration resistant prostate cancer registry: an observational study in the Netherlands (CAPRI).[18] In the CAPRI-registry, newly diagnosed CRPC-patients

between January 1, 2010 and December 31, 2015 were retrospectively included in 20 Dutch hospitals and followed until December 31, 2017 (N=3,616). Patients treated with docetaxel or androgen-receptor targeting agents for metastatic hormone-sensitive prostate cancer were excluded from the analysis (N=16). An estimated 20% of all patients with CRPC in the Netherlands is included in the study population.[18]

For this study, data of patients treated with at least one life prolonging drug (LPD) (i.e., docetaxel (DOC), cabazitaxel (CAB), abiraterone acetate plus prednisone (ABI+P), enzalutamide (ENZ), or radium-223 (Ra-223)) were included, while patients not treated with an LPD were excluded.

Missing values in the dataset were handled using multiple imputations by chained equations. For each treatment line, the following patient characteristics were imputed: World Health Organisation performance status (WHO PS), opioid use, prostate-specific antigen (PSA), alkaline phosphatase (ALP), haemoglobin (Hb), lactate dehydrogenase (LDH), bone metastases, and visceral metastases. These characteristics were both used as imputed and as predictive variables. Type of treatment, age, OS, and OS state (alive, death, or lost to follow-up) were only used as predictors for multiple imputations.[194]

Model type

The CRPC-population is heterogeneous and different patient and disease characteristics affecting the course of the disease. To be able to simulate individual patients with specific characteristics and events during their full disease course, patients were simulated by using a patient-level discrete event simulation model with a lifetime time horizon. This model type enables to model the course of a patient in a natural way by accounting for entities (patients) with attributes (patient characteristics), and events.[195]

Time-to-event

The OS was divided in three time periods (Figure 6.1). For each patient, time from start of first LPD (LPD1) until first event (TTE1) was calculated, which can be either start of second LPD (LPD2) or death. TTE2 (i.e., time from start of LPD2 to the either start of LPD3 or death) was determined in a similar way, while TTE3 was calculated as the time from third LPD (LPD3) to death. TTE3 can thus include multiple treatment lines, but since only 10% of patients received more than three treatment lines, the model only simulated three treatment lines. However, not all simulated patients received all three treatment lines, as patients could die earlier.

Regression models

Since a lifetime horizon is required for economic evaluations in the Netherlands,[15] survival data were extrapolated beyond the follow-up period by fitting several parametric models (i.e., exponential, Weibull, lognormal, log-logistic, generalized gamma, and Gompertz[196]) to the observed survival data. Log-logistic distribution had the best fit for TTE1, TTE2, and TTE3 (Table S6.1). Multivariate regression models were built to predict time to event. Based on literature and expert opinion,[197] the following predictive variables were included to predict TTE1, TTE2, and TTE3: type of treatment, age, WHO PS, opioid use, PSA, ALP, Hb, LDH, bone metastases, and visceral metastases (Tables S6.2-S6.4). As type of event of TTE1 and TTE2 could either be next treatment or death, multivariate logistic regression models for the probability of dying were used to predict these types of events. These multivariate logistic regression models included the same predictive variables as the TTE regression models (Tables S6.5+S6.6).

Model simulation

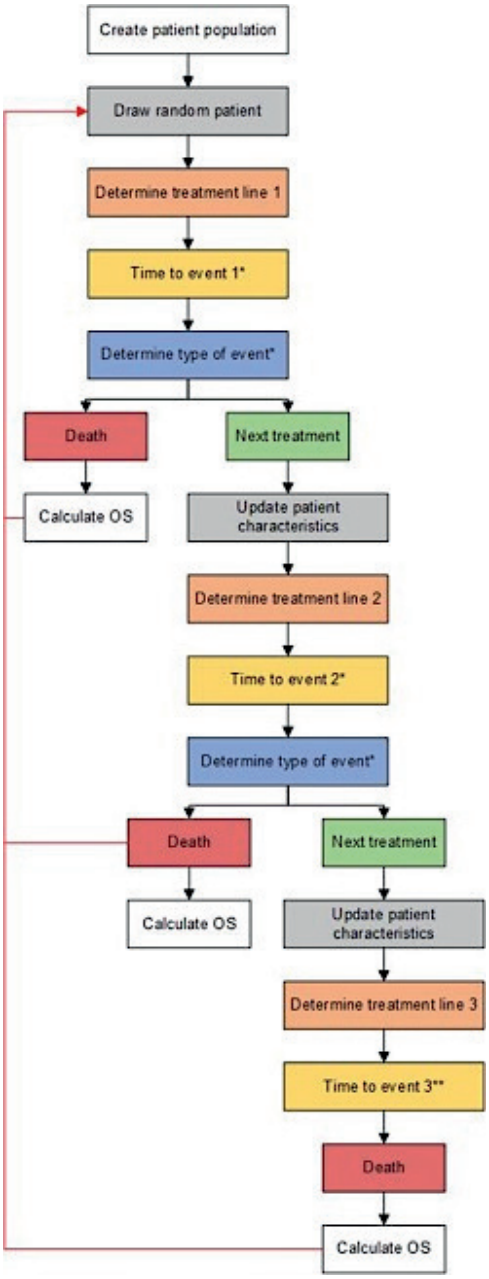
Patients from the CAPRI-registry were sampled with replacement to create a patient population for the simulation model. For each simulation, a population of 5,000 patients was simulated to get stable results. The individual patient simulation consisted of several steps (Figure 6.1). Firstly, a patient with specific patient characteristics was randomly drawn from the observed data. Secondly, type of treatment was assigned to each individual patient. LPD1 was based on the actual first treatment received in the CAPRI registry, while LPD2 and LPD3 allocation was based on probabilities conditional to the previous treatment as in the CAPRI-registry (Table S6.7). Thirdly, TTE1 was estimated using the TTE multivariate regression model (Table S6.2). Finally, type of event (i.e., next treatment or death) was estimated using the multivariate logistic regression model (Table S6.5). Second- and/or third-line treatment were simulated in a similar way except that death was the only possible event for TTE3 (Tables S3,4 6). Every time a patient started the next treatment line, patient characteristics were updated based on conditional probabilities depending on the patient characteristics in the previous line estimated from the CAPRI-registry (Tables S6.8+S6.9). All analyses were conducted using SPSS statistics 25 and R version 3.6.1.

Model validation

A valid model should be able to simulate the observed data while using the same baseline characteristics and simulated relative survival differences between treatments should be

similar to the observed differences between treatments. Therefore, internal validation of the model was performed by mimicking the real-world patient population (i.e., same patient characteristics at start LPD1, same LPD1) in the model.

Figure 6.1 Flow chart of the patient simulation



Results

Model validation

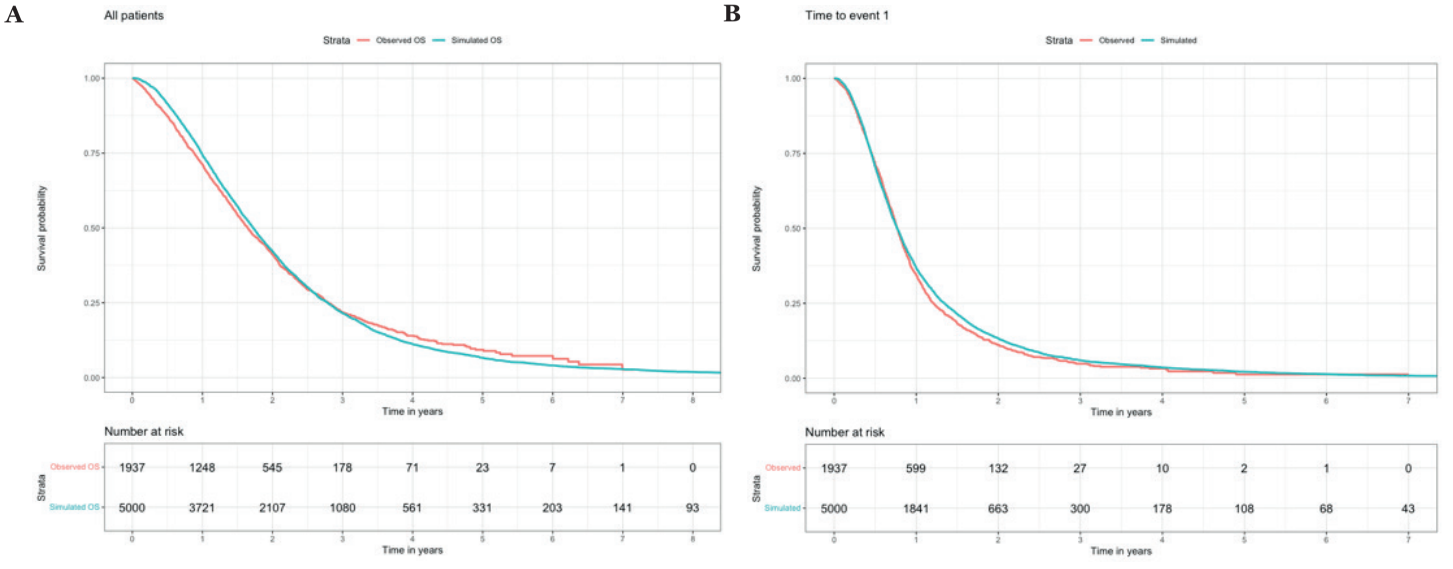
From the CAPRI-registry, 1,937 of 3,600 patients (54%) were eligible for analysis (excluded patients: no treatment (N=1,205) and patients received other (experimental) treatment (N=458)). Most patients were treated with DOC in the first line (N=1,131), while 407 patients received ENZ as LPD1, 373 patients ABI+P, and 26 patients Ra-223. Patient and disease characteristics of the simulated population were comparable to the observed population after multiple imputation (Table 1).

Table 6.1 Patient and disease characteristics of all patients at start LPD1

	Observed patients ***N* = 1,937**	**After multiple imputation** ***N* = 1,937**	**Simulated patients** ***N* = 5,000**
Age (years)			
Mean	73.4	73.4	73.2
Median (range)	74 (46-99)	74 (46-99)	73 (46-99)
WHO PS, %			
0-1	60	77	78
>1	12	23	22
Missing	28		
Bone metastases, %			
Yes	83	91	92
No	8	9	8
Missing	9		
Visceral metastases, %			
Yes	11	19	20
No	42	81	80
Missing	47		
Opioid use, %			
Yes	16	30	29
No	38	70	71
Missing	46		
PSA (µg/L), median (IQR)	99 (41-239)	98 (40-240)	99 (42-235)
Missing, %	9		
ALP (U/L), median (IQR)	139 (91-313)	142 (91-310)	140 (90-309)
Missing, %	14		
LDH (U/L), median (IQR)	231 (192-308)	236 (190-331)	239 (190-344)
Missing, %	28		
Hb (mmol/L), median (IQR)	7.8 (7-8.4)	7.8 (7-8.4)	7.8 (7.1-8.4)
Missing, %	15		

Abbreviations: ALP, alkaline phosphatase; Hb, haemoglobin; IQR, interquartile range; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; WHO PS, WHO performance status.

Figure 6.2 Survival curves of observed and simulated data of total population



A. Overall survival of observed and simulated total population
B. Time to event 1 of observed and simulated total population
Abbreviations: OS, overall survival.

Overall (including all treatments), this resulted into similar survival curves for the simulated and observed data. However, the simulation model overestimated OS during the first years and underestimated OS in later years (Figure 6.2A). TTE1 and TTE2 were similar between simulated and observed data in the first years, but were overestimated by the simulation model in later years (Figure 6.2B and Figure S6.1), while the simulation model underestimated TTE3 in later years (Figure S6.2).

Median TTE1 and type of event (i.e., next treatment or death) after LPD1 and LPD2 were similar for the simulated and observed population (Table 6.2). Simulated median TTE2 and TTE3 deviated from the observed data, although the differences were small (TTE2: 7.5 vs 7.1 months; TTE3: 7.9 vs 8.2 months). Median OS was 0.8 months longer in the simulated compared to the observed population (20.6 vs 19.8 months).

