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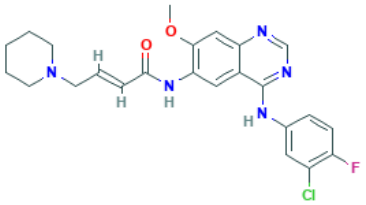
Location: **Rotterdam Erasmus University**
Word count: **14,201/20,000**

The cost-effectiveness of Dacomitinib in comparison with Gefitinib in patients with classical EGFR activating non-small cell lung cancer



Abstract

Background

Dacomitinib obtained market authorization from the European Medicines Agency (EMA) in 2019 and is sold under the brand name “Vizimpro”. It is approved for use as first-line treatment in patients with advanced, epidermal growth factor receptor activating, non-small cell lung cancer. Between 9.1% and 20% of all non-small cell lung cancer patients has an epidermal growth factor receptor activating mutation. About 75% of all newly diagnosed non-small cell lung cancers are stage 3 or higher. Consequently, 533 to 1255 people yearly are eligible for treatment with Dacomitinib in the Netherlands. This study aimed to investigate the cost-effectiveness of Dacomitinib compared to Gefitinib as first-line treatment in adult, epidermal growth factor receptor activating, advanced stage, non-small cell lung cancer patients in the Netherlands.

Methods

A partitioned survival model consisting of three health states for a lifetime horizon was constructed in Excel. Progression free survival and overall survival of Dacomitnib and Gefitinib were extracted from the ARCHER 1050 trial (NCT01774721). Overall survival and progression free survival duration were extrapolated using a Weibull method. A societal perspective for costs is taken. Data on health state utilities, costs, healthcare resource use, adverse events, indirect medical costs and direct non-medical costs were gathered from available literature. The health outcomes are expressed in quality adjusted life years (QALY’s) and natural life years. A univariate, multivariate, probabilistic, scenario and value of information analysis was performed.

Results:

The incremental cost for Dacomitinib compared to Gefitinib in this study was € 68,001. An additional 0.37 QALY’s were accrued by Dacomitinib, resulting in an incremental cost-effectiveness ratio (ICER) of € 181,558 per QALY. Furthermore, Dacomitinib yielded 0.81 more life years than Gefitinib, causing the ICER to be € 84,388 per life year. There was a 1% chance for Dacomitinib to be cost-effective compared to Gefitinib in a Dutch setting at a € 80,000 threshold as determined by the burden of disease. Sensitivity analysis illustrated the ICER to be most responsive to price and utility variations for Gefitinib and Dacomitinib, choice of extrapolation model and healthcare resource use and cost. A 66.1% price decrease is required to reach the threshold for the deterministic analysis.

Conclusion:

Dacomitinib effectively increased survival and accrued more QALY’s over a 20 year time horizon. However, Dacomitinib is not likely to be cost-effective compared with Gefitinib in the Netherlands at a threshold of € 80,000 per QALY. Since the initiation of the ARCHER 1050 trial newer treatment options became available, which warrants further research to the cost-effectiveness of Dacomitinib in the contemporary setting.

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Chapter 1: Introduction

1.1 Background EGFR+ non-small cell lung cancer

The field of non-small cell lung cancer therapy is rapidly developing (1). Currently, there is no study on the cost-effectiveness of Dacomitinib compared to contemporary medication as first-line treatment in adult epidermal growth factor receptor positive, advanced stage, non-small cell lung cancer patients in the Netherlands. Dacomitinib obtained market authorization from the European Medicines Agency (EMA) in 2019 and is sold under the brand name "Vizimpro". Dacomitinib fulfills the palliative, adjuvant, specific toxicity, quality of life, impact of treatment and level of evidence criteria to have received a positive advice for introduction on the Dutch market by the committee for judgement of oncological treatments (2). As a result of a limited healthcare budget, a cost-effectiveness analysis is indicated to determine the relative costs and effects of Dacomitinib in comparison with current treatment to inform policy making. This cost-effectiveness study will be based on the ARCHER 1050 trial (NCT01774721) (3).

1.2 Lung cancer

Lung cancer is malignant neoplasia of lung tissue. In general, lung cancer can be subdivided into small cell lung cancer and non-small cell lung cancer. Causes include, but are not limited to; smoking, exposure to other inducing substances such as asbestos, air pollution, familial predisposition, radiation and many more. Non-small cell lung cancer is more prevalent and can be further grouped according to histological characteristics into squamous, bronchioalveolar and adenocarcinoma, large cell carcinoma and sarcomatoid carcinoma. Advanced lung cancer is comprised of stages 3b and 4. In stage 3b the carcinoma is locally metastasized to lymph nodes, whilst lung cancer in stage 4 is metastasized to other organ tissue. Lung cancer often presents itself symptomatically as advanced, beyond a surgically resectable, stage (4). Increasingly, therapy is focused on molecular and genetic profiling rather than primarily on histology (5).

1,3 Epidemiology

Lung cancer has the third highest incidence in the Netherlands with 13792 new cases in 2019 (11.7% of all cancer incidence) (6). It has the highest number of deaths (22.8%) and is a leading cause of cancer related mortality in the Netherlands. Of diagnosed lung cancers in general about 71% or 9843 is non-small cell lung cancer (NSCLC) (2019 data) (6). The 5-year survival of NSCLC from 2014 to 2019 is about 21% (1). Incidence of epidermal growth factor receptor (EGFR) activating mutations in NSCLC in Europe is estimated to be between 6-41% of all NSCLC patients (7). In the Netherlands this was estimated to be in 9.1% (8) or between 11-20% according to a review on the prevalence of NSCLC (7). In 2018 the incidence in NSCLC of stage 4 tumors was 49% and stage 3 tumors 21%, which is supported by earlier research estimating an incidence of 75% of stage 3 or higher at diagnosis of all lung cancers (9, 10). Two types of EGFR mutations are most common. They make up 85% of all EGFR mutations, and are generally the mutations targeted with treatment (11). Consequently, about 533 to 1255 people yearly would be eligible for treatment with Dacomitinib.

Significant cost is associated with NSCLC in the Netherlands. Healthcare expenditure on EGFR+ NSCLC and healthcare in general is rising in the Netherlands (12). In 2017 an estimated 457 million euros was spent on lung cancer in the Netherlands (13). This was 7.8% of total expenditure on neoplasms and 0.52% of total healthcare spending in the Netherlands, which was estimated to be around 88 billion euros (13). Healthcare expenditure is expected to double to roughly 175 billion euros in the period of 2015 until 2040 (14). During this time the costs of treating neoplasms is expected to increase the fastest due to technological advancement. Neoplasms are expected to be the second most expensive healthcare category after psychological disorders in 2040, compared to being the seventh most

expensive category in 2015. Additionally, lung cancer is estimated to account for the largest disease burden as expressed by DALY's (disutility adjusted life years) among cancers in the Netherlands, and the sixth largest DALY contributor overall (15).

1.4 Pathophysiology

Activating mutations of the EGFR gene consist of alterations to exons 18-21 of the TK domain (11). In-frame exon 19 deletions are responsible for 44% of EGFR activating mutations. Single-nucleotide substitutions of L858R in exon 21 are responsible for about 41% of all activating mutations. Treating patients with EGFR TK activating mutations with first-line tyrosine kinase inhibitors (TKI) is evidently beneficial for overall survival, response rate and progression free survival (16, 17). Treatment of EGFR TK activated NSCLC with TKI is expected to be more effective in people with exon 19 deletions or exon 21 nucleotide substitutions (18, 19). Dacomitinib is a second generation TKI, targets HER-1, HER-2 and HER-4 receptors, and forms an irreversible attachment to the EGFR kinase domain (20).

1.5 Current treatment

First-line systemic therapies for patients with exon 19 deletions or exon 21 nucleotide substitutions may be first- or second-generation TKIs or erlotinib-bevacizumab. If Osimertinib is unavailable, first line systemic therapies for patients with exon 19 deletions or exon 21 nucleotide substitutions may be first or second generation TKIs or erlotinib-bevacizumab. Osimertinib (third generation) is not found to be cost-effective, but generally more effective than first generation TKIs such as Gefitinib and could potentially prevent resistance (21). First generation TKIs in the Netherlands include Gefitinib or erlotinib. Second generation TKIs include Afatinib or Dacomitinib. Erlotinib, Gefitinib and Afatinib are reimbursed in the Netherlands. Osimertinib is reimbursed as second line treatment and Dacomitinib is not currently compensated (22).

1.6 Dacomitinib trials

Currently two major phase 3 studies have compared the effectiveness of Dacomitinib to other EGFR TKI. ARCHER 1009 compared the effectiveness of Dacomitinib versus erlotinib in patients with advanced NCLSC that had progressed after initial chemotherapy (23). This study did not find Dacomitinib being superior to erlotinib in patients with NSCLC or KRAS-type mutations (23).

ARCHER 1050 is a phase 3 trial comparing Dacomitinib to Gefitinib as first-line treatment in patients with NCSLC with classical EGFR activating mutations (exon 19 deletion or exon 21 nucleotide substitution) excluding patients with central nervous system metastases (24). A majority of the patient population was Asian (77%), but this should not affect disease progression (25, 26). The ARCHER 1050 study did show improvement in the Dacomitinib group in progression free survival (PFS) at the cost of more overall adverse events (median PFS was 14.7 (95% CI 11.1–16.6) versus 9.2 (95% CI 9.1–11.0) months). Additionally, improved overall- survival (OS) was observed (median OS was 34.1 months (95% CI 29.5–39.8) versus 27.0 months (95% CI 24.4–31.6)). Dacomitinib is the first second generation TKI to show improvement in OS versus a standard EGFR TKI treatment (24).

Costs per patient per year for Dacomitinib are around €32.900 (27). Currently the median expected costs for complete treatment is estimated to be around €45.000 compared to €30.000 for Gefitinib (2). This number for Gefitinib is in accordance with earlier estimates of about €33.143 treatment cost for NSCLC patients in the Netherlands (28, 29). Osimertinib is seemingly more effective, but not cost-effective in comparison with other EGFR TKIs (21).

Chapter two consists of a theoretical framework to contextualize the following third chapter of the research methods. The results of the model are presented in chapter four and consequently discussed and elaborated on in chapter five. The policy implications are the conclusion of the study.

Chapter 2: Theoretical framework of health economic analysis

In the Netherlands cost-effectiveness research guidelines exist as a framework for researchers to ensure consistency and generalizability (30). The theoretical framework is based on current knowledge of health economic evaluation and this study will follow the Dutch guidelines regarding current knowledge on best evaluation practice (31, 32). The disciplinary origins of economic evaluation is possibly derived from welfarist and extra-welfarist approaches (32). Cost effectiveness analysis specifically likely originates from social decision making and therefore extra-welfarism, although cost-effectiveness analysis can also be justified in welfarist approaches.
Economic evaluation researches the costs and effects of interventions compared with existing intervention. Such an evaluation is always comparative, since it is impossible to derive the value of a single intervention without a comparator. Economic evaluation is not about saving costs but rather spending efficiently with the available resources in a restricted budget.

2.1 Types of analysis

In general, four types of analyses can be identified: Cost minimization analysis, cost benefit analysis, cost-effectiveness analysis and cost utility analysis. Of these cost-effectiveness and cost-utility analyses are most frequently used. In cost effectiveness analysis cost is expressed in monetary terms and effects in natural units, such as life-years gained. Cost utility analysis expresses the effects in utility values such as quality adjusted life years (QALY's), while the costs are also expressed in monetary units. In addition a budget impact analysis can be performed to assess the financial consequences for the entire budget.

2.2 Costs

It is essential that all relevant costs are measured accurately, credibly and adjusted for differential timing (discounting). Individually and societally people prefer to have money and resources now, rather than in the future, because we can make use of it in the meantime. Additionally, decisions in implementing healthcare resources "now" also impact current and future health. Health benefits are also preferred "now" over "later". Discounting is applied to correct for future costs and outcomes and convert those into "present value". It is debatable whether benefits and costs should be discounted at the same rate. Discounting costs at a higher rate could lead to Keeler and Cretins time postponement paradox (33). Since costs decrease at a higher rate compared to benefits, postponing the implementation will always be economical. Conversely, if costs are discounted at a lower rate it is always preferred to implement decision making immediately. Rates of discounting used in health economic modelling vary between countries (34). If data of effects and costs is used over a period of over a year, these costs and effects should be discounted. Costs can be direct or indirect. For example; direct costs could be the price of the treatment and indirect costs could be future medical costs due to a prolonged life. Of particular interest for cost measurement is the chosen perspective. There are two dominant perspectives in health economic analyses; healthcare and societal. The societal perspective includes all costs relevant to healthcare such as drug, employee and overhead costs, but is more inclusive as it also values productivity and informal care costs outside of provided care.