Table 6.2 Time to event and overall survival in observed and simulated population

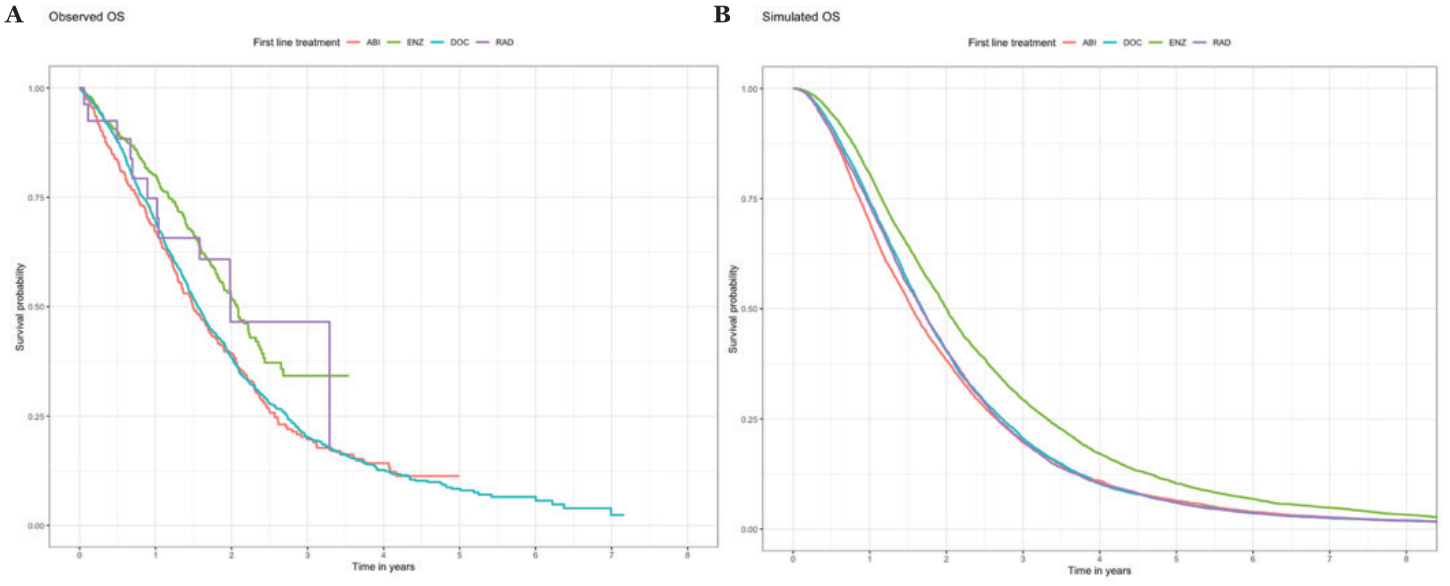
	Observed population **TTE (mo)** **Median**	**Simulated population** **TTE (mo)** **Median**
Type of event 1 (%)		
Next treatment	72	71
Death	28	29
Type of event 2 (%)		
Next treatment	57	57
Death	43	43
Median TTE1 (mo) [IQR]	9.2 [5.5-14.5]	9.2 [5.4-16.2]
Median TTE2 (mo) [IQR]	7.1 [4-12.4]	7.5 [4.4-13]
Median TTE3 (mo) [IQR]	8.2 [4.7-14.4]	7.9 [4.6-13.3]
Overall survival (mo) [IQR]	19.8 [10.6-33.5]	20.6 [11.9-33.5]

Abbreviations: IQR, interquartile range; mo, months; TTE, time to event.

Since for some patient characteristics (i.e., WHO PS, visceral metastases, opioid use, and LDH) missing values were frequent, simulation of TTE and OS was also performed with patients with complete data (N=411). Characteristics of these patients are presented in Table S6.10. The simulation model overestimated OS during the first years and underestimated in later years compared to the observed estimates (Fig S6.3). Simulated median TTE1 and TTE3 were comparable to the observed results. However, there were differences between simulated and observed median TTE2 (7.4 vs 6.4 months, difference: 1 month) and OS (20.2 vs 18.7 months, difference: 1.5 months) (Table S6.11).

Differences in median OS stratified by LPD1 between simulated and observed data were similar to the total population (0.8 months) for ABI+P (0.7 months) and ENZ (1 month). However,

Figure 6.3 Survival curves stratified by first-line treatment



A. Survival curves stratified by first-line treatment of the observed population
B. Survival curves stratified by first-line treatment of the simulated population
Abbreviations: ABI,abiraterone acetate plus prednisone; DOC,docetaxel; ENZ,enzalutamide; OS,overall survival; RAD,radium-223.

simulated median OS deviated from the observed outcomes for DOC (1.5 months) and Ra-223 (3.8 months) (Table 6.3). Plotted TTE1 stratified by LPD1 showed that the simulated curve deviated from the observed curves, especially for patients with DOC and ENZ (Fig S6.8-S6.11). Furthermore, Table 6.3 shows that the model was not able to validly replicate the differences between type of LPD1. For example, the difference in median OS between DOC and ABI+P was 1.6 months in the simulated data compared to 0.8 months in the observed data. In addition, the observed data showed crossing curves for ENZ and Ra-223 (Figure 6.3A), but the survival curves of these two treatments distant from each other in the simulated data, so the model was not able to replicate the observed differences between treatments in a similar way (Figure 6.3B).

Table 6.3 Observed and simulated time to event and overall survival stratified by first-line treatment

	Observed population	Simulated population
First-line ABI+P		
Median TTE1 (mo)	11.0 [5.8-20.3]	10.5 [6.6-18.1]
Median TTE2 (mo)	7.1 [4.3-10.2]	7.9 [4.6-13.6]
Median TTE3 (mo)	7.9 [4.1-22.7]	7.7 [4.7-12.8]
Overall survival (mo)	17.9 [9.1-30.8]	18.6 [10.4-31.8]
First-line ENZ		
Median TTE1 (mo)	15.5 [8.5-27.8]	14.8 [9.1-24.7]
Median TTE2 (mo)	7.3 [5-11.2]	7.9 [4.7-13.6]
Median TTE3 (mo)	7.5 [4-10.1]	7.8 [4.7-1.11]
Overall survival (mo)	25.0 [14-61.4]	24.0 [1.56-3.31]
First-line DOC		
Median TTE1 (mo)	8.2 [5-11.3]	7.5 [4.7-12.5]
Median TTE2 (mo)	7.0 [3.8-12.8]	7.4 [4.2-12.8]
Median TTE3 (mo)	8.4 [4.8-14.9]	8.4 [4.9-13.9]
Overall survival (mo)	18.7 [10.1-32.8]	20.2 [0.98-2.73]
First-line Ra-223		
Median TTE1 (mo)	6.9 [4.4-12.2]	7.2 [4.3-12.1]
Median TTE2 (mo)	12.8 [7.1-19.3]	8.5 [4.8-14.6]
Median TTE3 (mo)	10.2 [4-10.1]	7.9 [4.8-13.4]
Overall survival (mo)	23.8 [10.7 -39.5]	20.0 [11.5-32]

Abbreviations: ABI+P, abiraterone acetate plus prednisone; DOC, docetaxel; ENZ, enzalutamide; mo, months; Ra-223, radium-223.

Discussion

In this study, a full disease model of real-world CRPC-patients was developed. Internal validation showed similar TTE in the simulated and observed total CRPC population. However, simulated median OS deviated from the observed median OS (difference of 0.8 months) as simulated OS was overestimated during the first years, but underestimated in later

years. Model simulation based on only complete cases resulted in a larger overestimation of median OS (difference of 1.5 months). This disease model was not able to adequately estimate the differences between treatments, as these differences became smaller or larger in the model compared to the observed differences. We consider this as the main limitation of our disease model, since using these results for CEAs would lead to biased results. Although we were not able to build a valid model for CRPC-patients, we believe that in the context of honesty and transparency, this 'brilliant failure' should be reported as others may learn from our experiences and that can be beneficial for science.

Challenges of using RWD in disease models

During the development of the disease model, we faced several challenges using RWD. Although RWD provide insight into the effectiveness and safety of treatments in daily practice, RWD have important limitations in a disease model. Firstly, in the real-world, patients are not randomly allocated to a treatment, but treatment choices can be influenced by patient and disease characteristics, clinician experience or patient preference. It is challenging, maybe even impossible, to consider, identify, and measure all confounders in treatment decisions.[198] The real-world patient population is heterogenous, and the strict conditions for randomisation and a controlled setting are not applicable to RWD. As a consequence, the observed differences in outcomes between two treatment groups may be caused by case-mix or other (unmeasured) confounders and not type of treatment.[22]Although we tried to control for possible confounders by correcting for various patient characteristics that may influence treatment allocation and prognosis, this approach is inferior to a randomised design and may thus be biased. Simulated TTE and OS of all patients were comparable to the observed estimates, which was also true for ABI+P or ENZ as LPD*1*. *However, survival curves of simulated and observed patients with DOC or Ra-223 as LPD1* differed. Moreover, one of the main findings of this study is the inability of the disease model to validly replicate the differences between treatments, as these differences became smaller or larger in the simulated data compared to the observed data. Thus, despite using multivariate regression models to control for possible confounders, we could not adequately control for all differences between treatments. This might be due to unobserved differences between treatments (for example patient preference) that could not be identified and controlled by multivariate regression models. Therefore, the current disease model is not able to predict differences between treatments. Propensity score matching (PSM) is another method that could control for observed differences in patient characteristics and enables to compare a treatment to the comparator. However, since PSM is only able to match on observed characteristics, unobserved differences cannot be excluded. Moreover, PSM is not feasible for the comparison of more than two treatment options.[199,200] Since the model was

not able to adequately replicate the observed data (i.e., simulated data should be similar to the observed data and simulated relative differences should be similar to the observed differences between treatments), we considered the CRPC-model based on only RWD as invalid.

Secondly, RWD is prone to missing data, particularly when the follow-up period is long.[201,202] In this study, there were missing values on almost all patient characteristics, varying from 9% missing values on PSA to 47% on visceral disease state (Table 1). This is a disadvantage of retrospective data collection, which should be considered when designing a disease model. Multiple imputation could offer a valid solution for missing patient characteristics, provided the missingness of data is not related to unobserved variables.[201] We tested the disease model only including data from complete cases (i.e., without any missing values). Simulated results showed similar differences with observed results as when the imputed data of all patients was used. Despite dealing with missing values, observational data enables to analyse large amounts of data. Uncertainty regarding RWD will diminish when missing data will be minimised. Therefore, standardised reporting of data should be improved.

The third challenge of RWD is timeliness of reporting results. RWD can be collected from the moment a new treatment is approved by healthcare authorities and used in clinical practice. To provide insight into long-term effects of a certain treatment, the follow-up period should be of sufficient length. At the time results from RWD become available, treatment practices might already have changed due to new developments. RWD-results may thus lag behind. In the CAPRI-registry, first-line treatment with ABI+P, ENZ, and Ra-223 are underrepresented, since patients diagnosed with CRPC between 2010 and 2015 were included and ABI+P, ENZ, and Ra-223 became available as LPD1 in the Netherlands from 2014 onwards. The results of this disease model should thus be regarded against the backdrop of the time period in which data were collected and might not be representative for the clinical practice nowadays. Further research with more up-to-date data is recommended.

The update of patient characteristics and treatment allocation could be regarded as a limitation. In the current model, changes in patient characteristics and treatment allocation were only based on the value of the characteristic at the start of the previous treatment line or the previous treatment. These probabilities did not take other variables into account. With the simplified method we were able to replicate the mean patient characteristics of the CAPRI-registry, however, multivariate regression models, including other patient and disease characteristics as well, may yield better individual replications. Therefore, in future research, it is recommended to update patient characteristics by using multivariate regression models.

Potential opportunities and recommendations of using RWD in disease models

Although using RWD in disease models is associated with several challenges, RWD also have benefits. RWD provide insight into the use and uptake of new interventions in clinical practice. For example, the CAPRI-registry showed that in clinical practice, 40% of the patients who were fit for docetaxel according to the clinical guidelines was not treated with docetaxel.[203] Furthermore, where results from RCTs often lack generalisability to daily practice, RWD show the effectiveness of new treatments in the real-world. Real-world CRPC-patients differ from patients treated in clinical trials with in general unfavourable patient and disease characteristics (i.e., older, more comorbidities, and worse WHO PS). These differences in characteristics may result in the observed difference in median OS between trial and real-world patients.[18,21] Additionally, RWD could provide insight into the full disease course comprising sequential treatments. In the CAPRI-registry, a large range of different treatment sequences was observed (26 different sequences with N>20). This information could be used to compare various treatment sequences and to estimate which treatment sequence is most preferable in terms of effects and costs. Thus, RWD are of importance for obtaining insight into the use, uptake, and (cost-)effectiveness of a (new) treatment in daily practice.

Considering the challenges and benefits of RWD in disease models, a combination of RWD data with data from clinical studies in a disease model may offer the best of both worlds. RWD could provide insight into the effectiveness and safety of a treatment in daily practice, while RCT data provides an unbiased estimate of effectiveness of treatments. Both using RWD and RCT data might be an opportunity to build a well-performing disease model that is able to accurately replicate observed data. Furthermore, to increase the relevance of results from RWD, the use of up-to-date data is recommended. However, the urge to timely provide relevant results should not diminish a sufficient follow-up.

Conclusions

To conclude, we developed a disease model for CRPC-patients using RWD. The overall model was able to accurately replicate the observed data. However, observed differences in outcomes between treatments could not be replicated with the model. As a result, the model was considered as unable to replicate the differences in treatments in the observed data, which is crucial for a meaningful cost-effectiveness analysis. Therefore, the use of a combination of up-to-date real-world and RCT-data in disease models should be explored in further research.