2.3 Effects

QALY's are a subjective and multidimensional utility metric on an interval scale used to simultaneously measure quality gains due to reduced morbidity and to measure reduced mortality. QALY's are usually referred to as a measure of utility for cost utility analysis. They can be directly measured using a visual analogue scale, time trade-off or standard gamble. QALY's can also be indirectly measured through the use of general or disease specific questionnaires descriptive of health states. General questionnaires include the European quality of life index with 3 or 5 dimensions (EQ-5/3D), health utility index (HUI) and short form 36 items (SF-36). Disease specific questionnaires for non-small cell lung cancer include,

among others, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13), Functional Assessment of Cancer Therapy for the Lungs (FACT-L) and The Lung Cancer Symptom Scale (LCSS) (35).

2.4 Model types and structure

Decision analytic modelling, as used in health economics, include models such as: decision trees, state transition models (Markov), discrete event simulations and micro simulation models. Choice of model is dependent on the research objective and disease type. A decision tree has branches of mutually exclusive alternatives. Tree probabilities are conditional, whilst path probabilities are not. Markov models are structured per cycle and have a transition matrix with transition probabilities for the transition between health states. A partitioned survival model is similar to a Markov model, but uses existing survival curves from available research, instead of transition probabilities, to determine the number of people per state at any given time. A trace with probabilities of progressing to other states is fitted to a hypothetical population. These traces are sourced from overall survival and progression free survival in clinical trials. A Markov model and partitioned survival model is often used for long term modelling with a multitude of different events. In a partitioned survival model patients do not transition according to transition probabilities, but follow a survival curve. Patients cycle through these probabilities and health states in a Markov model. Following the trace in a partitioned survival model, there should be no patients left at the end of the simulation if the trace is fitted from a survival curve with 0% survival after follow-up. Simulated patients also “transition” from one trace to another, for example in the case of changing from progression free survival to progressed disease in a clinical trial. The progressed disease trace can in this case be inferred from the usual reported progression free- and overall survival curves. The transition probability for each cycle can be calculated as well, but differs from a Markov model in that the transition probability changes with each cycle. A half-cycle correction is applied to account for transitions happening at any point in time, instead of all transitions happening at the start or end of a cycle (to correct for over or underestimation of cost or utility values). Costs are consequently added to health states and the total costs are computed. A Markov and partitioned survival cohort model calculates the average expected costs for a group, but has no memory for individual patients. Individual patient simulations are possible, but complicate model structure and increase required time. If patient memory is important, a discrete event simulation can be done to slightly relief the time intensity and provide a completely free structure at the cost of data intensity. The time horizon is preferably an entire lifetime, shorter timeframes can be extrapolated to the length of a lifetime at the cost of increased uncertainty.

2.5 Uncertainty

Models take varying approaches in accounting for uncertainty. If a trial is done over a short timeframe and survival has not yet reached 0%, data extrapolation is needed for a lifetime horizon. Parametric models or methods for such extrapolation include; Weibull, Gompertz, log-logistic and lognormal. Scenario analysis is indicated to investigate the variance of results based on choice of distributions and models. The values used are estimates based on sample populations. A probabilistic sensitivity analysis is done to investigate the sensitivity of the cost-utility outcomes to changes in parameters. Probability distributions are applied to parameters and samples are randomly drawn to generate a distribution of the cost and consequences. The used distributions should be justified. A normal distribution does not always correspond with underlying assumptions. In the case of costs, it is impossible for negative costs to be sampled. A distribution that ranges from zero and larger is therefore indicated, such as a Gamma distribution. Probabilities are generally not higher than 100% or lower than 0%. A distribution that ranges from zero to one is then used.

2.6 Sensitivity analyses

In addition, univariate and multivariate deterministic sensitivity analyses can provide insight in the relative impact of singular parameters. Some premises need to be accounted for, or rationalized, when assessing uncertainty. Additionally, there is methodological uncertainty. For instance, the set rate of discounting. Patient heterogeneity is a source of variance for which a subgroup analysis could be done if individual patient data is available. Different treatment decisions can be made for different patient groups (based on age, sex or ethnicity). No patient level data is available to support a subgroup analysis in the ARCHER 1050 trial. A value of information analysis can be done to assess the consequences of the uncertainty on the outcome and the manner with which future research could reduce this uncertainty. It can be described as the health benefits that can be gained from patients if the uncertainty of the decision-making was resolved. The scale of the uncertainty can be derived from the PSA. The consequences of this uncertainty may be described in terms of net health benefits if the uncertainty regarding treatment decision could be solved. This is known as the expected value of perfect information (EVPI) (32). This EVPI is the additional value of making the treatment decision for individual patients without uncertainty. A time-horizon for use of this particular technology, and the discounted expected yearly incidence of eligible patients are determined to establish the population level expected value of information (popEVPI). The time-horizon is set, because of possible replacement of this treatment with further improved technology. The EVPI can furthermore be expressed, in technical terms, as the mean of the maximum net monetary benefit of all PSA iterations, minus the maximum of the mean net monetary benefit of all PSA iterations (32). The net monetary benefit is the chosen cost-effectiveness threshold multiplied by the acquired units of benefit (thus expressing the units of benefit in monetary terms) minus the cost of the intervention. This is done for both the intervention and comparator to establish the greater benefit, and therefore the most beneficial intervention in monetary terms.

2.7 Outcome

Lastly the incremental cost-effectiveness ratio (ICER), a metric expressing the added cost per extra unit of effect, is calculated for a decision rule. The choice of utility measurement techniques, uncertainty and model structure all influence the ICER. The threshold for cost-effectiveness varies across nations and is depending on willingness to pay for a unit of benefit (QALY or life years) by the decision-maker. It is related to the economic concept of opportunity cost, meaning the assessment of the intervention is compared to what is forfeited. A more expensive treatment, which also is very effective, has a chance to be cost-effective depending on the chosen cost-effectiveness threshold. The net monetary benefit for all PSA iterations yields a probability of cost-effectiveness for interventions at different thresholds in a partitioned survival model. The probability of the ICER falling in acceptable ranges is visualized with a cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC).

2.8 Objective and theory implementation

This study investigates the cost-utility of Dacomitinib in comparison with Gefitinib in first-line treatment according to the results of the ARCHER-1050 trial from a societal perspective in adults with classical EGFR activating non-small cell lung cancer without central nervous system metastases in the Netherlands. Furthermore, a scenario analysis is performed to estimate the best guess, most optimistic and most pessimistic outcomes. To find the most sensitive parameter and to investigate the uncertainty of the outcome univariate and multivariate deterministic and probabilistic analyses are produced. A value of information analysis is done to estimate the expected value of perfect information for the eligible population.

Chapter 3: Methods

This study adopts data from the ARCHER 1050 trial for a cost-utility analysis of Dacomitinib in comparison with Gefitinib. All required data is garnered from available relevant literature (preferably based on studies in the Netherlands). Data on patient characteristics, interventions, comparators, and treatment effects PFS, OS, and adverse events (AEs) are collected. Utility scores and disutility scores of AEs are extracted from literature. Input parameters include monthly transition probabilities for PFS, probability of adverse events per treatment, probability of death per treatment, health utilities and costs for all health states. Since Dutch guidelines are followed, some structural and methodological decisions are made according to the instructions of the guideline for the execution of economic evaluations in healthcare (30).

3.1 Perspective

The societal perspective for costs is taken as is indicated by ZIN (Zorginstituut Nederland) (36). The societal perspective is inclusive of all related costs. This includes costs within the healthcare sector, costs made by patients and family, and costs in other sectors. Similarly, all effects are included in the economic evaluation. These include improvements in quality of life, but also AEs.

3.2 Time-Horizon

Following the ZIN guidelines a lifetime horizon is carried out. The ARCHER 1050 trial had a follow-up of 48 months as indicated by the research protocol. After a median follow-up time of 48 months, as discussed in the paper regarding the updated overall survival analysis, 58.6% of patients had died in the Dacomitinib arm and 67.7% of patients had died in the Gefitinib arm (24). Extrapolation of the data is required to determine the lifetime effects of the treatment. The survival as presented in the ARCHER 1050 trial is similar to the survival observed in other EGFR+ NSCLC OS studies (37). A timeframe of 20 years is deemed sufficiently long to assume all patients to have passed based on disease severity (stage 3b or stage 4) and the median age of 61/62. Additional survival is not sufficiently lengthy to warrant investigating other costs incurred to the healthcare system as a result of added health issues (38). Checkup was done at 28 day intervals. Consequently, a cycle length of similar length is used in the model to most accurately match original data.

3.3 Population

Population data in the ARCHER 1050 trial is gathered from 71 universities and academic medical centers located in seven countries. Included are adult patients of 18 years or older (20 years or older in Japan and South Korea) with cytopathologically or histologically confirmed stage 3b or stage 4 NSCLC with at minimum one lesion that was not irradiated and with at least one EGFR mutation. Additionally, patients required an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 and adequate kidney, liver and hematological functioning. Patients with a history of brain metastases were not eligible for inclusion. The population consisted mostly of Asian patients (77%).

3.4 Intervention

Dacomitinib was given as a pill of 45 milligram once-daily in 28 day cycles in the ARCHER 1050 trial. In the event of toxicity dose reductions to 30 and 15 milligrams were possible. Treatment continued until progression, initiation of novel anticancer therapy, unacceptable toxicity, withdrawal of consent, non-compliance or death.

3.5 Comparator

Gefitinib was given as a pill of 250 milligram once-daily in 28 day cycles. In the case of toxicity Gefitinib was interrupted for the duration of the adverse event and consequently resumed daily or once every

two days. Similar to the intervention treatment continued until progression, initiation of novel anticancer therapy, unacceptable toxicity, withdrawal of consent, non-compliance or death.

3.6 Outcome

This study investigates the cost-utility of Dacomitinib in comparison with Gefitinib. A cost-utility analysis can incorporate benefits in measurements of health-related quality of life (HRQoL) and natural units. QALY's are used for this analysis as a utility metric in line with ZIN guidelines. The outcome in the trial was a survival benefit for the Dacomitinib treatment group, which could signify an increase in the overall utility (QALY's). Inputs from the ARCHER 1050 trial are; overall survival, progression-free survival, adverse event incidence and reported (HRQoL) (secondary source).

Reported results are total costs and effects, incremental costs and effects and an incremental cost-effectiveness ratio (ICER). A reimbursement decision will be advised based on the ICER and the cost-effectiveness thresholds per disease severity according to Dutch guidelines (30). The IMTA burden of disease calculator is used to compute the expected QALY's for a population of similar age without EGFR+ NSCLC (39). Consequently, the absolute and proportional shortfall of QALY's for the trial population from this lifetime remaining QALY expectation is calculated. The absolute shortfall is the complete number of QALY's the trial population will have foregone, whilst the proportional shortfall is the proportion of expected QALY's in relation the estimated number QALY's lost. These metrics are used to signify the burden of disease for determining the severity-adjusted cost-effectiveness threshold. This threshold can be € 20,000, € 50,000 or € 80,000 per QALY in the Netherlands (39).

3.7 Markov-structure

Based on the available data a state transition model (state partitioned survival model) is best suited for extrapolation of the data. A decision tree structure would be complex as a result of branching. A discrete event simulation would allow for individual patient data retention, risk profile updates and time flexibility, but for population level analysis these additional benefits would not be required and overcomplicate the model thus losing transparency. Transitioning from one health state to another is irreversible. The constant risk of transition to progressed disease or death state as graphed in PFS and OS graphs as included in the ARCHER 1050 trial are suitable for a partitioned survival model.