Supplemental material

Table S6.1 Goodness of fit for TTE1, TTE2, and TTE3

	TTE1	**TTE2**	**TTE3**
	AIC	*AIC*	*AIC*
Exponential	3,423.66	1,668.16	865.50
Weibull	3,220.06	1,584.53	835.07
Lognormal	3,227.62	1,500.51	827.22
Loglogistic	**3,095.27**	**1,481.12**	**803.97**
Gompertz	3,388.68	1,663.88	864.01
Gamma	3,161.05	1,541.37	822.92
Generalized gamma	3,136.03	1,490.00	813.53

Abbreviations: AIC, Akaike information criterion; TTE, time to event.

Table S6.2 Multivariate regression model time to event 1

	Coefficient	**SE**	**Z-test**	**P-value**
(Intercept)	-0.081	0.258	-0.312	0.755
Enzalutamide	0.313	0.064	4.868	0.000
Docetaxel	-0.377	0.054	-7.007	0.000
Radium-223	-0.423	0.165	-2.564	0.010
Age	-0.004	0.002	-1.427	0.154
WHO PS	0.033	0.045	0.745	0.456
Opioid use	0.029	0.043	0.669	0.503
PSA	0.000	0.000	0.872	0.383
ALP	0.000	0.000	0.512	0.609
HB	0.035	0.019	1.850	0.064
LDH	0.000	0.000	-2.208	0.027
Bone metastases	0.008	0.063	0.126	0.900
Visceral metastases	-0.087	0.047	-1.835	0.067

Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; Hb, haemoglobin; LDH, lactate dehydrogenase; SE, standard error; PSA, prostate-specific antigen; WHO PS, WHO performance status.

Table S6.3 Multivariate regression model time to event 2

	Coefficient	SE	Z-test	P-value
(Intercept)	-1.465	0.328	-4.468	0.000
Enzalutamide	0.290	0.065	4.472	0.000
Docetaxel	0.038	0.073	0.522	0.602
Cabazitaxel	-0.331	0.085	-3.878	0.000
Radium-223	0.139	0.100	1.390	0.165
Age	0.007	0.003	2.069	0.039
WHO PS	-0.082	0.063	-1.297	0.195
Opioid use	-0.105	0.055	-1.930	0.054
PSA	0.000	0.000	-0.469	0.639
ALP	0.000	0.000	0.778	0.437
HB	0.058	0.026	2.259	0.024
LDH	0.000	0.000	-1.280	0.201
Bone metastases	0.062	0.069	0.909	0.363
Visceral metastases	-0.024	0.059	-0.411	0.681

Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; Hb, haemoglobin; LDH, lactate dehydrogenase; SE, standard error; PSA, prostate-specific antigen; WHO PS, WHO performance status.

Table S6.4 Multivariate regression model time to event 3

	Coefficient	SE	Z-test	P-value
(Intercept)	-1.008	0.460	-2.192	0.028
Enzalutamide	-0.166	0.116	-1.429	0.153
Docetaxel	0.311	0.138	2.259	0.024
Cabazitaxel	-0.147	0.103	-1.431	0.152
Radium-223	0.075	0.125	0.602	0.547
Age	0.000	0.005	-0.059	0.953
WHO PS	-0.016	0.091	-0.172	0.863
Opioid use	0.113	0.080	1.399	0.162
PSA	0.000	0.000	-0.901	0.368
ALP	0.000	0.000	0.221	0.825
HB	0.124	0.035	3.560	0.000
LDH	0.000	0.000	-2.219	0.026
Bone metastases	-0.184	0.079	-2.339	0.019
Visceral metastases	0.084	0.081	1.035	0.301

Abbreviations: ALP=alkaline phosphatase; CI=confidence interval; Hb=haemoglobin; LDH= lactate dehydrogenase; SE=standard error; PSA=prostate-specific antigen; WHO PS=WHO performance status.

Table S6.5 Multivariate regression model type of event 1

	Coefficient	SE	Z-test	P-value
(Intercept)	-3.799	0.829	-4.583	0.000
Enzalutamide	-0.299	0.183	-1.636	0.102
Docetaxel	-1.130	0.152	-7.411	0.000
Radium-223	-1.183	0.529	-2.235	0.025
Age	0.055	0.008	6.825	0.000
WHO PS	-0.225	0.145	-1.549	0.121
Opioid use	-0.372	0.139	-2.681	0.007
PSA	0.000	0.000	0.659	0.510
ALP	0.000	0.000	-1.412	0.158
HB	-0.085	0.060	-1.416	0.157
LDH	0.000	0.000	-0.353	0.724
Bone metastases	0.482	0.217	2.227	0.026
Visceral metastases	-0.099	0.148	-0.665	0.506

Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; Hb, haemoglobin; LDH, lactate dehydrogenase; SE, standard error; PSA, prostate-specific antigen; WHO PS, WHO performance status.

Table S6.6 Multivariate regression model type of event 2

	Coefficient	SE	Z-test	P-value
(Intercept)	-2.804	0.889	-3.155	0.002
Enzalutamide	-0.323	0.167	-1.932	0.053
Docetaxel	-0.930	0.203	-4.592	0.000
Cabazitaxel	-0.536	0.226	-2.375	0.018
Radium-223	-0.629	0.285	-2.202	0.028
Age	0.042	0.009	4.643	0.000
WHO PS	0.109	0.166	0.655	0.512
Opioid use	0.022	0.144	0.156	0.876
PSA	0.000	0.000	-0.090	0.928
ALP	0.000	0.000	0.724	0.469
HB	-0.038	0.068	-0.551	0.581
LDH	0.000	0.000	0.389	0.697
Bone metastases	-0.197	0.178	-1.111	0.266
Visceral metastases	0.384	0.156	2.458	0.014

Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; Hb, haemoglobin; LDH, lactate dehydrogenase; SE, standard error; PSA, prostate-specific antigen; WHO PS, WHO performance status.

Table S6.7 Probabilities of second- and third-line treatment

Line 1	Line 2	Probability*
Abiraterone	Abiraterone	0.031
	Enzalutamide	0.208
	Docetaxel	0.547
	Cabazitaxel	0
	Radium-223	0.214
Enzalutamide	Abiraterone	0.204
	Enzalutamide	0.015
	Docetaxel	0.504
	Cabazitaxel	0
	Radium-223	0.277
Docetaxel	Abiraterone	0.478
	Enzalutamide	0.323
	Docetaxel	0.034
	Cabazitaxel	0.143
	Radium-223	0.021
Radium-223	Abiraterone	0.167
	Enzalutamide	0.556
	Docetaxel	0.167
	Cabazitaxel	0
	Radium-223	0.111
Line 2	**Line 3**	**Probability***
Abiraterone	Abiraterone	0
	Enzalutamide	0.201
	Docetaxel	0.157
	Cabazitaxel	0.534
	Radium-223	0.108
Enzalutamide	Abiraterone	0.201
	Enzalutamide	0
	Docetaxel	0.115
	Cabazitaxel	0.396
	Radium-223	0.288
Docetaxel	Abiraterone	0.279
	Enzalutamide	0.306
	Docetaxel	0.009
	Cabazitaxel	0.279
	Radium-223	0.126
Cabazitaxel	Abiraterone	0.593
	Enzalutamide	0.358
	Docetaxel	0
	Cabazitaxel	0
	Radium-223	0.049
Radium-223	Abiraterone	0.270
	Enzalutamide	0.378
	Docetaxel	0.297
	Cabazitaxel	0.054
	Radium-223	0

*Probabilities only applied to patients with event 'next line'.

Table S6.8 Updating patient characteristics at start line 2

Update based on probabilities conditional on previous line		
Patient characteristic line 1	*Patient characteristic line 2*	*Probability*
WHO PS 0	WHO PS 1	0.215
WHO PS 1	WHO PS 1	0.355
Opioid use 0	Opioid use 1	0.243
Opioid use 1	Opioid use 1	0.780
Bone metastases 0	Bone metastases 1	0.425
Visceral metastases 0	Visceral metastases 1	0.125
Update based on lineair regression models		
Patient characteristic	*Intercept*	*Coefficient*
PSA	144.765	0.625
ALP	126.478	0.393
Hb	2.410	0.644
LDH	132.531	0.684

Abbreviations: ALP, alkaline phosphatase; Hb, haemoglobin; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; WHO PS, WHO performance status.

Table S6.9 Updating patient characteristics at start line 3

Update based on probabilities conditional on previous line		
Patient characteristic line 2	*Patient characteristic line 3*	*Probability*
WHO PS 0	WHO PS 1	0.178
WHO PS 1	WHO PS 1	0.459
Opioid use 0	Opioid use 1	0.255
Opioid use 1	Opioid use 1	0.870
Bone metastases 0	Bone metastases 1	0.660
Visceral metastases 0	Visceral metastases 1	0.246
Update based on lineair regression models		
Patient characteristic	*Intercept*	*Coefficient*
PSA	269.672	1.075
ALP	83.136	0.756
Hb	2.316	0.634
LDH	197.351	0.464

Abbreviations: ALP, alkaline phosphatase; Hb, haemoglobin; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; WHO PS, WHO performance status.

Figure S6.1 Observed and simulated TTE2

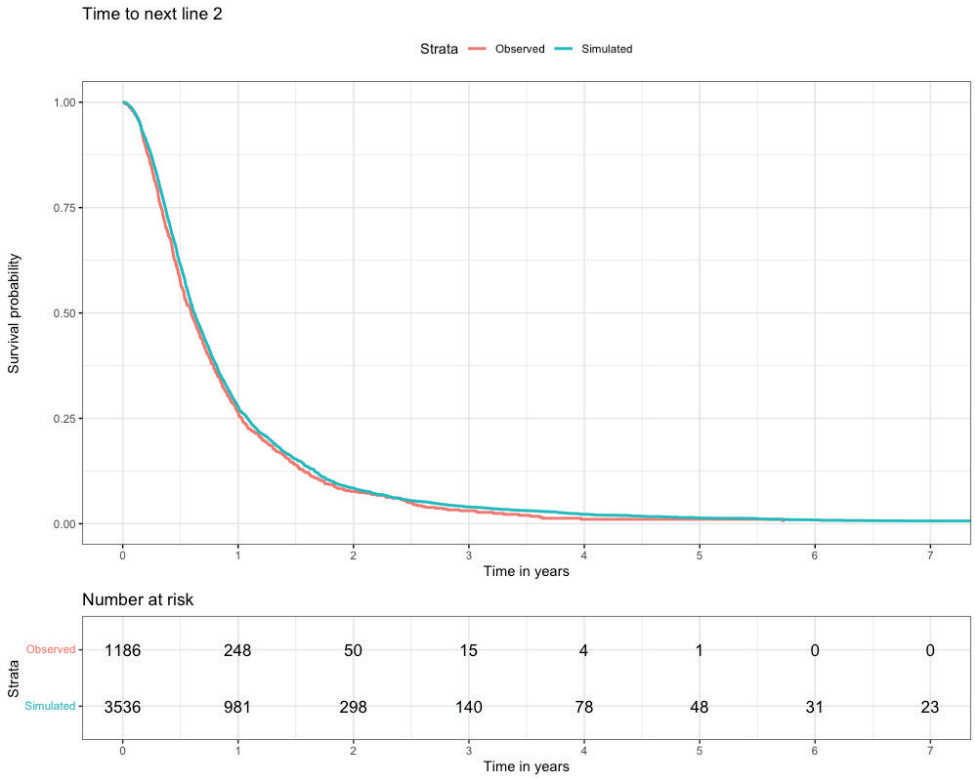


Figure S6.2 Observed and simulated time from start treatment line 3 to death

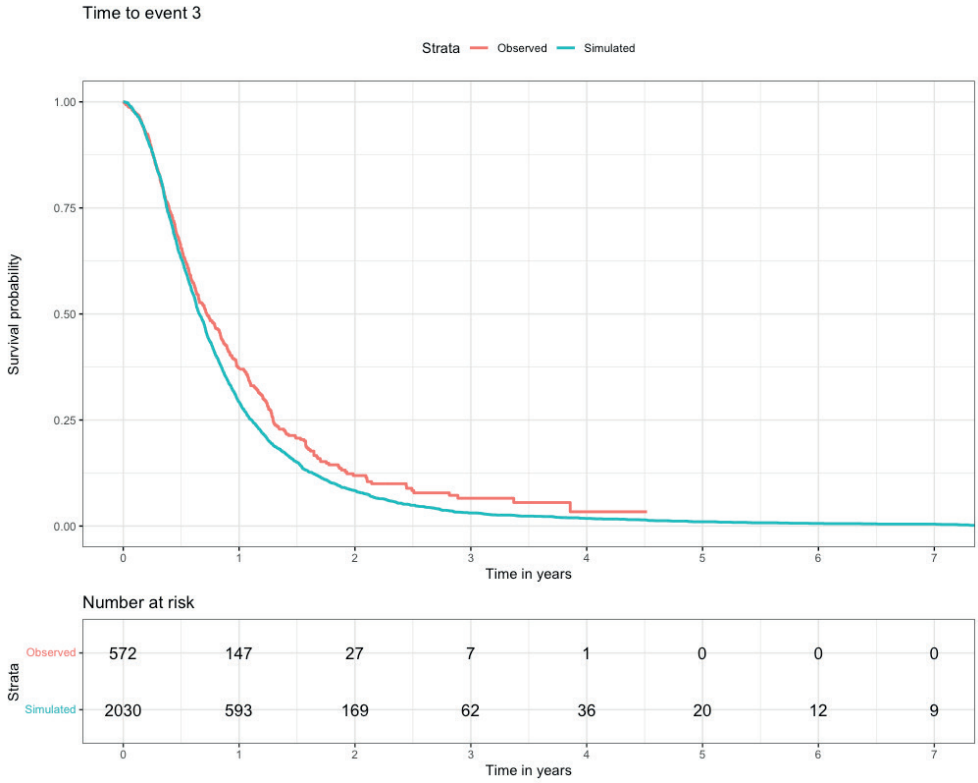
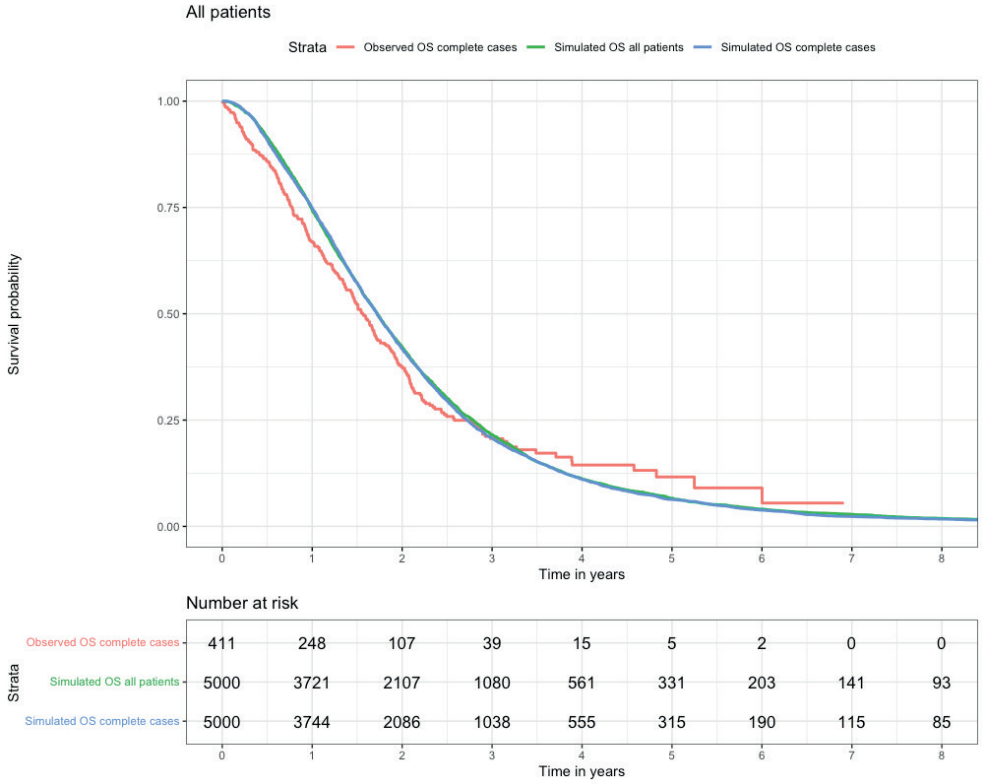


Figure S6.3 Observed and simulated overall survival based on complete cases



Abbreviations: OS, overall survival.

Table S610 Patient characteristics of complete cases at start first-line treatment

	Observed patients ***N* = 411**	**Simulated patients** ***N* = 5,000**
Age,		
Mean	72.1	72.3
Median (range)	72 (46-95)	72 (46-95)
WHO PS, %		
0-1	82	82
>1	18	18
Bone metastases, %		
Yes	90	90
No	10	10
Visceral metastases, %		
Yes	22	23
No	78	77
Opioid use, %		
Yes	32	29
No	68	71
PSA (µg/L**)**, median (IQR)	107 (36-242)	100 (34-229)
ALP (U/L), median (IQR)	164 (99-374)	164 (97-364)
LDH (U/L), median (IQR)	236 (190-335)	238 (190-337)
Hb (mmol/L), median (IQR)	7.8 (7.1-8.4)	7.8 (7.1-8.4)

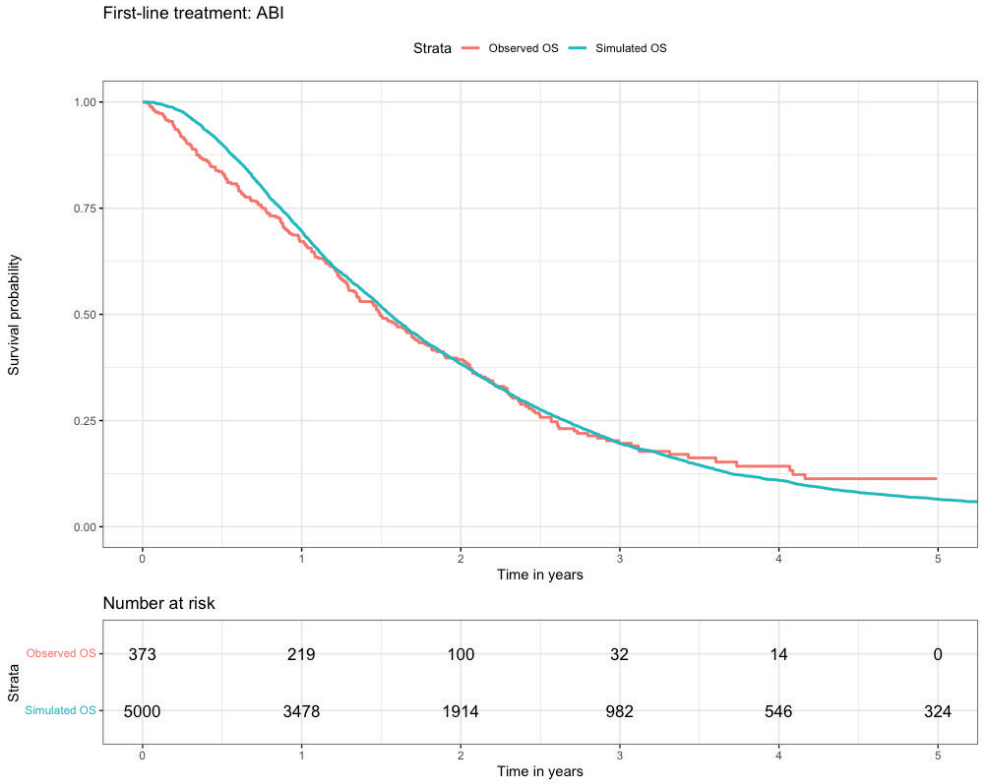
Abbreviations: ALP, alkaline phosphatase; Hb, haemoglobin; IQR, interquartile rate; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; WHO PS,WHO performance status.

Table S6.11 Time to event and overall survival in observed and simulated population based on complete cases

	Observed population **Time to event (mo) Median**	**Simulated population** **Time to event (mo) Median**
Type of event 1 (%)		
Next treatment	74	74
Death	26	26
Type of event 2 (%)		
Next treatment	55	57
Death	45	43
Median time to event 1 (mo)	8.9	8.6
Median time to event 2 (mo)	6.4	7.4
Median time to event 3 (mo)	7.9	7.3
Overall survival (mo)	18.7	20.2

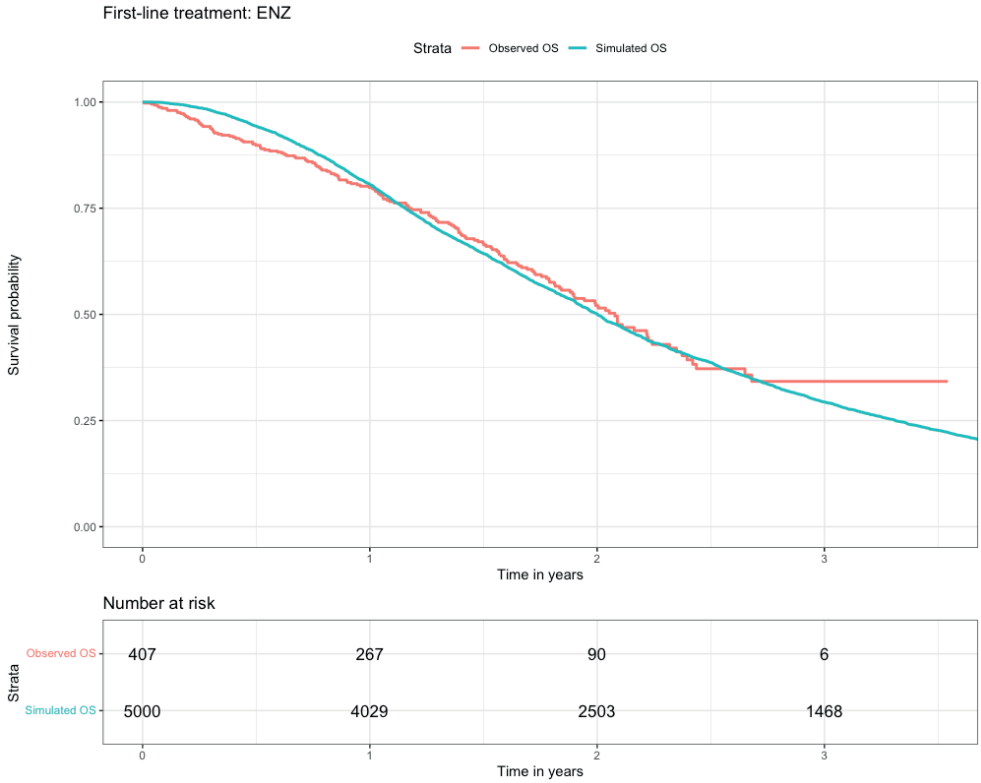
Abbreviations: mo, months.

Figure S6.4 Survival curves for patients initially treated with abiraterone



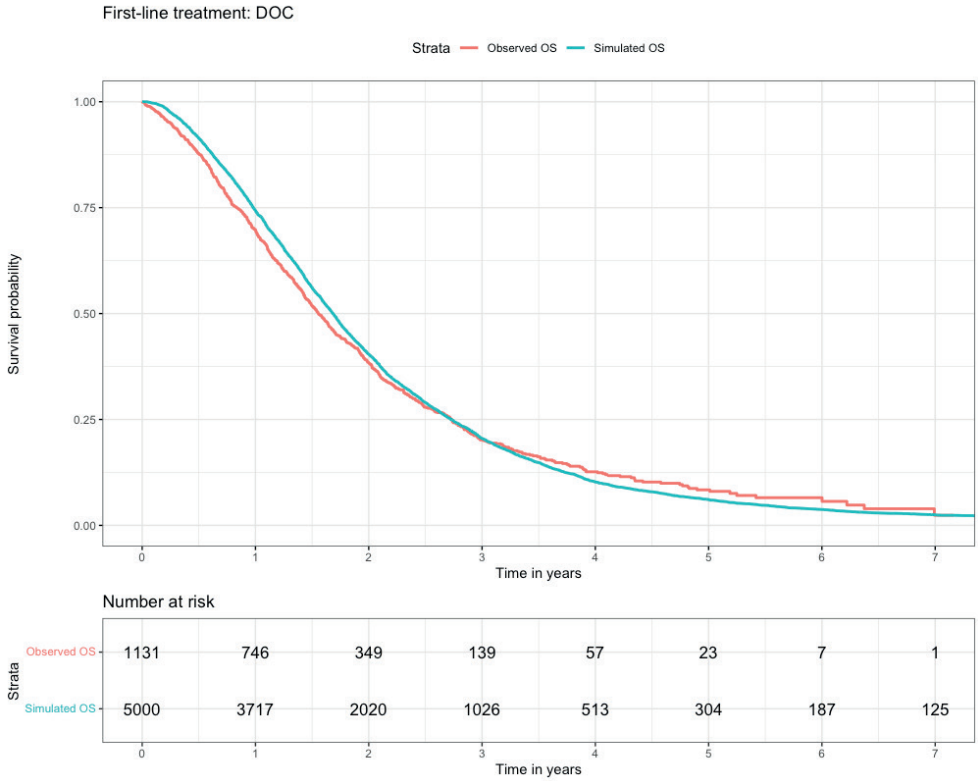
Abbreviations: ABI, abiraterone acetate plus prednisone; OS, overall survival.