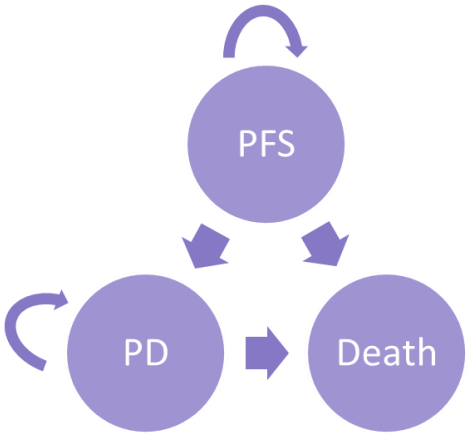

Figure 1: Markov structure

The structure of the model is kept purposefully simple and closely adapted to the trial set-up (see figure 1). The Markov structure does not include transition probabilities, since it is a partitioned survival model. Data for extrapolation of curves are gathered from the OS and PFS Kaplan-Meijer curves in the trial using "Webplotdigitizer 4.1" (40), resulting in four different curves (figure 2). The obtained data from the Kaplan-Meijer curves of the trial is located in the appendix (supplementary

table 1). The OS data was extracted using the updated survival data from Mok et al. (24). PFS data was extracted from the initial publication by Wu et al. from the Kaplan-Meijer curve as reported by the assessment of independent investigators (3). Three transition states are identified from the graphs per treatment; progression free state (PFS), progressed disease (PD) and death. All simulated patients start in the PFS cohort and can progress to the PD or death state. Similarly, patients in the PD cohort can progress to death. Simulated patients do not retransition to PFS. Transition probabilities from PD or PFS to death are assumed to be the same. The transition probability from PFS to PD should correct the numbers at any time. Pseudo individual patient data based on aggregate data were gathered using the method as described by Hoyle and Henley (41). Using the Kaplan-Meijer data, Rdata was obtained and implemented using the R code as provided by Hoyle and Henley (41). This data is used to generate the Cholesky decomposition of covariance matrix and to fit a model (The resulting matrices are presented in table 1). Four different models were fitted in Rstudio (42); Weibull, exponential, lognormal and loglogistic. Choice of extrapolation model is based on the Akaike information criterion (AIC) and on clinical and logical plausibility by reviewing illustrative graphs. The AIC evaluates the prediction error and compares the relative fit of models for a dataset (43). Lower AIC values are preferred. Uncertainty in the log-scale and intercept values are also taken into account for the probabilistic sensitivity analysis. A bivariate normal distribution was applied, because these values were assumed to be correlated. The Cholesky decomposition from variance-covariance matrices are used to draw random values from this bivariate distribution. For this, the Cholesky matrix is multiplied with a vector composed of random draws between 0-1. This is then added with the mean values resulting in another vector. The covariance matrices as yielded from Rstudio are presented in table 1. Since the overall survival did not reach zero in the ARCHER 1050 trial, the AIC score is not informative beyond the last month of follow-up. Weibull curves were used as a result of having the second lowest AIC score in both the OS and PFS groups and to prevent unrealistic survival length (see figure 2 and table 2). The data extrapolation as resulting from Rstudio and the extracted probabilities are used for constructing a state partitioned survival model in Microsoft Excel.

		PFS				**OS**			
		Daco		**Gefi**		**Daco**		**Gefi**	
		intercept	log(scale)	intercept	log(scale)	intercept	log(scale)	intercept	log(scale)
Exponential	intercept	0.085		0.075		0.087		0.082	
Weibull	intercept	0.068	0	0.050	0	0.070	0	0.057	0
	log(scale)	0.014	0.074	-0.006	0.062	0.022	0.075	0.010	0.070
Lognormal	intercept	0.084	0	0.061	0	0.088	0	0.068	0
	log(scale)	0.018	0.064	0.006	0.057	0.022	0.064	0.015	0.061
Loglogistic	intercept	0.077	0	0.056	0	0.076	0	0.062	0
	log(scale)	0.011	0.073	0.002	0.065	0.016	0.074	0.011	0.069

Table 1: Covariance matrices

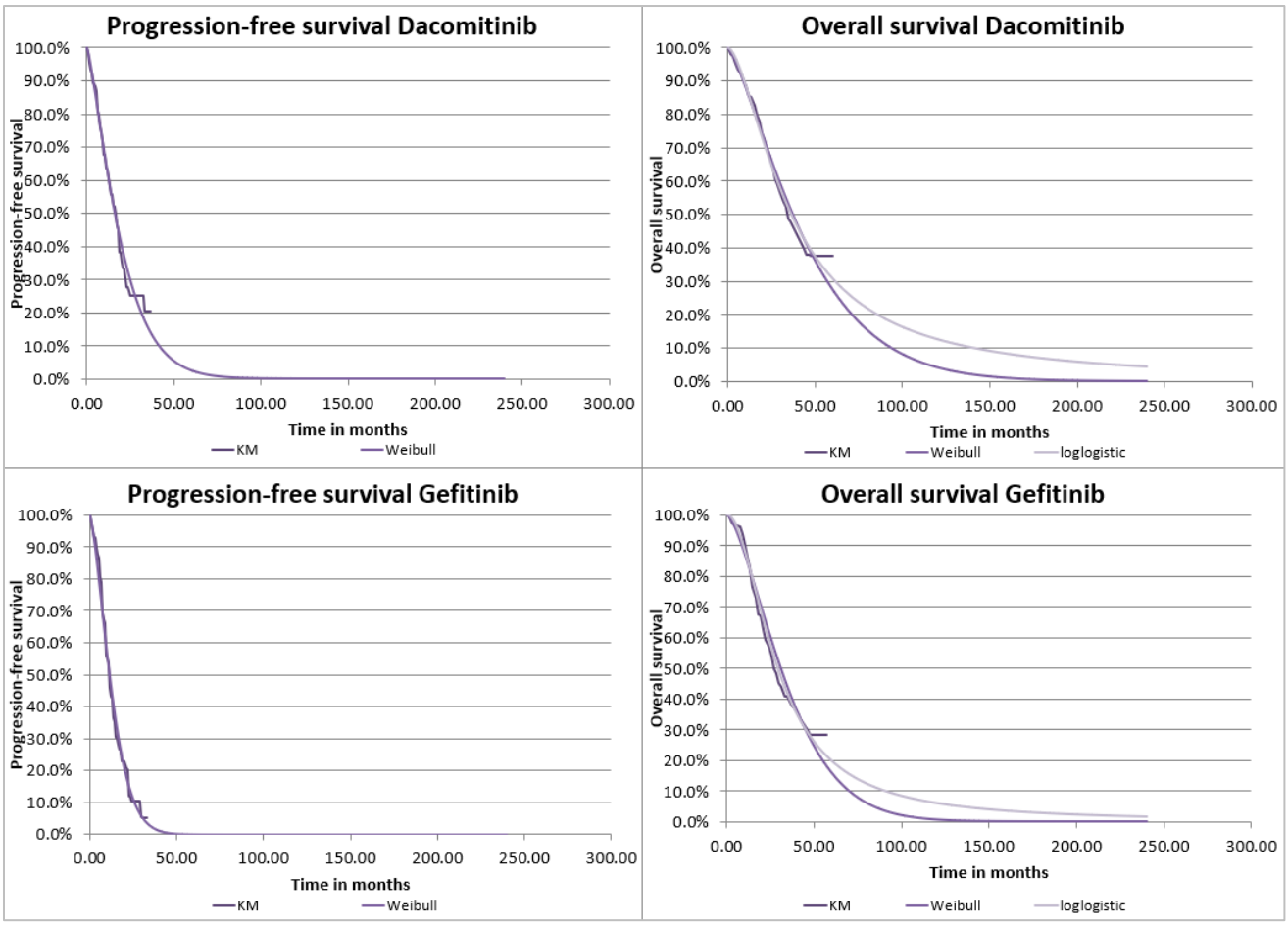

Figure 2: Kaplan-Meijer with Weibull for PFS and Weibull and loglogistic for the OS state

AIC Value				
Curve \ Distribution	**Exponential**	**Weibull**	**Lognormal**	**Loglogistic**
OS Dacomitinib	1218.276	1210.201	1220.093	1209.779
OS Gefitinib	1286.736	1263.979	1265.501	1256.172
PFS Dacomitinib	1041.668	1034.486	1046.921	1038.962
PFS Gefitinib	1171.519	1139.062	1158.828	1144.558

Table 2: Akaike information criterion values

A cycle length of 28 days (including half-cycle correction) is indicated to match the checkup interval from the trial. A half-cycle correction is done to average varying timing of transition in parameters that do not structurally vary at designated cycle times. This simulation is run until fewer than 0.01% of patients are not in the death state, which is the lifetime horizon of 20 years. The set rate for discounting is 4% for costs and 1.5% for effects as advised by ZIN to convert costs and effects to present value.

3.8 Treatment effect

The outcomes on OS and PFS from the ARCHER 1050 trial are used for the model. In this trial the median OS was 34.1 months for Dacomitinib and 27.0 months for Gefitinib. The PFS was 14.7 months

in the Dacomitinib group, and 9.2 months in the Gefitinib group. At the cut-off date for follow-up 133 and 152 deaths occurred in the Dacomitinib and Gefitinib groups respectively.

3.9 Quality of life and (dis)utilities

The utilities used for the treatment lines of Dacomitinib and Gefitinib in this model are extracted from the literature and based on the reported EQ-5D-3L values from the trial as calculated with the UK tariff (44, 45). These utilities are 0.78 for Dacomitinib and 0.828 for Gefitinib respectively. The Utilities were not mentioned in the supplementary file of the ARCHER 1050 trial, but in other studies with access to added data. See supplementary table 2 and 3 for the distributions used in the probabilistic sensitivity analysis.

The utility of progressed disease state is determined based on utility values for advanced stage non-small cell lung cancer from Chouaid et al. (46). The number of patients per treatment line as reported in the ARCHER 1050 trial are used to calculate the average utility for patients in progressed disease state from the Gefitinib or Dacomitinib groups. The number of patients receiving one, two, three or more treatments are given the appropriate utility per treatment line as described by Chouaid et al. (46). Patients receiving more than one treatment are assumed to receive each line for equal duration, hence their utility is calculated as the average utility for their received treatment lines. The utility for treatment-line 1 is 0.67, treatment-line 2 is 0.59, and treatment-line 3 or more is 0.46. 18% of patients receive three treatments and have an average utility of treatment lines 1, 2 and 3, accounting for having received higher utilities in treatment line 1 and 2, which adds 0.10 to the total PD treatment utility (see table 3). Additionally, patients who received no further treatment and continued on best supportive care are given a utility weight of 0.166 as sourced from progressed disease from Nafees et al. (47).

Group	Treatment line	incidence	utility	weighted qaly's	adjusted for consecutive Rx weighted qaly's
Dacomitinib	1st line	0.42	0.67	0.28	0.28
	2nd line	0.19	0.59	0.11	0.12
	3rd line	0.18	0.46	0.08	0.10
	>3rd line	0.21	0.46	0.10	0.11
		Utility of treatment PD Dacomitinib			**0.62**
Gefitinib	1st line	0.47	0.67	0.32	0.32
	2nd line	0.22	0.59	0.13	0.14
	3rd line	0.14	0.46	0.07	0.08
	>3rd line	0.16	0.46	0.08	0.09
		Utility of treatment PD Gefitinib			**0.63**

Group	Treatment	Incidence	Utility	Weighted Utility
Dacomitinib	BSC	0.43	0.17	0.07
	Treatment	0.57	0.62	0.35
	Utility of PD Dacomitinib			**0.43**
	BSC	0.35	0.17	0.06
	Treatment	0.65	0.63	0.41
	Utility of PD Gefitinib			**0.46**

Table 3: Calculation of Utility for treatment and total

Disutility values for grade 3 or higher adverse events with an incidence of equal to, or higher than, 5% are included. Disutilityies for the adverse events are similarly extracted from the literature. Disutility for diarrhea, dermatitis acneiform, hypokalemia and paronychia are used from Nafees et al. (48). This study seeks to specifically provide health state UK societal utility values for non-small cell lung cancer based on the EQ-5D. Dermatitis acneiform and paronychia are assumed similar to rash. Increased alanine aminotransferase (ALT) and hypokalemia are assumed to have a disutility value similar to febrile neutropenia in the study of Nafees et al.

Duration of diarrhea is determined to be 5.53 days (49). Duration of increased alanine aminotransferase is established to be about 45 days, or 1-2 months (50). Duration of dermatitis acneiform and hypokalemia are assumed to be one cycle length, whilst paronychia is sourced from the literature to be 7 days (51).

To determine the QALY loss, the average disutility per adverse event is calculated (see table 4). The average duration of adverse events is converted from days to years, and consequently multiplied by the disutility to determine the QALY loss per event. The probability of each specific adverse event occurring is then applied to the QALY loss per particular event. Lastly, these are added to establish the average QALY loss per simulated patient. This value is subtracted as a one-off of the accrued QALY's for the Dacomitinib and Gefitinib cohorts.