Figure S6.5 Survival curves for patients initially treated with enzalutamide



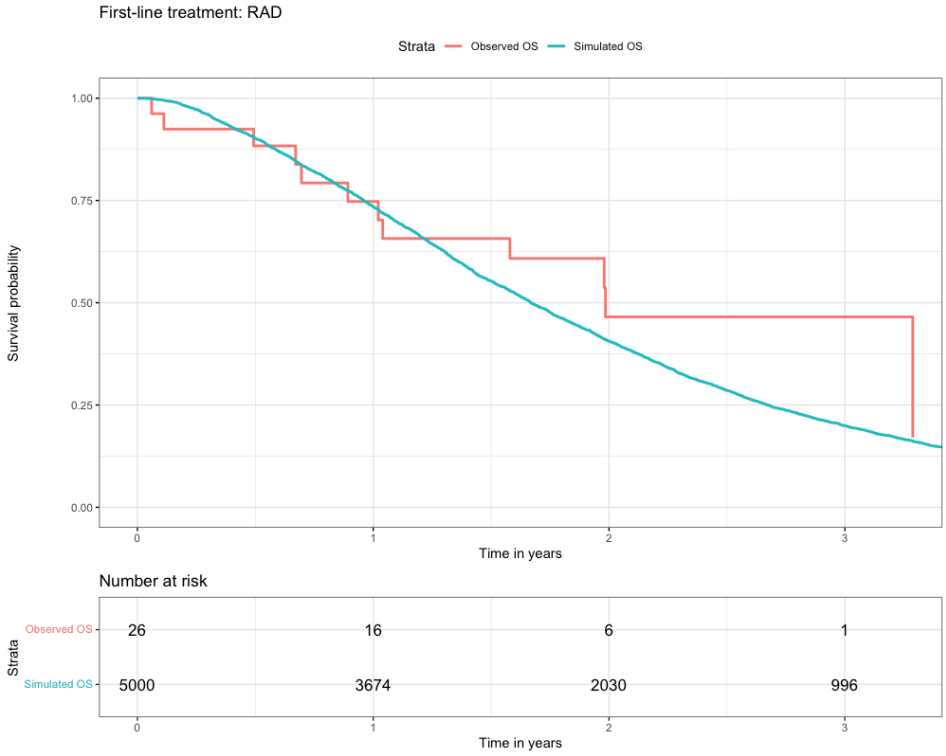
Abbreviations: ENZ, enzalutamide; OS, overall survival.

Figure S6.6 Survival curves for patients initially treated with docetaxel



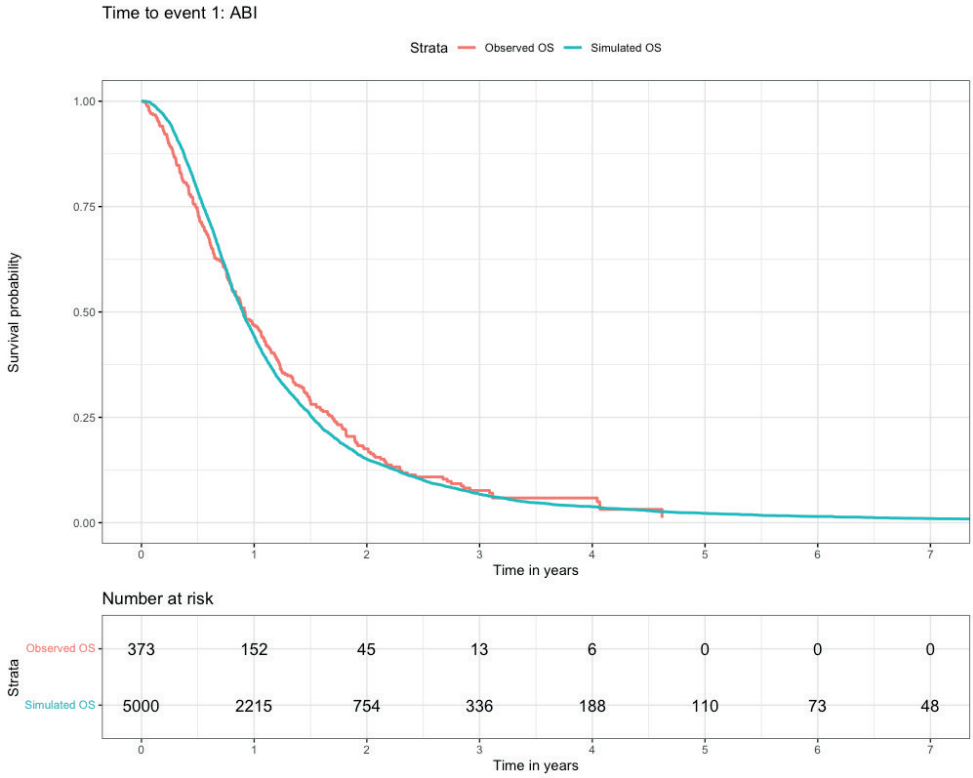
Abbreviations: DOC, docetaxel; OS, overall survival.

Figure S6.7 Survival curves for patients initially treated with radium-223



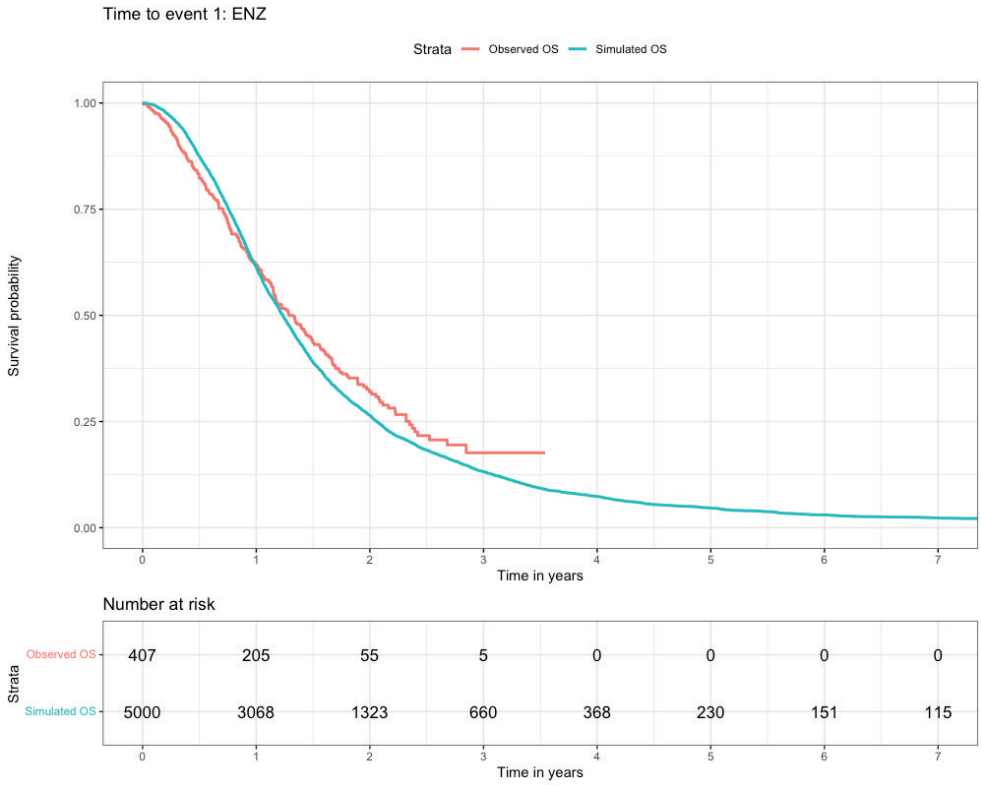
Abbreviations: RAD, radium-223; OS, overall survival.

Figure S6.8 TTE1 for patients initially treated with abiraterone



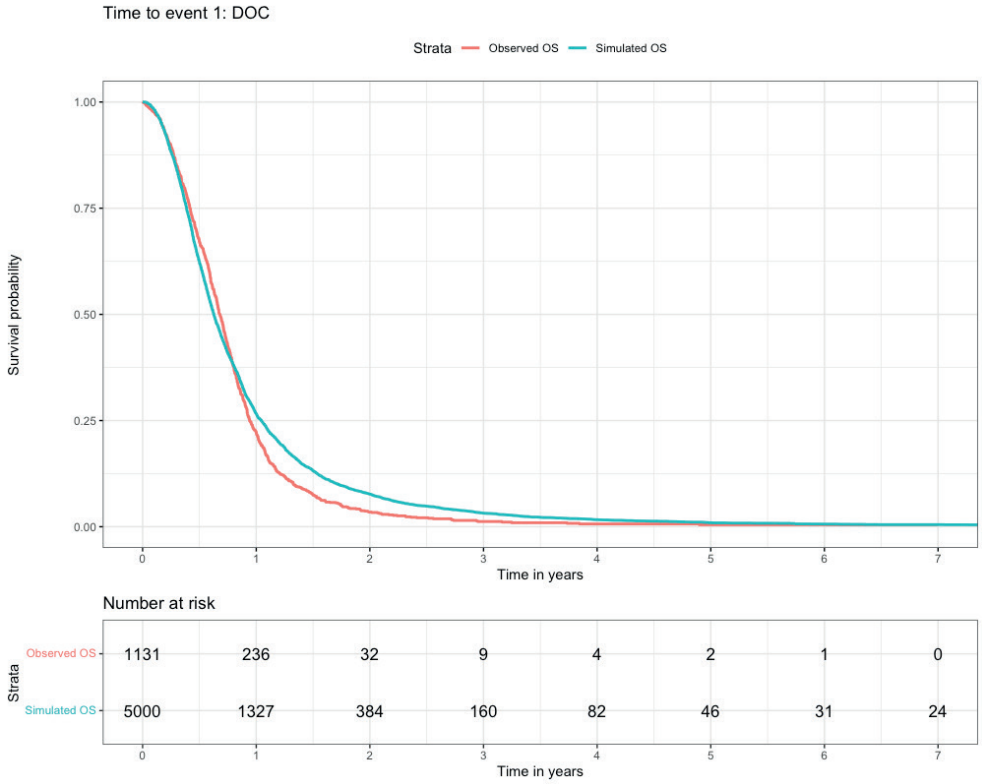
Abbreviations: ABI, abiraterone acetate plus prednisone; OS, overall survival.

Figure S6.9 TTE1 for patients initially treated with enzalutamide



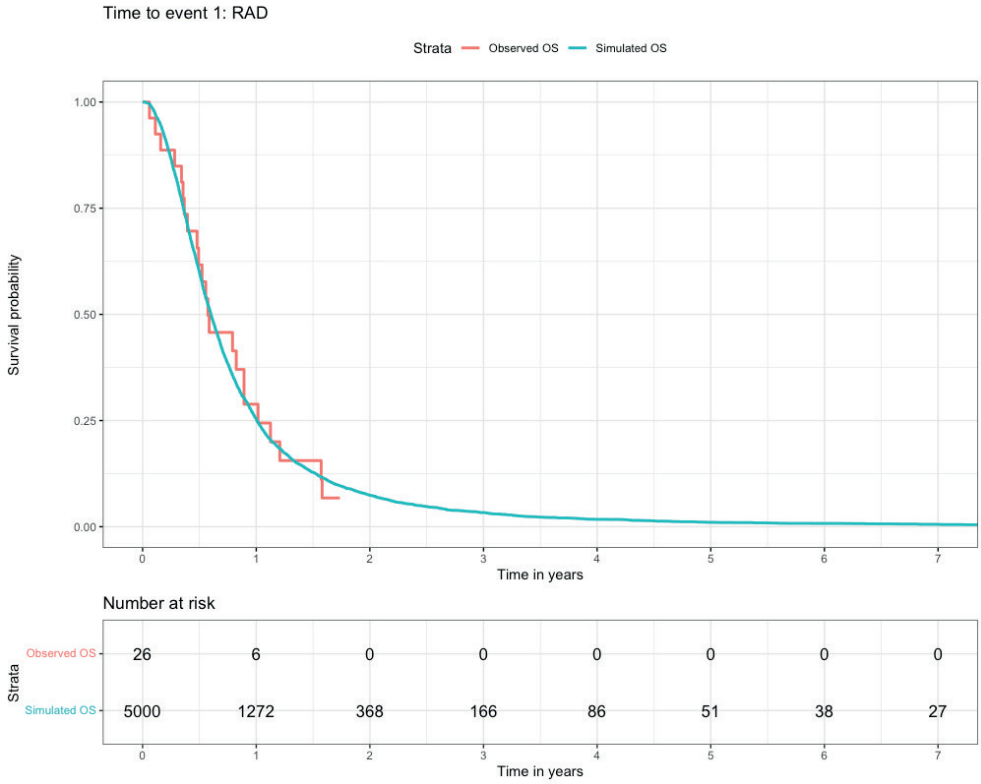
Abbreviations: ENZ, enzalutamide; OS, overall survival.

Figure S6.10 TTE1 to next line for patients initially treated with docetaxel



Abbreviations: DOC, docetaxel; OS, overall survival.

Figure S6.11 TTE1 for patients initially treated with radium-223



Abbreviations: RAD, radium-223; OS, overall survival.