Group	AE	Incidence	Disutility	Duration (years)	Qaly loss per AE	Expected Qaly loss per AE
Dacomitinib	Diarrhea	0.0837	0.0468	0.0151	0.0007	0.0001
	Paronychia	0.0793	0.0325	0.0192	0.0006	0.0000
	Dermatitis acneiforme	0.1366	0.0325	0.0767	0.0025	0.0003
	ALT increased	0.0088	0.0900	0.1232	0.0111	0.0001
	Hypokalemie	0.0529	0.0900	0.0767	0.0069	0.0004
			Total disutility AE Dacomitinib			**0.0009**
Gefitinib	Diarrhea	0.0089	0.0468	0.0151	0.0007	0.0000
	Paronychia	0.0133	0.0325	0.0192	0.0006	0.0000
	Dermatitis acneiforme	0.0000	0.0325	0.0767	0.0025	0.0000
	ALT increased	0.0844	0.0900	0.1232	0.0111	0.0009
	Hypokalemie	0.0178	0.0900	0.0767	0.0069	0.0001
			Total disutility AE Gefitinib			**0.0011**

Table 4: Calculation of total Disutility

3.10 Resources and costs

Costs in this study are primarily composed of the respective mean reported value per the most recent date as reported in the Dutch Healthcare Authority database, drug costs website, and IMTA-costing tool (52-54). Prices are indexed to year 2019/2020 using the Dutch derived consumer price index or extracted with a more recent estimate from 2020/2021, if available (55) (see table 5 for the index values). This index differs from the regular consumer price index in the exclusion of changes caused by targeted taxation (for example tobacco or alcohol or other consumption related taxes or subsidies). Table 5 includes the normal CPI to provide context.

Yearly Price Adjustment		
Indexing Parameter	Inflation CPI	Inflation CPI derived
index 2002/2003	2.1	1.9
index 2003/2004	1.3	0.9
index 2004/2005	1.7	1.4
index 2005/2006	1.1	1.5
index 2006/2007	1.6	1.5
index 2007/2008	2.5	2.2
index 2008/2009	1.2	0.9
index 2009/2010	1.3	1.1
index 2010/2011	2.3	2.2
index 2011/2012	2.5	2.1
index 2012/2013	2.5	1.3
index 2013/2014	1	0.6
index 2014/2015	0.6	0.4
index 2015/2016	0.3	0.3
index 2016/2017	1.4	1.4
index 2017/2018	1.7	1.4
index 2018/2019	2.6	1.6
index 2019/2020	1.3	1.2

Table 5: CPI for indexing

		incidence of AE	cost per patient
Dacomitinib	Diarrhea	0.08	€ 129.74
	Paronychia	0.08	€ 148.91
	Dermatitis acneiforme	0.14	€ 256.46
	ALT increased	0.01	€ 12.24
	Hypokalemie	0.05	€ 13.82
Gefitinib	Diarrhea	0.01	€ 13.78
	Paronychia	0.01	€ 25.04
	Dermatitis acneiforme	0.00	€ 0.00
	ALT increased	0.08	€ 117.32
	Hypokalemie	0.02	€ 4.65

Table 6: Cost per AE

Costs for treatment include drug costs and adverse event costs. Adverse event costs for Diarrhea, Paronychia and dermatitis were sourced from Wehler et al. (56). Similarly, the cost of increased ALT and hypokalemia were obtained from Campone et al. (57). The costs per patient are then calculated with the cost per adverse event and the incidence (see table 6 and supplementary table 3 for the cost and source per adverse event). A 50% wastage of remaining pills per package of 30 pills is assumed for each patient discontinuing treatment. This because on average it is likely for patients to transition to death or other treatment half-way through their package. This resulted in a cost of € 1471 and € 765 for the wastage of Dacomitinib and Gefitinib, respectively. Wastage for subsequent treatment or at any other stage of the model is not taken into account. Drugs for progressed disease are distributed proportionally as described in the appendix (see supplementary table 2 and 3). Costs are calculated based on the required dosage as monotherapy and cost per milligram for the appropriate indication according to the Dutch Healthcare institute (53) (see table 7 and 8). The required dosage is calculated with the recommended dosage and the average adult Dutch body surface area according to te

Biesebeek et al. (58). The cost per medication is then used in combination with the incidence of that treatment to calculate the medication cost for the Gefitinib and Dacomitinib cohorts per cycle (see table 9). The share of patients not receiving further treatment are given best supportive care as described in the ARCHER 1050 trial and sourced from the Dutch Healthcare Authority. Finally, the proportions of patients receiving BSC and medication are used to compute the total PD cost per cycle per treatment arm (see table 10). Administration costs for intra-venous administration is calculated based on the share of patients receiving the treatment, and the share of treatments received per patient and per cycle (see table 11). The cost of administration is 140 euros per operation (see supplementary table 3).

	Description of calculation per treatment	
	dosage required:	**per period:**
Pemetrexed	500 mg/m2	24.5 days (3 weeks to 4 weeks)
Carboplatin	400 mg/m2	28 days (4 weeks)
Cisplatin	50-120 (average 85) mg/m2	22.5 days (3 weeks to 3.5)
Osimertinib	1 tablet of 80 mg	per day (30 per package)
Docetaxel	75mg/m2	24.5 days (3 weeks to 4 weeks)
Gefitinib	1 tablet of 250 mg	per day (30 per package)
Erlotinib	1 tablet of 150 mg	per day (30 per package)

Table 7: Dosage per treatment

	Cost per mg	administrations per cycle	mg required per treatment	Cost per cycle
Pemetrexed	€ 2.26	1.14	960.00	€ 2,480.46
Carboplatin	€ 3.34	1.00	768.00	€ 2,562.05
Cisplatin	€ 0.45	1.23	163.20	€ 90.99
Osimertinib	€ 2.56	0.93	2400.00	€ 5,740.28
Docetaxel	€ 4.52	1.14	144.00	€ 743.62
Gefitinib	€ 0.20	0.93	7500.00	€ 1,428.56
Erlotinib	€ 0.47	0.93	4500.00	€ 1,957.20

Table 8: Cost per cycle PD treatment

	Dacomitinib		Gefitinib	
	share of total PD medication	cost share	share of total PD medication	cost share
Pemetrexed	0.27	€ 662.08	0.26	€ 644.39
Carboplatin	0.13	€ 337.11	0.15	€ 392.06
Cisplatin	0.16	€ 14.71	0.16	€ 14.57
Osimertinib	0.18	€ 1,035.84	0.19	€ 1,082.69
Docetaxel	0.11	€ 83.87	0.06	€ 47.63
Gefitinib	0.08	€ 107.41	0.09	€ 132.18
Erlotinib	0.07	€ 139.80	0.08	€ 160.20
	Total	**€ 2,380.82**	**Total**	**€ 2,473.72**

Table 9: Proportional PD costs

	proportion treatment	proportion BSC	Cost treatment	Cost BSC	Total cost
Dacomitinib	0.57	0.43	€ 2,380.82	€ 1,359.68	**€ 1,944.47**
Gefitinib	0.65	0.35	€ 2,473.72	€ 1,359.68	**€ 2,082.57**

Table 10: Total PD treatment cost

Dacomitinib		Share of patients using treatment	Doses per cycle	Cycle administration cost
Dacomitinib	Pemetrexed	0.27	1.14	€ 42.57
	Carboplatin	0.13	1.00	€ 18.36
	Cisplatin	0.16	1.23	€ 27.77
	Docetaxel	0.11	1.14	€ 17.99
Gefitinib	Pemetrexed	0.26	1.14	€ 41.43
	Carboplatin	0.15	1.00	€ 21.36
	Cisplatin	0.16	1.23	€ 27.51
	Docetaxel	0.06	1.14	€ 10.22

Table 11: Administration Cost

Healthcare usage is sourced from a study on the resource usage and cost in the Netherlands in patients with advanced EGFR+ NSCLC (59). Healthcare resource usage is converted from yearly values to cycle values. Resource cost was replaced by more current values, as can be found in the database of the Dutch Healthcare Authority (54) (see supplementary table 3). These values are indexed to 2020 values when necessary. Van Pompen et al. describes the average yearly resource usage for two groups; one group that received best supportive care after the first-line treatment, and the other that received further treatment. The total healthcare resource cost is calculated by multiplying the incidence of patients using the resource with the average amount of usage of this resource and its cost (see table 12). This is further processed in the model by calculating resource cost for the proportions receiving best supportive care or further treatment with their respective usage as mentioned in van Pompen et al. (see table 13). Radiotherapy is only used for patients in the best supportive care group in the ARCHER 1050 trial. Consequently, the cost and utilization of radiotherapy is only calculated for the proportion of patients in best supportive care. It is assumed people in the PFS state accrue less costs, so a 10% decrement is applied.

	Resource use /cycle	Resource use /cycle	% Patients	% Patients	Cost per cycle	Cost per cycle
2nd line:	Treatment	BSC	Treatment	BSC	Treatment	BSC
Outpatient visits	2.09	3.18	1.00	1.00	€ 294	€ 449
Hospitalizations	0.42	0.54				
Total length stay	2.81	3.60	1.00	1.00	€ 1,871	€ 2,403
Microorganisms	0.43	0.79	0.68	0.77	€ 14	€ 30
Pathology	0.32	0.47	1.00	1.00	€ 21	€ 30
Radiotherapy	0.42	0.98	0.43	0.35	€ 187	€ 357
CT scan	0.55	0.51	1.00	0.85	€ 85	€ 66
Bronchoscopy	0.09	0.18	0.86	0.73	€ 35	€ 56
Lung function	0.09	0.13	0.64	0.53	€ 4	€ 5
X-ray thorax	0.97	1.13	1.00	0.97	€ 43	€ 49
Xray abdominal	0.10	0.23	0.32	0.26	€ 4	€ 8
Xray spine and hips	0.19	0.35	0.46	0.32	€ 7	€ 9
MRI	0.15	0.16	0.43	0.39	€ 16	€ 15
Ultrasound/Doppler sound	0.14	0.31	0.61	0.46	€ 11	€ 18
Scintigraphy	0.12	0.17	0.82	0.47	€ 26	€ 20
PET scan	0.08	0.14	0.36	0.34	€ 34	€ 52
				Total cost per Cycle	**€ 2,652**	**€ 3,568**

Table 12: Resource use and cost

	Treatment	2nd line	Proportions	Total adjusted for proportions	
PFS	Daco	BSC	0.43	€ 1,525	
		Treatment	0.57	€ 1,412[a]	€ 2,643[b]
	Gefi	BSC	0.35	€ 1,253	
		Treatment	0.65	€ 1,600 [a]	€ 2,567[b]
PD	Daco	BSC	0.43	€ 1,525	
		Treatment	0.57	€ 1,412 [a]	€ 2,936
	Gefi	BSC	0.35	€ 1,253	
		Treatment	0.65	€ 1,600 [a]	€ 2,852

Table 13: Calculation cycle cost Resource use, [a] Treatment groups were multiplied with total cost minus radiotherapy, [b] PFS costs were assumed to be 10% lower

Informal care costs are calculated using values from the IMTA costing tool for the replacement cost of unpaid labor (52). It is assumed that 8 hours of informal care per week is given on average in the PFS state and 12 hours of informal care per week in the PD state. This is in accordance with an earlier report for the Dutch healthcare institute (60). The total cost per cycle for Dacomitinib and Gefitinib were equal (see table 14).

Hours per week	Cost per hour	Cost per cycle
8	€ 14.90	€ 476.94
12	€ 14.90	€ 715.41

Table 14: Informal care cost

Productivity costs are measured with the friction-cost method. The friction period is assumed to be 12.1 weeks as according to the IMTA costing tool (52) (3 $\frac{1}{28}$ cycles). It is assumed that 90% of patients stop working after the diagnosis. Additionally, it is assumed that working patients in the PFS state will work 2 days per week and quit entirely after progression. This equals a loss of 3 working days for these patients. These assumptions are in line with an earlier report for the Dutch healthcare institute (60). The average number of hours worked is sourced from the Dutch bureau of statistics for a population of age 45-75 (61). The median reported age was 62 for the Dacomitinib arm and 61 for the Gefitinib arm. The age range reported in the trial was from 28-87. The average number of hours worked part-time resulted in 23.13 hours per week (see table 15). The mean number of hours worked full-time is assumed to be 37.5 hours per week, as this is the cut off according to the Dutch central bureau of statistics (61). These were consequently combined with their prevalence to produce the average hours worked per week (see table 16). The average Dutch wage as sourced from the IMTA costing tool is consequently used in combination with the average number of hours worked to determine the productivity loss for the friction period (see table 17). For the PFS state, 10% of patients will remain working for 2 days a week, translating to a loss of 3 days per week for the duration of the friction period. Lastly the total cycle productivity cost for the PFS and PD states is calculated (see table 18).

	Share of people	Hours per week
6 (0-12)	0.14	0.84
16 (12-20)	0.15	2.35
24 (20-28)	0.33	7.99
31.5 (28-35)	0.38	11.94
total average hours for part-time workers:		**23.13**

Table 15: Computation of part-time hours

	Probability	Hours per week	Average hours per week
Percentage full-time	0.46	37.5	29.2
Percentage part-time	0.51	23.1	
Unemployment	0.02		

Table 16: Average hours worked per week

	Average wage	Hours	Based on average wage	Cost per cycle
Cost per week	€ 36.99	29.2	€ 1,080.12	€ 4,320.49
Cost per (work)day	€ 36.99	5.8	€ 216.02	€ 864.10
Cost per working patient per week in PFS	€ 36.99	17.5	€ 648.07	€ 2,592.29

Table 17: Cost per cycle

	Proportion	Costs	Total
Cost PD per cycle	1	€ 4,320.49	€ 4,320.49
Cost PFS per cycle	90%	€ 4,320.49	€ 4,147.67
	10%	€ 2,592.29	

Table 18: Total cost per cycle for the friction period

Terminal care costs are based on a report of the Dutch healthcare institute (62). It assumes that 38% of patients require an average of 10.1 additional nursing days in the last three months of life. Costs reported in this document were indexed to the current year and tallied for patients entering the Death state (see table 19).

Incidence	Nursing days	Cost per day	Total cost per patient
38%	10.1	€ 1,172.91	€ 4,501.63

Table 19: Terminal care costs

Travel costs and average distances to the hospital or general practitioner are based on the IMTA costing tool (52). It is assumed that patients use public transportation, taxis or cars in equal measure and never go by foot or bike (see table 20). It is also assumed that parking is always required when patients are travelling by car, causing parking costs to always be added as one third of the original cost (as seen in supplementary table 3 to account for other methods of transportation). For healthcare resource use it is assumed that laboratory and diagnostic tests are combined with hospitalizations, acquiring medication or general practitioner visits. For medication in progressed disease the rationale is that patients travel to the hospital when medication is intra-venously administered, or travel to the pharmacy when it is taken orally after their package is calculated to be empty (30 days). The cost is calculated for each medication separately in the PD state. The final cost is the acquired by computing the cost per proportion receiving the medication (see table 21). The distance to the general practitioner is 1.1 kilometer for outpatient visits. The distance to the pharmacy for picking up pills is 1.3 kilometers. Lastly, the distance to the hospital for intra venous administration, laboratory or diagnostic tests is 7 kilometers. Travel costs are higher in the PD state as a result of requiring intra venous administration at a hospital (see table 22).

	Public transit	Taxi	Car	Average
Cost per km	€ 0.20	€ 3.14	€ 0.20	€ 1.18

Table 20: Average costs per km

		Share treatment	Trips per cycle	Cost parking	Travel cost (p/km)	Distance (km)	Total travel cost
PFS	Outpatient visits		2.1	€ 1.06	€ 1.18	1.1	**€ 4.93**
	Hospitalizations		0.4	€ 1.06	€ 1.18	7	**€ 3.94**
	Treatment		0.9	€ 1.06	€ 1.18	1.3	**€ 2.53**
PD	Outpatient visits		3.2	€ 1.06	€ 1.18	1.1	**€ 7.52**
	Hospitalizations		0.5	€ 1.06	€ 1.18	7	**€ 5.01**
	Dacomitinib						**€ 14.58**
	Pemetrexed	0.27	1.1	€ 1.06	€ 1.18	7	€ 3.74
	Carboplatin	0.13	1.0	€ 1.06	€ 1.18	7	€ 2.15
	Cisplatin	0.16	1.2	€ 1.06	€ 1.18	7	€ 2.96
	Osimertinib	0.18	0.9	€ 1.06	€ 1.18	1.3	€ 1.25
	Docetaxel	0.11	1.1	€ 1.06	€ 1.18	7	€ 2.28
	Gefitinib	0.08	0.9	€ 1.06	€ 1.18	1.3	€ 1.10
	Erlotinib	0.07	0.9	€ 1.06	€ 1.18	1.3	€ 1.10
	Gefitinib						**€ 14.27**
	Pemetrexed	0.26	1.1	€ 1.06	€ 1.18	7	€ 3.67
	Carboplatin	0.15	1.0	€ 1.06	€ 1.18	7	€ 2.33
	Cisplatin	0.16	1.2	€ 1.06	€ 1.18	7	€ 2.94
	Osimertinib	0.19	0.9	€ 1.06	€ 1.18	1.3	€ 1.26
	Docetaxel	0.06	1.1	€ 1.06	€ 1.18	7	€ 1.82
	Gefitinib	0.09	0.9	€ 1.06	€ 1.18	1.3	€ 1.13
	Erlotinib	0.08	0.9	€ 1.06	€ 1.18	1.3	€ 1.11

Table 21: Calculation of travel costs per cycle per patient

		Cost	Total cost
PFS	Outpatient visits	€ 4.93	
	Hospitalizations	€ 3.94	
	Treatment	€ 2.53	**€ 11.40**
PD	Outpatient visits	€ 7.52	
	Hospitalizations	€ 5.01	
	Dacomitinib PD	€ 14.58	**€ 27.11**
	Outpatient visits	€ 7.52	
	Hospitalizations	€ 5.01	
	Gefitinib PD	€ 14.27	**€ 26.80**

Table 22: Total travel costs per cycle, treatment and disease state

3.11 Sensitivity analysis

This economic evaluation includes a univariate sensitivity analysis, probabilistic sensitivity analysis, multivariate scenario analysis and a value of information analysis. The decision to model the PFS curves using a Weibull distribution is made based on having the lowest AIC values. The decision to model the OS curves with a Weibull distribution is not based on having the lowest AIC value, but on having the second lowest AIC value in combination with a more plausible survival duration (see table 2 and figure 2). The effect of using the loglogistic curve for the OS group is evaluated in the scenario analysis. Additionally, the effect of using other methods of extrapolation for both arms is investigated. Other researched scenario's include using utilities from varying papers, researching the effect of increasing or decreasing the time-horizon, and excluding wastage and informal care costs. Utility values for their respective scenario are selected because of their use in other studies and the preexisting use of the

disutility values for adverse events in this analysis (45, 63). Investigating the timeframe is similarly done to accommodate comparison across cost-effectiveness research. The effect of additional cost of travelling to each intervention individually for healthcare resource use, such as x-rays, is investigated. Lastly, taking into account the gender pay gap and reported male to female ratio from the trial, the productivity costs are calculated again and used for a scenario analysis.

A univariate sensitivity analysis is done to test the impact of variation in singular parameters. A 15% variation for all parameters (except multiway probabilities or variation in the extrapolation function) is used to research the relative impact on the ICER. A multiway sensitivity analysis is done to investigate the effect of changes in several linked parameters, such as increasing all healthcare resource costs, travel costs, AE costs, medication costs for PD and PFS state, and utilities and disutilities. These parameters are varied with both 10% and 20% to see their relative impact and the influence of increasing variation. A probabilistic sensitivity analysis is run for 1000 iterations, varying parameters and the extrapolation function simultaneously based on their assumed distributions. A gamma distribution is chosen for costs, disutilities and resource use as advised by the literature (31). The values, standard errors, distributions and sources of parameters used in the PSA are presented in supplementary tables 2 and 3. Most cost parameters were varied with a 10% standard error assumption. Healthcare resource use was varied with a standard error based on a calculation of a standard deviation with the median, sample size, minimum and maximum value based on data from Pompen et al. as described by Wan et al. (59, 64). The standard deviation of PD utility was available and used to compute the standard error. Beta and Dirichlet variations were determined using the sample size and incidence. The required cost-effectiveness threshold is calculated using the IMTA burden of disease calculator (39). A value of information analysis is performed with the resulting iterations of the PSA.

A technical validation was done using the TECH-VER Checklist (65) (see Appendix 7.7). The results of this assessment are located in the appendix. This verification is done to determine whether there are no crucial coding mistakes, if relevant parameters are investigated in the sensitivity analyses, if the right distributions are used, and if there are no other oversights in Excel or the methodological approach. No large deficiencies were identified, but a validation from an external institution using multiple validation techniques is indicated for a more credible assessment.

Chapter 4: Results

4.1 Deterministic results:

The total cost for Dacomitinib and Gefitinib result in € 272,424 and € 204,422 on average, respectively, per patient for the total duration of treatment in the base case analysis (see table 23). The main influential increments accrued are the treatment costs in the PFS state (€ 36,031.62), the healthcare resource costs in PFS and PD state (€17,871.96 and €7,494.34) and the QALY's in the PFS state (0.35) (see table 3). All costs are higher for the Dacomitinib group, except for productivity cost in both the PFS and PD states. More QALY's are accrued in the Dacomitinib arm in comparison with the Gefitinib arm, respectively 2.11 and 1.74 with an increment in favor of Dacomitinib of 0.37 (table 2). The ratio of incremental costs and QALY's results in a deterministic base case ICER of € 181, 558 per QALY gained. Additionally, the ratio of incremental costs and life years results in € 84,388 per life year gained. This is not cost-effective using the highest threshold operated in the Netherlands of € 80,000. Most costs are accrued from healthcare resource use (see table 24). The largest increment from the disaggregated results is from the first-line treatment (€ 36,032). The largest number of life years and QALY's are accrued in the PFS state.

Treatment	Costs	QALY	LY
Dacomitinib	€ 272,424	2.11	3.78
Gefitinib	€ 204,422	1.74	2.98
Increment	€ 68,001	0.37	0.81
ICER:		**incremental costs/QALY**	**incremental costs/LY**
Dacomitinib vs Gefitinib		€ 181,558	€ 84,388

Table 23: Deterministic results

Treatment	Dacomitinib	Gefitinib	Increment
Costs in PFS state			
Drug acquisition costs PFS	€ 56,155	€ 20,124	€ 36,032
HC resource use PFS	€ 54,034	€ 36,162	€ 17,872
AE costs PFS	€ 561	€ 161	€ 400
Informal care PFS	€ 9,751	€ 6,719	€ 3,033
Productivity costs PFS	€ 12,099	€ 12,101	-€ 2
Travel costs PFS (incl. resource travel)	€ 233	€ 161	€ 72
Drug Wastage PFS	€ 1,378	€ 732	€ 647
Costs in PD state			
Drug acquisition costs PD	€ 45,479	€ 44,672	€ 806
Administration costs PD	€ 2,495	€ 2,156	€ 339
Informal care PD	€ 16,732	€ 15,346	€ 1,387
Productivity costs PD	€ 293	€ 318	-€ 26
Travel costs PD	€ 634	€ 575	€ 59
HC resource use PD	€ 68,679	€ 61,184	€ 7,494
End of life costs			
End of life costs	€ 3,899	€ 4,012	-€ 113
Life years accrued			
LYs accrued in PFS state	1.66	1.12	0.54
LYs accrued in PD state	2.12	1.86	0.27
Quality adjusted life years accrued			
QALYs accrued in PFS state	1.27	0.92	0.35
QALYs accrued in PD state	0.85	0.83	0.02
QALYs lost due to adverse events	-0.0009	-0.0011	0.0002

Table 24: Disaggregated deterministic results

4.2 Univariate sensitivity analysis:

In the univariate sensitivity analysis parameters are individually varied with 15% to discern their relative impact on the cost per QALY and LY ratios (see supplementary table 4). Most impactful were variations in cost and utility of treatment with Gefitinib and Dacomitinib. The absolute largest variation in cost per QALY is estimated to be after 15% variation in the utility of Dacomitinib (€ 120,417 to € 368,827). The highest cost per life year ratio is found in a 15% increase in the cost of Dacomitinib (€ 73,678 to € 95,098). The lowest cost per life year is approximated to be after a change in distribution from a Weibull to a lognormal distribution (€66,475). Variations in the discount rate of costs and outcomes were also impactful on the cost per QALY and LY outcomes relative to similar changes made in other parameters. Furthermore, the cost and length of hospitalization, variations in cost of- or hours per week of delivered informal care, the proportions of treatment versus best supportive care in progressed disease state and their respective utilities, and choice of distribution were relatively more influential on the ICER. The impact of variations in the cost of Dacomitinib and Gefitinib are as a result also shown in the tornado diagram with the results of the multiway sensitivity analysis (see figure 3). The effects of 15% variations in most other parameters are presented in supplementary table 4.

4.3 Multivariate sensitivity analysis:

The multiway sensitivity analysis varies multiple parameters simultaneously with 10% and 20%. Parameters that are related to each other were varied concurrently. The price of Gefitinib and Dacomitinib are also included, despite not consisting of multiple variables, because of their expected effect on the ICER. Varying the primary treatment utility, price of Dacomitinib and healthcare resource use costs had the most significance for the ICER (see figure 3 and supplementary table 5). Varying the disutilities for the adverse events had the least impact on the ICER (see supplementary table 5) (ICER at +20%: € 181,542 versus -20%: € 181,574). At +20% of the utility of Gefitinib and Dacomitinib, the ICER decreased to € 151,309 per QALY, whilst it increased to € 226,923 per QALY at -20% of the utility parameters. Decreasing the utility had a larger influence on the ICER than increasing it (+20%: -€ 30,249 versus -20%: € 45,365), likely because a reduction in utility reduces the incremental QALY's per cycle and total QALY's gained. Varying parameters with 20% increased the discrepancies between the two extremities to a greater extent when compared to a 10% variation (see figure 3 and supplementary table 5). The incremental costs, incremental QALY's and ICERS for all varied parameters are located in supplementary table 5.