Chapter 7

General discussion

Healthcare expenditures account for a substantial proportion of the Gross Domestic Product in the Netherlands (12.7% in 2015).[5] Moreover, expenditures on healthcare are increasing, as with unchanged policy, healthcare expenditures are expected to increase until 2060 by 2.8% per year. Costs due to cancer are an important driver of the increasing healthcare expenditures, which is caused by the elaborate number of available (expensive) cancer treatments. Since a large number of cancer treatments are in the pipeline, these increasing costs are expected to continue for a longer period.[5,6] As publicly financed resources are scarce, healthcare decision makers have to make choices about which healthcare programmes, treatments, and services should be reimbursed. At the time healthcare decision makers have to make such reimbursement decisions, there is still uncertainty around the real value of a new programme, treatment, or service. This is particularly problematic in oncology treatments, as evidence from clinical trials is often inappropriate for real-world practice and off-label use of treatments widely occurs.[143]

Randomised controlled trials (RCTs) are considered the golden standard to prove the efficacy of a treatment, as the controlled conditions ensures to test the effectiveness in an unbiased way. In RCTs, the new treatment is compared to at least one alternative treatment (i.e., standard of care).[19] However, in the case of non-small cell lung cancer (NSCLC) and castration-resistant prostate cancer (CRPC), several new treatments have been introduced over a longer period of time and these treatments are not and will not be compared head-to-head in an RCT. Explanation for this might be the unavailability of eligible comparators at the time a new treatment was investigated and the fact that a treatment will show less beneficial outcomes when compared to another promising treatment. As a consequence, the comparative effectiveness of all available treatment options for a certain disease area is unknown. Moreover, evidence from clinical trials lacks generalisability, as patients in clinical trials differ from patients in daily practice. To ensure unbiased results in an RCT, there is a low prevalence of comorbidities among the included patients to avoid potential confounding. Although this ensures internal validity, it harms the external validity of the study results. The cost-effectiveness of a new treatment is often based on data from clinical trials. Healthcare decision makers should have evidence on the clinical and economic value of a new treatment to decide on its reimbursement. At the time such reimbursement decisions should be made, the evidence of a new treatment is usually based on RCTs, which lacks generalisability to real-world patients.[143] As a result, the effectiveness, safety, and cost-effectiveness of a new treatment is surrounded by uncertainty at the time it is introduced to the market. Therefore, it is of importance to provide evidence on a new treatment to support healthcare decision making. In this thesis, several types of evidence are studied. This chapter reports the main

findings and describes future improvements by answering the following questions: 1) How can evidence from network meta-analyses (NMAs) inform healthcare decision making? 2) How can evidence on costs and cost-effectiveness of targeted therapies and from registry-based RWD inform healthcare decision making? 3) What is the value of registry-based RWD in addition to RCT evidence in healthcare decision making? 4) How can risk-sharing arrangements (RSAs) inform healthcare decision making?

How can evidence from NMAs inform healthcare decision making?

Treatment of patients with cancer has become more personalised, as a large range of targeted therapies and immunotherapies have been introduced to the market.[204] For patients with NSCLC harbouring epidermal growth factor receptor (EGFR) mutations (10-38% of all NSCLC-patients), several EGFR tyrosine kinase inhibitors (TKIs) are available. These agents have shown an improved response rate and progression-free survival (PFS) compared to standard chemotherapy. Although five different EGFR-TKIs are indicated for EGFR mutation-positive NSCLC-patients, head-to-head trials of these targeted therapies are missing. In such cases, a network meta-analysis (NMA) of RCTs could solve this problem. In an NMA, all available treatment options could be compared to each other, as it uses and combines both direct and indirect evidence from different trials.[72] Head-to-head comparisons by means of an NMA of these five EGFR-TKIs were performed in Chapter 2. This NMA showed that first-line osimertinib had a potentially better effectiveness in terms of PFS and overall survival (OS) compared to the other first-line TKIs in patients with EGFR mutation-positive NSCLC. For patients treated with afatinib or dacomitinib, the risk of adverse events was high. As anticancer drug development is an ongoing process, performing an NMA should be regarded as an ongoing process as well. Currently, several EGFR-TKIs are in the pipeline, which may be introduced to the market in the near future.[205,206] When evidence from clinical trials of new treatments becomes available, the NMA should be updated to ensure that clinicians have the most up-to-date evidence available. Moreover, it is important that NMAs should be updated when new or updated evidence from treatments already included in the NMA becomes available. The study in Chapter 2 also indicated that by including additional evidence from new RCTs and updating results in the network, new results were obtained (while previous NMAs did not found significant differences between EGFR-TKIs, we found a significant better PFS and OS for osimertinib compared to other EGFR-TKIs). Therefore, evidence from an NMA can inform healthcare decision makers on the relative effectiveness and safety of a new treatment when it will be introduced to the market and various treatments within

the same indication area are already available. However, an NMA should not be regarded as a static, but as a dynamic phenomenon, which is continuously subject to change. There are some points that should be considered before performing an NMA. One of the most important assumptions of NMAs is the transitivity assumption. This means that no important differences on clinical and methodological characteristics between the trials should exist. If the transitivity assumption holds, NMA might be a good way to compare direct and indirect evidence, but if the assumption is harmed, use of only direct evidence might be preferred. Therefore, vital to a valid application of NMAs is the availability and use of detailed protocol or checklist for performing an NMA. Such protocol gives researchers tools for performing an NMA, improves transparency, and avoids selective use of indirect comparisons. Moreover, to be able to build an NMA, at least one study per treatment arm is needed and a control arm must be available, as the network needs to be connected.[207] Another important point is the need of a qualitative good systematic literature review, as it should be sensitive enough to pick up any relevant study. The following key issues contribute to a systematic review of good quality: a well-defined research question, selecting outcomes of interest and study designs, and defining clear in- and exclusion criteria. Use of a checklist (e.g., the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement) is recommended to transparently report a systematic review.[208] Additionally, considering the complex statistics of an NMA, collaboration with a (bio)statistician is recommended.[86]

How can evidence on costs and cost-effectiveness of targeted therapies and from registry-based RWD inform healthcare decision making?

To keep healthcare affordable, decisions should be made between treatments, programmes, and facilities. Healthcare decision makers should be informed not only about the clinical effectiveness of a new treatment, but also about its costs (compared to its effects). In the Netherlands, it is preferred to perform such evaluation of the costs and effects of a treatment from a societal perspective, but perspectives may differ between countries. A societal perspective means that all relevant societal costs and effects should be considered.[15] In Chapter 2, it was reported that osimertinib had the most favourable PFS and OS compared to the other EGFR-TKIs. Chapter 3 of this thesis also showed that osimertinib improved life-years and quality-adjusted life-years (QALYs) compared to the other TKIs. However, with a total discounted cost per patient of €131,997, costs were also higher compared to the other treatments. Osimertinib could not be regarded as cost-effective with an incremental cost-effectiveness ratio (ICER) of €128,343 per QALY gained compared to afatinib. In the

Netherlands, depending on the disease severity, a maximum threshold of €80,000 per QALY is used to assess whether a treatment could be considered as cost-effective.[12] At a threshold of €80,000 per QALY, a price reduction of 30% is required for osimertinib to be regarded as cost-effective compared to afatinib. Osimertinib is a promising treatment for patients with EGFR mutation-positive NSCLC, as it has a significant better PFS and OS compared to the other EGFR-TKIs. However, negotiations on the price of osimertinib are required for the treatment to become cost-effective. Although, price negotiations on drug prices between the minister of healthcare and pharmaceutical companies frequently occur in the Netherlands, the result of such negotiations are kept secret. Transparency on price negotiations is desirable to gain more insight into the impact of such negotiations on the affordability of healthcare.

Afatinib was the second most effective EGFR-TKI (Chapter 3) and showed an ICER of €41,504 per QALY compared to erlotinib, which was well below the Dutch threshold of €80,000/ QALY. However, afatinib also showed a higher risk of adverse events compared to other EGFR-TKIs (Chapter 2). Since life expectancy is relatively short for NSCLC, it is reasonable that the main focus is on improving survival, but due to the short life expectancy, improving quality of life of NSCLC patients is also of importance. Although adverse events occur less frequent in targeted therapies compared to chemotherapy,[209] frequency of adverse events within the pool of available targeted therapies could differ. For example, for afatinib, the risk of grade ≥3 diarrhoea is 6 to 12 and the risk of rash is 1 to 4 times higher compared to the other EGFR-TKIs. Although adverse events are considered in a cost-effectiveness analysis (CEA) and could be regarded as tolerable on population-level, an individual patient could regard adverse events differently. To further improve patient's quality of life, more attention should be paid to adverse events by better reporting to gain more information on the toxicity and safety of treatments. More information on adverse events could improve shared decision-making between physician and patient on the decision which treatment to take.

The clinical results of EGFR-TKIs are promising for NSCLC-patients with EGFR mutations. However, patients who are EGFR mutation-negative will gain more benefit from platinum-based chemotherapy.[210] Therefore, for patients with advanced NSCLC, testing on driver mutations (mutations that promote cell growth and spread and cancer development) at time of initial diagnosis is crucial.[30] In clinical practice, lots of improvements can be made, as previous studies showed that a substantial number of eligible patients did not undergo molecular testing, received chemotherapy before testing results were available, or was treated with chemotherapy despite having EGFR-mutations.[211] While a large group of patients is tested on molecular drivers, only a proportion of the patients is mutation-positive. Costs of testing are made by a large population and should therefore be considered in the budget

impact.[212] Testing costs may also increase the ICER, especially when the prevalence of the specific molecular drive is low. Development of tests that enable to identify multiple molecular drivers may be a way to minimise the testing costs. Next-generation sequencing (NGS) might be a promising technology as it enables to sequence an entire human genome.[211,213]

Costs and cost-effectiveness could be based on evidence from clinical trials. As patients in clinical practice differ from patients studied in clinical trials, cost calculations should be based on RWD, for example, registry data, to obtain insight into the economic value of a treatment in clinical practice. To illustrate, in Chapter 5, the real-world costs of CRPC treatment in the Netherlands were estimated to be €67,174. Over half of these costs were caused by the costs of systemic treatment (59%). It was also seen that the costs of second- and third-line treatment were higher compared to first-line treatment. Clinicians might consider whether an additional treatment line is worth its costs, especially when the expected survival benefit is minimal, it might be better to focus on quality of life. Anti-cancer treatments may reduce quality of life, as they are often associated with (severe) adverse events. Some patients are willing to endure these side-effects of anti-cancer treatments to extend life, but some patients prefer to live the last part of their life in the best possible quality of life. As a result, trade-offs can be made between length of life and quality of life. Previous research showed that patient's age and health status are important factors in this trade-off (i.e., young patients in a good condition are more willing to take aggressive cancer treatments, older patients give high value to quality of life).[214] Therefore, in clinical guidelines, more attention should be paid on dialogues between clinician and patient in which they should agree upon the aim and added value of a treatment.[215]

CEAs provide insight into the additional costs and effects of a new treatment compared to standard of care. Such evidence could inform healthcare decision makers to allocate the financial resources to optimise health. Moreover, a CEA of a targeted therapy could be useful for decision makers to define the patient population who is eligible for a specific drug, as targeted therapies may only improve survival in patients with specific molecular drivers.

To keep healthcare affordable, it is important to continuously monitor the costs. Therefore, evidence on the costs of cancer treatments obtained from real-world data is vital, as it provides insight into the real-world costs. Furthermore, it is important to consider whether these costs weigh against the clinical effects. We built a disease model aiming to obtain insight into the cost-effectiveness of sequential CRPC treatments (Chapter 6). However, due to validation problems, which will be discussed below, we were not able to estimate the cost-effectiveness of CRPC treatments. Therefore, in future research, a cost-effectiveness analysis of CRPC treatments using a disease model should be performed.

What is the value of registry-based RWD in addition to RCT evidence in healthcare decision making?