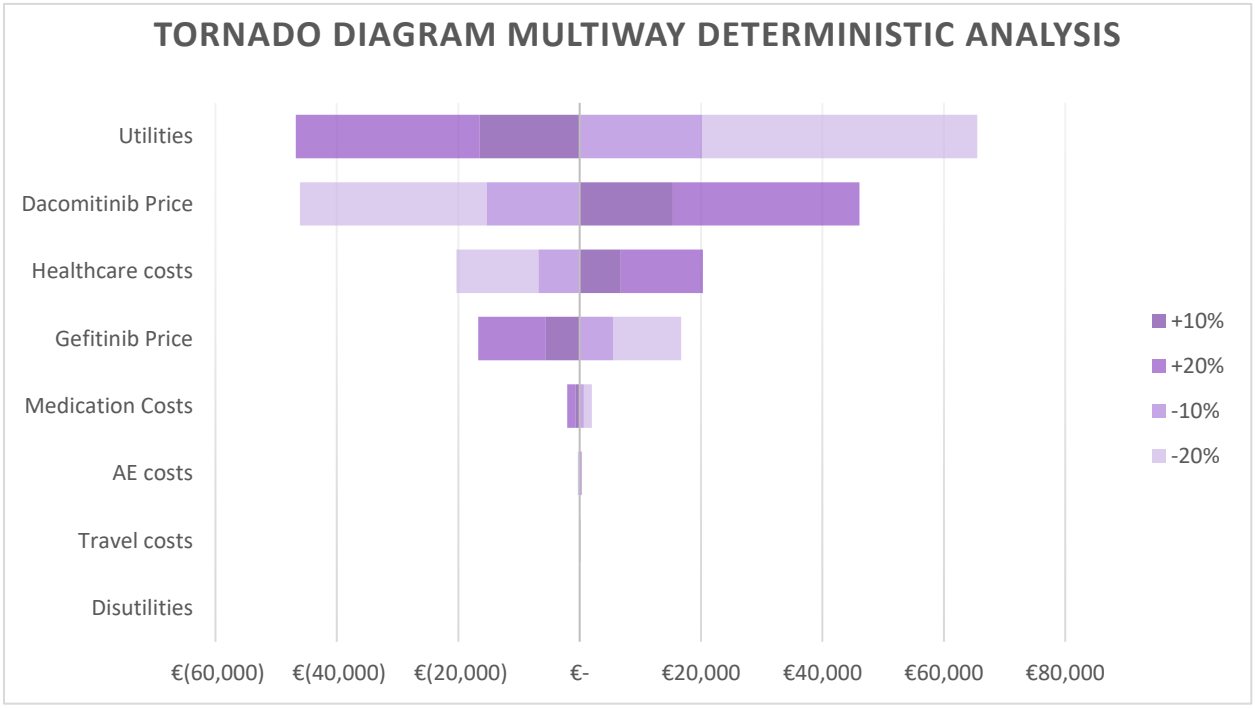

Figure 3: Tornado diagram of Multiway sensitivity analysis and price variation

4.4 Scenario analysis:

The ICER increased when shortening the time horizon, and reached a point between 1 and 3 years where it is no longer beneficial to use Dacomitinib regardless of price due to larger accumulation of QALY's by patients treated with Gefitinib (see supplementary table 6). This is exemplified by the ICER turning negative (-€ 585,750 per QALY), meaning in this case that the incremental QALY's are negative and the treatment has increased costs for decreased benefits in comparison to Gefitinib. This is the consequence of Dacomitinib being assumed to have a lower utility than Gefitinib. Setting the time horizon to 1 year yields the highest cost per life year in this scenario analysis (€ 16,665,212 per life year). Changing the extrapolation function decreases the ICER in all instances, and the most when using a lognormal function (€ 137,022 per QALY) (see supplementary table 6). Additionally, utilizing a lognormal function also decreases the cost per life year to the minimum in the scenario analysis (€

68,849). Changing the utilities in accordance with values not from the ARCHER 1050 trial all decreased the ICER. Using values from a Dutch report to the Dutch healthcare institute decreased the ICER the most of these values (€ 121,258 per QALY), possibly because it has the highest PD utility value. This is further exemplified when changing the utilities to the values of Nafees et al. (2017), where the PFS is the highest utility value of the three utility scenario's but the ICER is not affected the most (cost per QALY is € 137,453) (see supplementary table 6).

Excluding the wastage cost lowered the ICER (cost per QALY is € 179,831) (see supplementary table 6). Excluding informal care cost was more influential, causing the ICER to drop to € 169,758 per QALY. Controlling for the gender wage gap and disproportionate male to female ratio did not significantly impact the ICER (€ 181,632 per QALY), nor did increasing the travel costs by having patients travel to all healthcare resource use separately (€ 182,408 per QALY). The incremental costs, incremental QALY's and ICERS for all scenarios are located in supplementary table 6.

4.5 Cost-effectiveness threshold:

The results from the IMTA burden of disease calculator are illustrated in table 25. The inputs from the PSA, excluding discounting, illustrate a mean expected number of life years of 1.8 for Gefitinib, with a standard deviation of 0.13. The mean absolute shortfall is calculated to be 17.4 years (see table 25). Furthermore, the mean proportional shortfall is estimated to be 0.91. There is a 100% chance of a €80,000 threshold for this disease severity in the Netherlands. To reach this threshold, the price of Dacomitinib is supposed to decrease with 66.1% from € 98.09 to € 33.24 per pill.

	Deterministic results - Mean	Probabilistic results - Mean ; 95%CI	Lower	Higher
Remaining QALYs with standard treatment	1.8	1.8	1.55	2.05
QALYs without disease (corrected for age and gender)	19.59	19.2	18.13	20.17
Absolute QALY loss (absolute shortfall)	17.79	17.4	18.12	16.58
Proportional shortfall	0.91	0.91	0.89	0.92

Table 25: : IMTA burden of disease calculator results

4.6 Probabilistic sensitivity analysis:

The probabilistic sensitivity analysis was run for 1000 simulations. The mean cost of Dacomitinib is € 272,433 versus € 204,513 for Gefitinib (see table 26). The 95% ranges are € 233,203- € 317,654 for Dacomitinib and € 176,053- € 235,631 for Gefitinib. The 95% interval for life years gained is 3.27-4.37 for Dacomitinib and 2.65-3.34 for Gefitinib. Similarly the 95% extent for QALY's is 1.78-2.46 for Dacomitinib and 1.50-1.98 for Gefitinib (see table 26).

The mean ICER, calculated with the mean incremental cost and utility, is € 178,791. This is relatively similar to the base case deterministic ICER of € 181,558. The resulting 95% ICER range is € -293,210 to € 760,415.19. The complete range is from € -28,536,689 to € 10,536,084 after a thousand simulations. These high and low values are the consequence of the probability of small (close to zero) incremental utilities occurring as a result of the chosen utility of Dacomitinib being lower than Gefitinib. The average cost per life year is € 84,633, as calculated with the mean incremental cost and life years. This is again similar to the base case ICER of € 84,388 per life year. The 95% ICER range is € 27,495 to € 110,763 per life year gained. The maximal ICER range is € 11,080 to € 141,683 per life year gained. The results are illustrated in figures 4 and 5. Figure 4 shows all the iterations of the PSA and their respective differences in costs and QALY's. The line is a depiction of the cost-effectiveness threshold, which is established to be € 80,000 per QALY. Iterations falling below this line are considered to be cost-effective, since the cost per QALY would be below this threshold. The CEAC is a representation of the probabilities of these simulations to be cost effective at different thresholds. The probability of Dacomitinib being cost-effective at a threshold of € 80,000 is 1%, as can be seen in figure 4 and 5.

	Cost Dacomitinib	Cost Gefitinib	LY Dacomitinib	LY Gefitinib	QALY Dacomitinib	QALY Gefitinib
Mean	€ 272,433	€ 204,513	3.78	2.98	2.12	1.74
Minimum	€ 208,891	€ 161,696	2.90	2.50	1.52	1.36
Maxium	€ 373,448	€ 283,472	5.00	3.52	2.71	2.10
St dev	€ 21,346	€ 15,707	0.28	0.18	0.17	0.12
2.5th percentile	€ 233,203	€ 176,053	3.27	2.65	1.78	1.50
97.5th percentile	€ 317,654	€ 235,631	4.37	3.34	2.46	1.98

Table 26: Probabilistic results

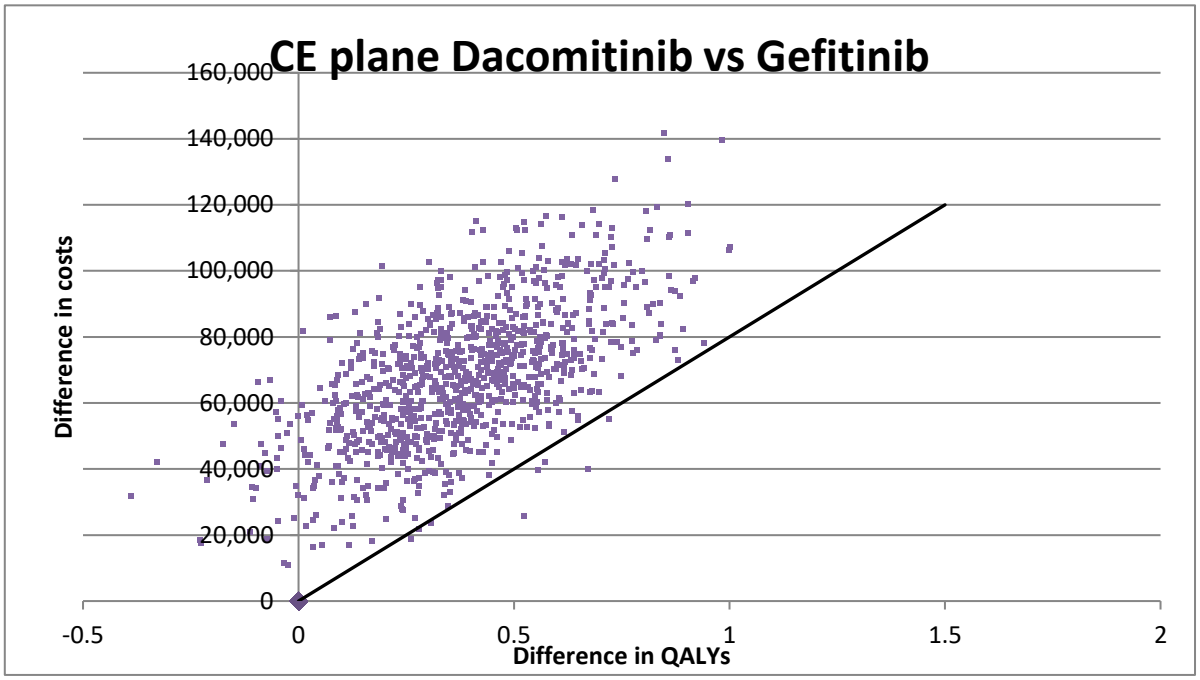

Figure 4: cost-effectiveness plane

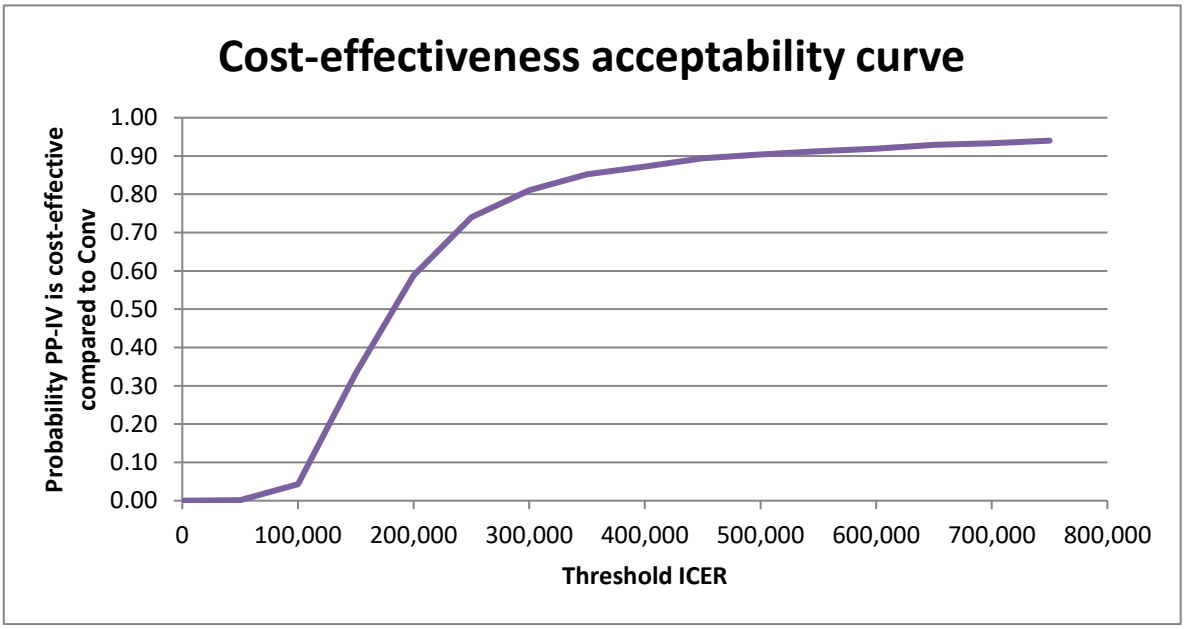

Figure 5: Cost-effectiveness acceptability curve

4.7 Value of information analysis:

At a threshold of € 80.000 Dacomitinib is unlikely to be cost-effective. At this threshold the expected value of perfect information for the entire population is expected to be between € 570,607 and € 82,914 (see table 27 and figures 6, 7 and 8). This is an indication of the risk of reimbursement. This value is based on the probabilistic analysis and only takes uncertainty in varied parameters into account. Assumptions and decisions, such as the choice of extrapolation model, are not accounted for in this analysis. The risk is dependent on the current ICER and changes in price or other parameters will change the risk paired with reimbursement. Three scenarios for the expected time horizon of the new treatment are included. The two extremes of the calculated number of eligible patients were used for this analysis (533-1255 new patients). In total 6 different EVPI scenarios are presented in table 27 and figure 6.

	population 1255	population 533
10 years	570,607	242,337
5 years	313,189	133,012
3 years	195,230	82,914

Table 27: popEVPI results at threshold

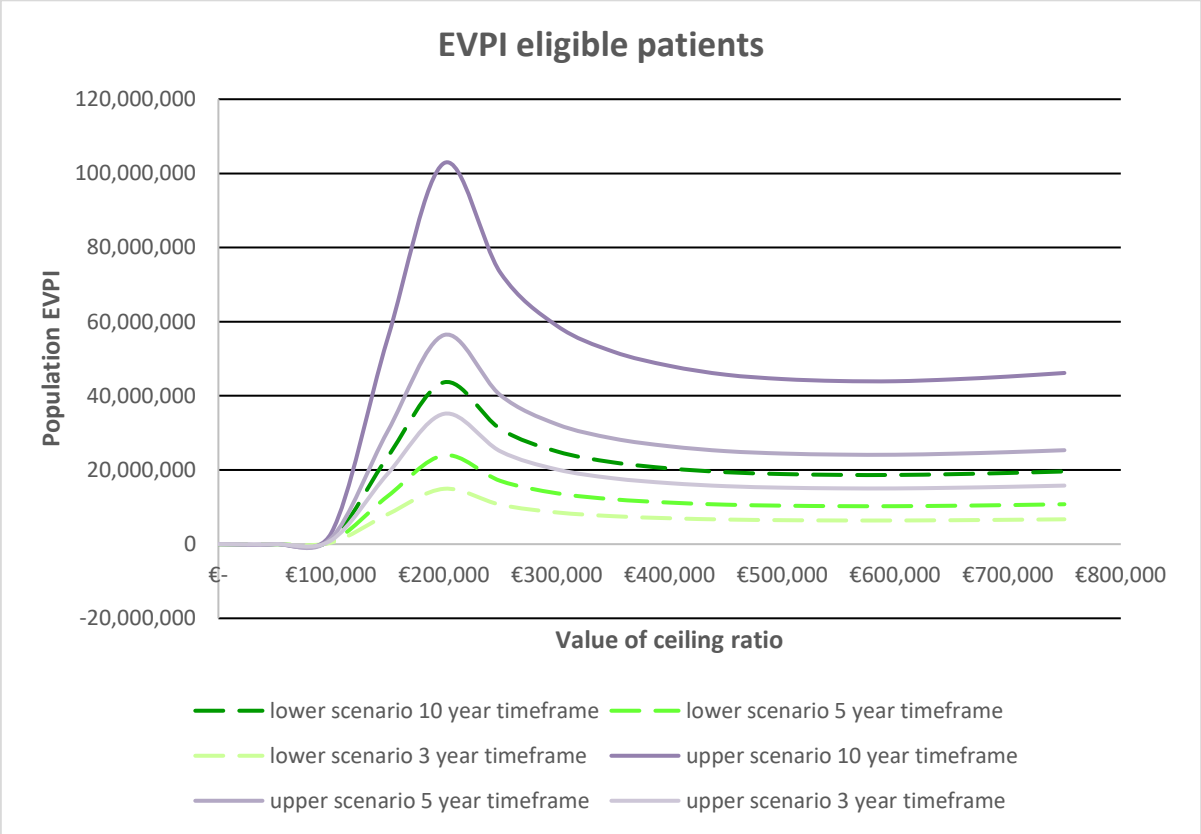

Figure 6: EVPI of lower and upper scenario for 3,5 and 10 years

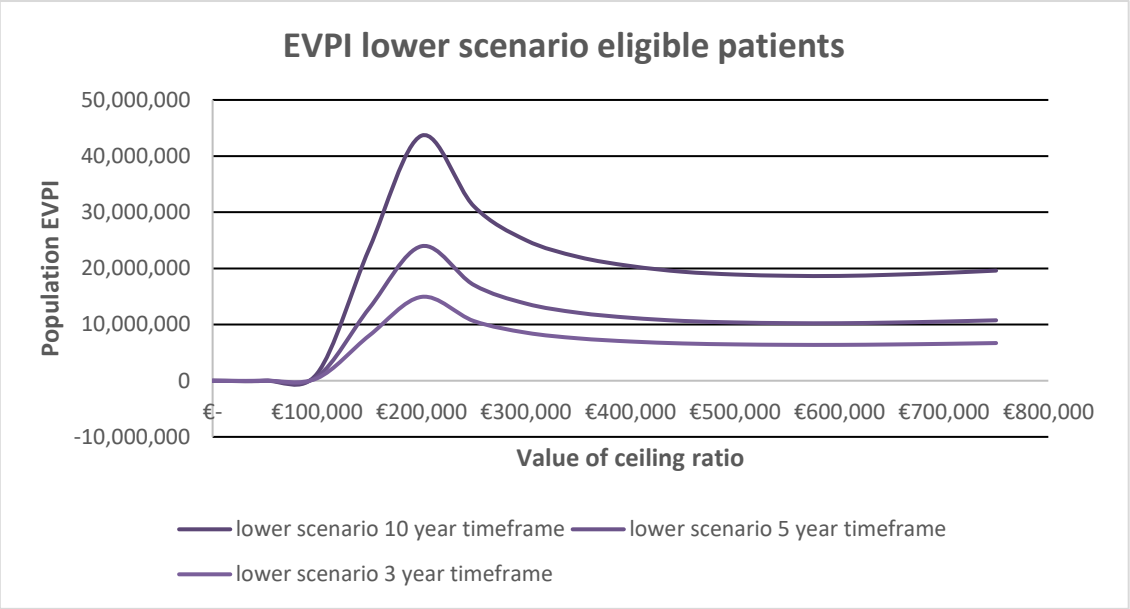

Figure 7: Separate EVPI lower population scenario

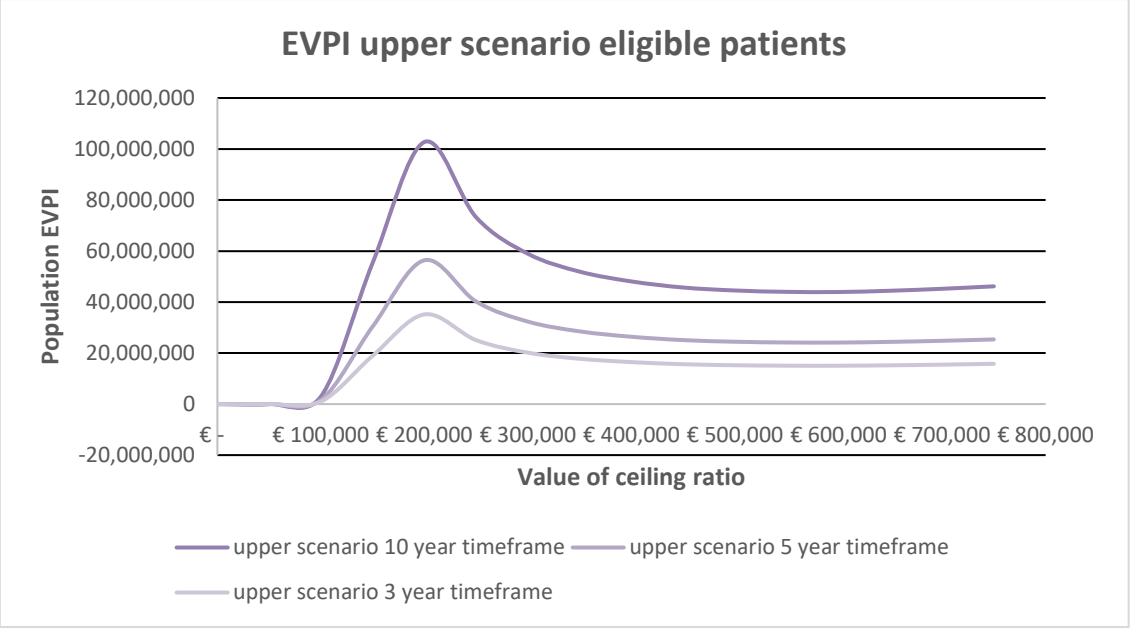

Figure 8: Separate EVPI upper population scenario

Chapter 5: Discussion

5.1 Literature

Current literature is not unanimous on the cost-effectiveness of Dacomitinib. All current studies do base their research on the ARCHER 1050 trial. Dacomitinib did appear to be cost-effective in comparison with Gefitinib in a Chinese study from 2018 (ICER of CNY 62,852 (€8,108) per QALY) (44), but not in a Spanish study from 2021 (ICER of € 111,048 per QALY) (63). The Chinese study by Yu et al. lacked detail since it was published as a poster, but assumed a willingness to pay threshold of 3 times the Gross domestic product per capita (GDP) (44). Using this threshold for the Netherlands yields a cost-effectiveness threshold of € 140,142 utilizing 2019 data (66). The remaining difference can be explained by the higher healthcare resource use cost and lower progressed disease utility in this study. The Spanish study by Aguilar-Serra et al. used a 15-year time-horizon in which Dacomitinib had a remaining overall-survival of 20% at the end of modelling. Compared with Gefitinib, Dacomitinib had significantly extended time to accrue QALY's which could clarify the lower reported ICER. Additionally, the cost for Gefitinib is about 30% higher in the study by Aguilar-Serra et al. as opposed to this study, while the cost per cycle for Dacomitinib is similar. The healthcare costs in this study are also higher, increasing the cost per QALY. A Swedish study found Dacomitinib to be cost-effective in comparison with Osimertinib and Afatinib, but did not compare Dacomitinib to Gefitinib (45). It is likewise possible that Dacomitinib is cost-effective versus Osimertinib and Afatinib in the Netherlands. The National Institute for Health and Care Excellence (NICE) reconsidered an initial recommendation based on changes in drug pricing (67). It currently recommends the use of Dacomitinib for treatment when provided according to the commercial agreement. The ICER and price agreement are confidential, which complicates making a comparison. The Pan-Canadian oncology drug review from 2019 found an ICER after reanalysis of the submitted model of $114,350 (€77,470) per QALY (68). An incremental cost of $ 38,521 canadian dollars (€ 26,230) and an incremental QALY of 0.34 are reported. This study had a similar incremental QALY of 0.37. The difference Is therefore caused by a difference in costs. Since no disaggregated results are reported, a cause of the difference in incremental cost cannot be identified. A study from a US payer perspective from 2021 did not find Dacomitinib cost-effective versus Gefitinib (ICER of $329,120.85/€271,918 per QALY) (69). The study by Zhang et al. reports high Dacomitinib costs, which could be explanatory for the increased cost per QALY compared to this study. In contrast, another study in a US and China setting did find Dacomitinib to be cost-effective (70). This study by Xu et al. found an incremental QALY of 0.55 and an incremental cost of 330.14 dollars for a US setting, resulting in an ICER of 600.69 US dollars. The ICER for China was not reported, since Dacomitinib was cheaper and more effective. The difference in price between Gefitinib and Dacomitinib was lower: $ 7,385 versus $ 6,218 for Dacomitinib and Gefitinib, respectively. Healthcare costs other than medication were not reported, and could have influenced the result.