Since patients enrolled in an RCT are not representative for patients in clinical practice, evidence from RCTs is not generalisable to the real-world. Therefore, there is an increasing interest in real-world data (RWD), as it could provide insight into, for example, the real-world effectiveness of treatments. Moreover, insight into sequential treatment lines is often lacking as RCTs usually only investigate one treatment-line with a primarily focus on disease recurrence or progression and a limited follow-up time.[23,143] Chapter 6 of this thesis showed that there are potential opportunities for RWD to be used in disease models, as RWD provide insight into the use, uptake, and effectiveness of new treatments in the real-world and into treatment sequences. However, it was also found that the lack of a randomised design is the most important limitation of using RWD in disease models. Chapter 6 showed that despite controlling for possible confounders by applying multivariate regression models, it was not possible to adequately control for all differences between treatments, as the disease model was not able to validly replicate the differences between treatments. Propensity score matching (PSM) is another method that could control for differences in patient characteristics when comparing two treatment arms. However, PSM is not feasible in a disease model with multiple (sequential) treatment options.[200] Moreover, Chapter 6 showed that patients who received treatment A differed substantially from patients who received treatment B (e.g., patients who were treated with docetaxel were younger than patients treated with abiraterone). As a consequence, causality is hampered. Furthermore, in the first years (2010-2013) of patient enrolment in the CAPRI-registry, only docetaxel was available as first-line treatment. From 2014 onwards, four different first-line treatments were available (docetaxel, abiraterone, enzalutamide, and radium-223). This may have induced chronological bias.[216]

In observational data, techniques like PSM and multivariate regression models are able to correct for confounding up to a certain point, however, they are not able to correct for unobserved differences between treatment groups. Internal validity of RWD is an important point of concern and RCTs will always be superior in terms of internal validity compared to RWD. Considering the beforementioned challenges of RWD, it is recommended for disease models to use RWD in combination with RCTs/NMA. Use of RCT evidence ensures the internal validity and RWD provide information on treatments in the real-world. RWD could be used to model the base case treatment, subsequently, Hazard Ratios of novel treatments that are obtained from NMAs can be applied to the model.[217] Pragmatic clinical trials (PCTs) are another method that could be applied to provide decision makers insight into the real-world effectiveness of a treatment. Contrary to an RCT, a PCT investigates a treatment in the broad

spectrum of daily clinical practice. PCTs maximise the generalisability of the outcomes, as it studies the effectiveness of a treatment in the real-world. This is achieved by incorporating all relevant treatment options, including patients who are representative for the real-world population, studying a large number of clinical outcomes, and involving decision makers in the trial design to ensure study results that are relevant for decision-making.[143,218]

Predicting the real-world costs of CRPC patients was another challenge we faced. To correct for differences in costs that might be induced by differences in patient characteristics and treatments, costs should be predicted using multivariate regression models. Although we used various methods to correct and predict the costs, we were not able to sufficiently correct for differences in patient characteristics and treatments. As a result, it was not possible to validly predict the real-world costs of CRPC patients and estimate the cost-effectiveness of different treatment sequences. The inability to predict the costs might be due to unobserved differences between treatment arms, which should be studied in further research.

The timeliness of RWD is another challenge, as at the time results from RWD about the use, uptake, and/or (cost-)effectiveness of certain treatments or treatment sequences become available, clinical guidelines may already have been revised. In the CAPRI-registry, patients were included between 2010-2015. Before 2013, only docetaxel was available as first-line treatment for CPRC-patients. From 2013 onwards, various other first-line treatments were introduced to the market. As a consequence, the results are outdated and not representative for the current clinical practice. Adding data from clinical studies of new treatments could make outdated results relevant again. Furthermore, to be able to report on the most up-to-date treatment patterns, data collection should become less complicated and time-consuming. This would reduce the time between data collection and analyses and give results that are relevant for current daily practice.

Furthermore, missing data are another challenge of RWD. One is often faced with missing data in RWD, especially when the follow-up is long. From Chapter 6, it was seen that there were missing values for almost all patient characteristics, varying from 9-47%. However, if missing data is not related to unobserved variables, multiple imputation could be a valid method to deal with missing data. Since missing data was considered to be not related to unobserved variables in the CAPRI-registry, multiple imputation was applied in Chapter 6 of this thesis to impute missing values.

RWD collection of a large number of patients is also very time-consuming, as clinical data and resource use have to be extracted from medical records and inserted into a safe digital environment. Often, data from different databases should be linked, which induces new

challenges such as keeping patients unidentifiable. Data registries may benefit from IT developments in the future, which could make data collection more convenient and less time-consuming. In addition, if data on quality of life and other healthcare use are desired (which is the case if the cost-effectiveness of a certain treatment have to be assessed from a societal perspective), questionnaires have to be sent to patients on multiple time points and usually, reminders have to be sent to the patients. Since patients have to fill in the questionnaires multiple times and the follow-up is relatively long, the representativeness of the patient sample could be jeopardised, if the responders are relatively young and in a good condition. For example, in the PRO-CAPRI study, a side study of CAPRI, the sample size was small and the included patients had a better condition compared to the patients in the CAPRI study, which might limit the generalisability of the outcomes.[219] On the other hand, it could be argued that if particularly younger patients filled in the questionnaires, the response might be better, as younger patients might understand the questions better than older patients. If patients would be interviewed about their quality of life during hospital visits (i.e., doctor appointments) instead of sending the questionnaires to patients at home, the number of responses and the representativeness of the patient sample may improve.

How can RSAs be used in healthcare decision making?

To mitigate the uncertainty around the real value of a new drug, RSAs are used. In such RSAs, the risk will be shared between the payer (in the Netherlands: health insurer or government) and the pharmaceutical company. Chapter 4 of this thesis showed that RSAs could reduce the risk to the payer in clinical settings with uncertainty regarding response rates, survival, patient numbers, or any other characteristic which affect budget impact. The impact of RSAs could differ between different types of RSAs as well as between treatments within the same RSA. Therefore, based on the type of outcomes expected, and the type of uncertainty one aims to manage/reduce/share, it should be decided whether and which type of RSA to use. For example, when there is uncertainty around the benefits of a treatment (i.e., response rate, PFS, or OS), 'money-back guarantee', 'conditional treatment continuation', or 'price linked to outcome' could be appropriate RSAs. In case there is uncertainty around the average treatment duration, 'utilisation caps'- or 'fixed cost per patient'-arrangements could be a way to manage such uncertainties. However, in case a performance-based RSA is agreed upon and the drug performs less than expected, difficulties may occur for the payer to achieve refunds or price cuts, as patients are already receiving the drug and the drug could not easily be removed from the market. Therefore, to accomplish a good execution of RSAs, the negotiating power of the

payer should be reinforced by for example improving transparency, increasing competition, and working together with other countries.[220,221]

Price negotiations between the pharmaceutical company and the government are more common nowadays. However, the outcome of these negotiations (i.e., the price reduction) is usually kept secret from the public. As a result, the real drug price is unknown and the impact of an RSA (i.e., price negotiation) is not clear. Collaboration between countries on pricing and reimbursement (e.g., the European Network for Health Technology Assessment (EUnetHTA), a network collaboration across European countries on health technology assessment and BeneluxaI, an international collaboration on pharmaceutical policy between Belgium, the Netherlands, Luxemburg, Austria, and Ireland)[221,222] might be a step forward to improve timely access to and affordability of treatments. Price negotiations may become more effective when countries work closely together, by improving transparency on pricing and sharing knowledge between countries. In particular, small countries might benefit from international collaboration, as they have more negotiating power in such a collaboration.

In the Netherlands, the DRUG access protocol has been started since 2021, in which new expensive treatments for rare cancer types are provided for free for the first months. As a result, patients have earlier access to new treatments, the real-world effectiveness and safety of the new treatment could be monitored, and price negotiations could be arranged. The first drug that became available through the DRUG access protocol is cemiplimab for squamous cell carcinoma of the skin. The first four months of treatment are financed by the pharmaceutical company, if the treatment shows beneficial effects, the treatment will be reimbursed by the health insurance.[223] Such arrangement could be beneficial for the patient (earlier access to treatments), pharmaceutical company (no RCT needed), and the healthcare decision maker (price negotiations). If this arrangement shows beneficial results, this could also be implemented for other treatments that cannot be studied in an RCT.

Final remarks

In this thesis, we discussed various types of evidence in the field of NSCLC and CRPC that could inform healthcare decision makers. NMAs could be used to assess the (cost-)effectiveness of multiple treatments when head-to-head comparisons are missing. RWD could provide information on the resource use and costs of cancer treatments. It could also indicate potential cost-savings when evidence RWD provide insight into the main driver of the costs. Moreover, in contrast to RCTs, RWD give evidence on the costs and effects that are generalisable, which could reduce uncertainty around the value of a new treatment for healthcare decision makers.

However, RWD have important challenges, in particular, the internal validity of RWD. Both using evidence from RWD and RCT is advisable, as it overcomes the limitations of both types of evidence. Several types of RSAs are available to alleviate the uncertainty around the real value of a new treatment. Good administration of the treatment effects and more negotiating power for the payer are needed for successful execution of RSAs. Collaboration between countries on pharmaceutical policy should be improved to benefit from shared knowledge to enhance timely access to and affordability of treatments. Considering the ongoing increase of cancer costs mainly caused by the availability of a large number of treatments, healthcare decision makers have to continuously endeavour to achieve the most optimal allocation of the financial resources to maximise people's health. Continuously improving the evidence to inform healthcare decision-making is necessary to accomplish this goal.

Summary

Introduction

With increasing healthcare expenditures, healthcare induces great pressure on countries' public spending. Since the financial resources are limited, healthcare should be kept affordable. Therefore, healthcare decision makers should decide what healthcare treatments, programmes, and services should be reimbursed. To be able to make such choices, healthcare decision makers should be informed with evidence on the (cost-)effectiveness of these healthcare treatments, programmes, and services. Clinical effectiveness of a new treatment is usually investigated in a randomised controlled trial (RCT). In an RCT, selected patients are studied under strictly controlled conditions. As patients in clinical practice differ from patients included in an RCT (i.e., RCT-patients are usually younger and have no comorbidities), there is uncertainty around real value of the treatment. To mitigate this uncertainty, different types of evidence on the value of a new treatment are available (e.g., network meta-analysis (NMA) and registry-based real-world data (RWD)) that could inform healthcare decision makers.

In this thesis, different types of evidence on new treatments to inform healthcare decision-making are discussed in two clinical areas: lung cancer and prostate cancer.

Non-small cell lung cancer

Chapter 2 reports on an NMA of five different epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) for patients with non-small cell lung cancer (NSCLC) harbouring EGFR mutations. Based on a relatively good efficacy and mild toxicity pattern, osimertinib was considered as the most favourable first-line EGFR-TKIs for EGFR mutation-positive patients with NSCLC.

Chapter 3 reports a cost-effectiveness analysis (CEA) of four different first-line EGFR-TKIs (i.e., gefitinib, erlotinib, afatinib, and osimertinib) in patients with EGFR mutation-positive NSCLC. Data on the effectiveness of the TKIs was based on the NMA-study as described in Chapter 2. Total discounted per patient costs were the lowest for erlotinib (€64,035) and the highest for osimertinib (€131,997). Osimertinib also yielded the highest amount of QALYs per patient (2.01). From the CEA it was observed that erlotinib dominated gefitinib. Afatinib compared to erlotinib yielded €41,504/QALY gained. Osimertinib versus afatinib resulted in €128,343/QALY gained. At a Dutch threshold of €80,000/QALY, the price of osimertinib should be reduced by 30% to be considered as cost-effective.

In **Chapter 4**, we evaluate the impact of six Qypes of risk-sharing arrangements (RSAs) for NSCLC therapies based on RWD. Several "what-if"-analyses were performed to evaluate the

costs and benefits that might be associated with these RSAs. The analyses were done in both metastatic and non-metastatic patients. Large cost reductions were observed for erlotinib and pemetrexed/platinum treatment in patients with metastatic NSCLC. In patients with non-metastatic NSCLC, relatively small changes in costs were observed. We conclude that only when the type of RSA matches the setting and type of uncertainty, RSAs may be useful to mitigate uncertainty around the incremental cost-effectiveness or budget impact of drugs.

Castration-resistant prostate cancer

Chapter 5 reports on the real-world costs of castration-resistant prostate cancer (CRPC) treatments in the Netherlands. Data were obtained from the Castration-resistant Prostate Cancer Registry (CAPRI). Patients who received at least one life-prolonging drug were included in the analysis (N=1,937). Mean total per patient costs accounted for €67,174. Largest proportion of the total costs were systemic treatment costs (59%). Monthly costs per treatment line increased when more subsequent lines were given (line 1: €3,421; line 2: €5,083; line 3: €6,841). It seems that systemic treatment costs are the main driver of the CRPC costs. Therefore, when new treatments become available, its additional costs and effects should be compared to existing treatment options.

Chapter 6 discusses whether a disease model based on RWD could be used to estimate the cost-effectiveness of CRPC treatments. We developed a patient-level simulation model, using patient-level data from the CAPRI-registry. Internal validity of the model was tested by comparing the time to event (TTE) and overall survival (OS) from the simulation model to the observed registry outcomes. It was seen that patient characteristics and survival outcomes of the simulated data were comparable to the observed data (median OS of 20.6 vs 19.8 months respectively). However, the disease model was not able to accurately estimate differences between treatments, as the modelled differences were smaller or larger than the observed differences. This might be induced by unobserved differences between treatments that could not be identified and controlled by multivariate regression models. Consequently, the disease model was not able to predict differences between treatments. This was considered as the main limitation of the disease model, since using these results to estimate cost-effectiveness would lead to biased outcomes. Considering the high internal validity of RCT-data and the generalisability of RWD, the use of a combination of both types of data in disease models should be explored in further research.

Discussion

This thesis aimed to provide evidence on new treatment in the field of lung and prostate cancer to inform healthcare decision making. This thesis showed that when head-to-head studies are missing, NMAs are useful to assess the (cost-)effectiveness of multiple treatments. RSAs could be used to alleviate the uncertainty around the incremental cost-effectiveness or budget impact of treatments. However, good administration and more negotiating power for the payer are necessary for RSAs to be effective. RWD could provide information on the costs and effects of patients in clinical practice that are, contrary to RCT data, generalisable. However, RWD have important challenges. One of the main challenges we faced was the poor internal validity of RWD due to unobserved differences between treatments. Using a combination of RWD and RCT is something that should be explored in future research. As healthcare costs, including cancer costs, are increasing, healthcare decision makers have to decide what healthcare drugs, programmes, or services to reimburse. Therefore, continuously improving the evidence to inform healthcare decision makers is of utmost importance.

Samenvatting

Introductie

De toenemende zorguitgaven creëren een grote druk op de publieke uitgaven van landen. Aangezien de financiële middelen beperkt zijn moet de gezondheidszorg betaalbaar blijven. Daarom moeten beleidsmakers in de gezondheidszorg bepalen welke medische behandelingen, programma's en services vergoed dienen te worden. Voor het maken van zulke beslissingen moeten beleidsmakers beschikken over bewijs van de (kosten)effectiviteit van deze medische behandelingen, programma's en services. Klinische effectiviteit van een nieuw middel wordt veelal onderzocht in een randomised controlled trial (RCT). In zo'n RCT worden patiënten onder strikt gecontroleerde omstandigheden onderzocht. Aangezien patiënten in de dagelijkse praktijk verschillen van patiënten die geïncludeerd zijn in een RCT (zo zijn RCT-patiënten vaak jonger en hebben ze geen comorbiditeiten), bestaat er onzekerheid over de werkelijke waarde van een nieuwe behandeling op het moment dat deze op de markt komt. Om deze onzekerheid verminderen bestaan er verschillende soorten bewijs van de waarde van een nieuwe behandeling (bijvoorbeeld netwerk meta-analyse (NMA) en data uit de dagelijkse praktijk) die beleidsmakers in de gezondheidszorg kunnen informeren. In dit onderzoek zijn verschillende soorten bewijs van nieuwe behandelingen die beleidsmakers in de gezondheidszorg kunnen informeren besproken in twee verschillende klinische gebieden: longkanker en prostaatkanker.

Niet-kleincellige longkanker

Hoofstuk 2 rapporteert over een NMA van vijf verschillende epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) voor patiënten met niet-kleincellige longkanker met EGFR-mutaties. Op basis van een relatief goede effectiviteit en een milde toxiciteit werd osimertinib beschouwd als de meest gunstige eerstelijns EGFR-TKI voor patiënten met niet-kleincellige longkanker en EGFR-mutaties.

Hoofdstuk 3 rapporteert een kosteneffectiteitsanalyse (KEA) van vier verschillende eerstelijns EGFR-TKIs (gefitinib, erlotinib, afatinib en osimertinib) bij patiënten met niet-kleincellige longkanker en EGFR-mutaties. Data over de effectiviteit van de TKIs was gebaseerd op de NMA-studie uit Hoofdstuk 2. De totale verdisconteerde kosten per patiënt waren het laagst voor erlotinib (€64.035) en het hoogst voor osimertinib (€131.997). Osimertinib had ook de meeste QALYs per patiënt (2.01). De KEA toonde aan dat erlotinib gefitinib domineerde. Afatinib vergeleken met erlotinib leidde tot €41,504 per gewonnen QALY. Osimertinib versus afatinib resulteerde in €128,343 per gewonnen QALY. Wanneer de Nederlandse drempelwaarde van €80,000 per QALY gehanteerd wordt dan moet de prijs

van osimertinib met 30% verminderd worden om als kosteneffectief beschouwd te worden.

In **Hoofdstuk 4**, evalueerden we de impact van zes soorten regelingen om risico te verdelen omtrent de echte waarde van behandelingen voor niet-kleincellige longkanker gebaseerd op data uit de dagelijkse praktijk. Verschillende "wat-als'-analyses zijn uitgevoerd om de kosten en effecten te evalueren die zouden kunnen voortkomen uit dergelijke regelingen. In de analyses zijn zowel gemetastaseerde als niet-gemetastaseerde patiënten meegenomen. Grote reducties van de kosten werden gezien bij erlotinib en pemetrexed/platinum behandeling bij patiënten met gemetastaseerde niet-kleincellige longkanker. Bij patiënten met niet-gemetastaseerde niet-kleincellige longkanker werden relatief kleine veranderingen in de kosten geobserveerd. We concluderen dat alleen als het type regeling om risico te verdelen aansluit bij de setting en het type onzekerheid, dergelijke regelingen nuttig zijn voor het verminderen van de onzekerheid rondom de incrementele kosteneffectiviteit of budget impact van een medicijn.

Castratie-resistente prostaatkanker

Hoofdstuk 5 rapporteert de kosten in de dagelijkse praktijk van behandelingen voor castratie-resistente prostaatkanker in Nederland. Data waren afkomstig uit de Castration-resistant Prostate Cancer Registry (CAPRI). Patiënten die minstens een levensverlengende behandeling hebben gekregen werden in de analyse meegenomen (N=1,937). Gemiddelde totale kosten per patiënt bedroegen €67.174. Het grootste deel van de totale kosten werden veroorzaakt door kosten van de systemische behandeling (59%). Maandelijkse kosten per behandellijn namen toe naarmate meer opeenvolgende behandellijnen gegeven waren (lijn 1: €3.421; lijn 2: €5.083; lijn 3: €6.841). Kosten van systemische behandelingen lijken de belangrijkste kostendrijver te zijn van kosten voor castratie-resistente prostaatkanker. Daarom moeten, wanneer nieuwe behandelingen op de markt komen, de extra kosten en effecten vergeleken worden met bestaande behandelopties.

In **Hoofdstuk 6** bespreken we of een ziektemodel gebaseerd op data uit de dagelijkse praktijk gebruikt kan worden om de kosteneffectiviteit van behandelingen voor castratie-resistente prostaatkanker te schatten. We hebben een simulatiemodel op patiënt-niveau ontwikkeld waarbij we data op patiëntniveau afkomstig uit het CAPRI-register hebben gebruikt. De interne validiteit van het model was getest door de tijd tot event en overleving in het simulatiemodel te vergelijken met de geobserveerde uitkomsten uit het register. We zagen dat de patiënt karakteristieken en overleving van de gesimuleerde data vergelijkbaar waren met de geobserveerde data (mediane overleving was respectievelijk 20.6 en 19.8 maanden). Het ziektemodel was echter niet in staat om goed de verschillen tussen

behandelingen te schatten, want de gemodelleerde verschillen waren kleiner of groter dan de geobserveerde verschillen. Dit zou kunnen komen door niet-geobserveerde verschillen tussen behandelingen die we niet konden identificeren en waarvoor we niet konden corrigeren in multivariate regressiemodellen. Het ziektemodel was daardoor niet in staat om verschillen tussen behandelingen te voorspellen. Dit wordt gezien als de belangrijkste beperking van het ziektemodel aangezien het gebruik van dit model voor het schatten van kosteneffectiviteit zou kunnen leiden tot verkeerde uitkomsten. Gezien de sterke interne validiteit van RCT-data en de generaliseerbaarheid van data uit de dagelijkse praktijk zou het gebruik van een combinatie van beide typen data in ziektemodellen onderzocht moeten worden in toekomstig onderzoek.

Discussie

Het doel van dit onderzoek was om bewijs te leveren van nieuwe behandelingen voor longkanker en prostaatkanker om beleidsmakers in de gezondheidszorg te informeren. Dit onderzoek liet zien dat als er geen één-op-één studies zijn, NMA;s zinvol zijn om de (kosten) effectiviteit van meerdere behandelingen te onderzoeken. Regelingen voor het verdelen van risico kunnen gebruikt worden om de onzekerheid rondom de incrementele kosteneffectiviteit of budget impact van behandelingen te verminderen. Een goede administratie en meer onderhandelingsmacht aan de kant van de betaler zijn nodig voor een effectieve werking van dergelijke regelingen. Data uit de dagelijkse praktijk kunnen informatie geven over de kosten en effecten van patiënten uit de dagelijkse praktijk dat, in tegenstelling tot RCT-data, generaliseerbaar is. Data uit de dagelijkse praktijk hebben echter belangrijke uitdagingen. Een van de grootste uitdagingen waar wij mee te maken kregen was de matige interne validiteit van de data vanwege niet-geobserveerde verschillen tussen behandelingen. Het gebruik van een combinatie van data uit de dagelijkse praktijk en RCT zou in toekomstig onderzoek onderzocht moeten worden. Aangezien de zorgkosten, inclusief kosten als gevolg van kanker, toenemen moeten beleidsmakers in de gezondheidszorg bepalen welke medische behandelingen, programma's of services vergoed moeten worden. Om dat te doen is continue verbetering van het bewijs om beleidsmakers te informeren van groot belang.

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PhD portfolio

PhD portfolio

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Copromotor: Dr. Maiwenn J. Al

PhD training

Research Master in Health Sciences - Netherlands Institute for Health Sciences (2014-2016)
Introduction to Bayesian Methods in Clinical Research – Netherlands Institute for Health Sciences (2016)
Klaar in 4 jaar – Erasmus University Rotterdam (2016)
Academic Writing – Erasmus University Rotterdam (2016)
Basic didactics – Erasmus University Rotterdam/RISBO (2017)
Group dynamics – Erasmus University Rotterdam/RISBO (2017-2018)
Patient Level Modelling in R – Erasmus University Rotterdam (2017-2018)
Making an academic poster that stands out – Erasmus University Rotterdam (2017)
Indirect and Mixed Treatment Comparisons – University of Bristol (2017)
Systematic Literature Review in PubMed – Erasmus Medical Centre (2018)
Systematic Literature Review in Other databases – Erasmus Medical Centre (2018)
Identification and Review of Evidence to Inform Cost Effectiveness Models – University of Sheffield (2018)
Network Meta-Analysis – Erasmus University Rotterdam (2018)
Coaching en intervisievaardigheden – Erasmus University Rotterdam (2021)

Teaching

Kwaliteit en Doelmatigheid – Tutor (2016-2018)
Bachelor thesis - Supervisor (2016-2019)
Advanced Economic Evaluation – PC lab instructor (2017)
Kwantitatief leeronderzoek (M&T 4) – Tutor (2017-2018)
Advanced Health Economic Modelling – PC lab instructor (2018-)
Participating in Health Technology Assessment – PC lab instructor (2018-2019)
Master thesis - Supervisor (2020-2021)
Afstudeerproject – Coach (2020-2021)

Podium presentation

Cost-effectiveness analysis of first-line osimertinib in patients with EGFR mutation-positive non-small cell lung cancer

Presented at the International Society for Pharmacoeconomics and Outcome Research (ISPOR) 21th Annual European Congress, Barcelona 12-14 November 2018

Poster presentations

Gefitinib, erlotinib, or afatinib for EGFR-mutated NSCLC patients? A meta-analysis and indirect comparison of the efficacy of first-line tyrosine kinase inhibitors

Presented at the International Society for Pharmacoeconomics and Outcome Research (ISPOR) 19th Annual European Congress, Vienna 31 October-2 November 2016

Cost-utility analysis of first-line gefitinib, erlotinib and afatinib for patients with non-small cell lung cancer harbouring EGFR-mutations

Presented at the International Society for Pharmacoeconomics and Outcome Research (ISPOR) 19th Annual European Congress, Vienna 31 October-2 November 2016

Determining the comparative value of outcome-based money-back guarantee scenarios in non-small cell lung cancer using real-world data

Presented at the International Society for Pharmacoeconomics and Outcome Research (ISPOR) 20th Annual European Congress, Glasgow 6-8 November 2017

Other

Board member of the ISPOR Student Chapter Rotterdam (2018-2019)

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Dankwoord

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Vermelden, HEER,
U dank bewijzen;
'k Zal U in 't midden van de goôn,
Op hogen toon,
Met psalmen prijzen;
Ik zal mij buigen, op Uw eis,
Naar Uw paleis,
Het hof der ho - ven,
En, om Uw gunst en waarheid saâm,
Uw groten naam
Eerbiedig loven.

About the author

About the author

Marscha Holleman was born in Taipei (Taiwan) on May 25, 1993. She studied Health Policy & Management at the Erasmus University Rotterdam from 2011 to 2014. In 2016, she obtained a master's degree in Health Sciences (research). She started as a PhD candidate at the Erasmus University Rotterdam in 2016 under supervision of prof. dr. C.A. Uyl-de Groot and dr. M.J. Al, which resulted in this thesis. During her PhD trajectory, she worked on several cost-effectiveness analyses of new drugs. She also taught various bachelor and master courses at the Erasmus School of Health Policy & Management and supervised bachelor and master theses.