Discrepancies between the studies can generally be explained by the perspective taken and variations in costs and utilities used (due to national differences in cost of labor or medication). Taking the societal perspective could increase costs, as well as having higher labor costs and a higher Dacomitinib price. Additionally, large variations in healthcare resource costs and usage is reported in studies taking a societal or hospital perspective. Healthcare usage in this study is based on relatively old data for patients with advanced NSCLC in the Netherlands (2005) and might be an overestimation of current additional healthcare use for patients with novel treatment for EGFR+ advanced NSCLC. Especially taking into account that patients with EGFR activating mutations respond better to TKI and report less toxicity compared to NSCLC patients without EGFR activating mutations (71). This could also translate to making less use of healthcare resources. Other studies report using time horizons of 10 (Zhang et al., Xu et al.) or 15 (Aguilar et al., Wu et al., Nilsson et al., pan-Canadian oncology drug review) years

(3, 45, 63, 68-70). The pan-Canadian oncology drug review shortened the time-horizon to seven years in the reanalysis, increasing the ICER. Shortening the time-horizon in this study also increased the ICER, but a horizon of 15 or 9 years did not impact the ICER significantly.

5.2 Inputs

The decision to extrapolate OS and PFS using a Weibull function was impactful on the ICER. According to the AIC the loglogistic function was a better fit for the overall survival arm, and this results in a lower ICER (€ 171,894 versus € 181,558). Choosing an exponential or lognormal function further decreases the cost per QALY. This is the result of prolonged survival of Dacomitinib, increasing the incremental QALY's and lowering the ICER. A survival beyond 20 years of larger proportions of the study population seems unlikely even for patients with TKI for EGFR activating mutations (25). As a result, the second best fit was picked for the base case analysis. A scenario analysis was consequently executed to evaluate and illustrate the impact of using a loglogistic, lognormal or exponential method for extrapolation on the ICER.

Since the utilities for PD and PFS are sampled individually, it is possible for the utility of PD to be higher than the utility of PFS in the PSA. This is not likely to be reflective of reality. The utility for Dacomitinib is assumed to be lower than the utility of Gefitinib. This can cause a negative increment in utility, or a very low increment causing high extremities in the cost per QALY in the PSA. The decision to model Dacomitinib with lower utility than Gefitinib comes from self-reported health related quality of life in the ARCHER 1050 study (44, 45, 72). There is reason to assume a lower utility for Dacomitinib, but not all available cost-effectiveness studies do so (63, 69). Scenario's with values for utility according to Nafees 2008, 2017 and as used in a Dutch study for the Dutch healthcare institute were researched (47, 48, 73). For comparison, Aguilar et al. used Nafees et al. (2008), Xu et al. used values from Nafees et al. (2017) (47, 48, 63, 70). The values from the Dutch report on Pembrolizumab were investigated, since they were gathered from a Dutch population. The decision was made to use the utility values as reported in the trial for the base case scenario, because these were specific to Dacomitinib and Gefitinib and used the British EQ-5D tariff for generalizability with the adverse events. The utilities from the Pembrolizumab report do not make a distinction between squamous and non-squamous NSCLC. All scenario's using similar utility values for Dacomitinib and Gefitinib resulted in lower costs per QALY, regardless of the height of the utility for the PFS or PD state. It is notable that the lowest ICER was found using the Dutch tariff, and this may be an indication to do further research on the Dutch utility values for EGFR+ NSCLC patients on different treatment regiments. Utility in the last three months could be lower due to worsening of disease, this was not modelled. Lowering utilities in the last three months of life would lower the amount of QALY's accrued in the PD state and as a result lower the incremental QALY's. This would result in a higher ICER.

Grade 3 AEs occurring in 5% or more of the population were modelled as a one-off. AEs that were rare but very costly may as a result be missing from the analysis. The incidence of adverse events is based on the ARCHER 1050 trial and could not be reflective of Dutch real-world frequency and prevalence due to patients with brain metastases not being included, usage of other treatment options in PD state in the Netherlands, or unknown factors causing a discrepancy. Disutility values of AEs do not meaningfully impact the ICER in the univariate and multiway sensitivity analyses. Disutility values for increased ALT and hypokalemia are assumed to be similar to febrile neutropenia, and values for dermatitis acneiform and paronychia are assumed to be comparable to rash. This result could be an over or under estimation. Similarly, the duration of dermatitis acneiform and hypokalemia are assumed to be one cycle length. The cost of paronychia and dermatitis acneiform were again assumed to be similar to rash. Changes in the disutility, duration, cost or incidence of adverse events are not

expected to cause significant variation in the ICER according to the univariate and multivariate sensitivity analyses.

The cost of Gefitinib and Dacomitinib is based on the cheapest available option on the Dutch drug cost database (27). Dacomitinib does not vary in price, but Gefitinib can come in more expensive variants produced by other manufacturers. Increasing the cost of Gefitinib would lower the cost per QALY. The price of Dacomitinib and Gefitinib are not varied in the PSA, as the current price of Dacomitinib is only available at one price and does not vary. It is compared to the best case of Gefitinib, where it is assumed that the least expensive option is used by healthcare providers. Wastage costs are only calculated for first line treatment with Dacomitinib and Gefitinib. Wastage was not calculated for Gefitinib in the PD state for patients transitioning from Dacomitinib to Gefitinib. Adding wastage for the PD state could increase the ICER due to the Dacomitinib arm having an extended period for wastage cost accumulation.

The cost of progressed disease medication is based on the cheapest variant from the same drug database as the first line treatment. Only cost is varied in the PSA, dosage remains constant. The body surface are is varied, nevertheless causing the required dosage to alter slightly between iterations. The incidence of these treatments are based on the reported proportions in the ARCHER 1050 trial, and the use of second- and third-line treatment could be different in Dutch clinical practice. For example, treatment was assumed to be given as monotherapy since no information on combination treatment was available. In reality chemotherapy is often given in combination therapy of two or more.

Healthcare resource usage is varied using a standard error calculated with the number of patients per parameter, and a standard deviation based on the range and median as calculated with a method by Wan et al. (64). This method does assume a normal distribution of the original usage. It is not unlikely that the original distribution is skewed, and this method for the estimation of the standard deviation might not be reflective of reality. The healthcare costs do impact the ICER and a smaller or larger standard error due to incorrect calculations could impact the uncertainty of the outcome found in the PSA. It is assumed radiotherapy is only given in the best supportive care state, as happened in the ARCHER 1050 trial. Contemporary Dutch practice deviates from this, and radiotherapy is given in the PFS state for locally metastasized NSCLC. This would increase the costs overall and specifically for the Dacomitinib arm as a result of longer progression free survival, potentially increasing the ICER.

Parameters with unknown distributions and insufficient information to calculate the standard error are varied with a standard error of 10%. This assumption is done similarly in other economic analyses and based on similar sized variations in parameters with known distributions. This assumption could be unfounded. Most cost parameters are varied with a standard error of 10% in this study, but apart from the cost of hospitalization or informal care these parameters are unlikely to impact the ICER. The cost of hospitalization is influential on the ICER, but uncertainty is coupled with the length of stay. The length of hospital stay is varied independently with a computed standard error estimate based on the standard deviation from the article by Wan et al. instead of an assumption. This should incorporate sufficient and more realistic variation for the uncertainty in cost of hospitalization compared to exclusively using a 10% standard error assumption for both cost and length of stay.

Informal care is assumed to be 8 hours a week in PFS state and 12 hours per week in PD state. This is not determined based on population research and could deviate from reality. Since informal care costs do impact the ICER, increased hours of unpaid work will raise the ICER. Similarly, the assumptions for productivity costs of 90% quitting after diagnosis and the remaining ten percent continuing with work for 2 days per week during the PFS state may not hold in reality. However, productivity costs do not impact the ICER significantly as can be seen in the univariate analysis.

The expected value of information for the two population scenario's is based on a rough calculation of the eligible population and does not take into account patients rejecting the medication or being excluded as a result of comorbidities. Nor does it take into account trends in lung cancer incidence or trends for the stage at time of diagnosis.

This study took a model approach, because of the absence of available real-world data. As a result, the outcome of this study is conditional on the legitimacy of the assumptions made in the model. These assumptions were tested with various sensitivity analysis, which illustrate the influence of the uncertainty of these assumptions on the result. Since this model was based on survival data from the ARCHER 1050 trial, characteristics of the trial might limit generalizability. The ARCHER 1050 population consisted disproportionately of Asian patients (77%) and might therefore be less reflective of a Dutch population. Current research does not suggest problematic heterogeneity as a result, since disease progression between the groups is similar (25, 26). Similarly, the health status of these patients at randomization could be regarded as better than expected in the general population as a result of inclusion and exclusion criteria. Additionally, patients with central nervous system metastases were not included in the trial. The effect of Dacomitinib on patients with CNS metastases is unknown and could influence the ICER by cause of changing the number of accrued QALY's. Lastly, this study did not take dose reductions into account. For Dacomitinib the current listed price of reduced doses does not differ from the usual dose. For Gefitinib dose reductions could potentially reduce costs and therefore increase the incremental costs and ICER.

Further research could focus on doing a subgroup analysis of patients with the different mutations (exon 19 deletion and L858R mutation), and on Asian and non-Asian population. This data is already available in the ARCHER 1050 trial, although the subgroup analysis of non-Asian people would be limited by the small number of patients. A cost-effectiveness study using a network meta-analysis to compare Dacomitinib with Osimertinib is also indicated.

5.3 Policy implications:

Dacomitinib is authorized for the European market but is not currently reimbursed in the Netherlands. Treatment in the first-line of EGFR activating NSCLC with Dacomitinib is beneficial but costly compared to Gefitinib. The willingness to pay threshold is calculated to be € 80,000 for the burden associated with stage 3b or 4 NSCLC. The cost per QALY ratio in this analysis remains above this threshold in all instances. Only in the most optimistic instance, combining scenarios lowering the ICER, there is a chance for cost-effectiveness of Dacomitinib compared with Gefitinib from a societal perspective in the Netherlands. Other advisory institutions for policymaking abroad have already advised against the reimbursement of Dacomitinib, or have re-evaluated earlier decisions based on undisclosed pricing agreements (67, 68). At the time of the ARCHER 1050 trial research, Gefitinib was a treatment option in the first-line treatment of EGFR activating NSCLC patients. More treatment options are currently available in the Netherlands, such as Erlotinib, Afatinib and Osimertinib (2). Osimertinib is preferable as it is related to longer OS and PFS, but it is not cost-effective in a Dutch setting (21). Additionally, Osimertinib is paired with better quality of life. Research comparing the effectiveness and cost-effectiveness of Osimertinib versus dacomitinib is warranted. An agreement with a price reduction of about 66% is seemingly necessary to reach the cost-effectiveness threshold in this study. A strategy to mitigate waste could aid slightly in reducing the Dacomitinib price. The significant life extension of treatment with Dacomitinib does necessitate further discussion to prevent a negative reimbursement decision.

6. References:

6: References

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7. Appendix:

7.1 Extracted KM values

PFS			OS		
	Dacomitinib	Gefitinib		Dacomitinib	Gefitinib
Time (months)	*KM*	*KM*	**Time (months)**	*KM*	*KM*
0.00	1	1	**0.00**	1	1
0.75	0.987049	0.992317	**1.50**	0.980677	0.992014
1.50	0.957191	0.950048	**3.00**	0.975667	0.974634
2.25	0.933224	0.929627	**4.50**	0.953911	0.970553
3.00	0.923427	0.930155	**6.00**	0.934504	0.964786
3.75	0.895062	0.899932	**7.50**	0.922137	0.963117
4.50	0.885036	0.875712	**9.00**	0.897466	0.940417
5.25	0.869426	0.867581	**10.50**	0.88301	0.903128
6.00	0.808849	0.805377	**12.00**	0.85698	0.864522
6.75	0.795488	0.79048	**13.50**	0.850551	0.827874
7.50	0.758988	0.690532	**15.00**	0.827825	0.76816
8.25	0.744401	0.673097	**16.50**	0.79801	0.730935
9.00	0.720732	0.661446	**18.00**	0.779089	0.676639
9.75	0.675095	0.560545	**19.50**	0.743873	0.671124
10.50	0.675094	0.536701	**21.00**	0.727203	0.627695
11.25	0.636595	0.457266	**22.50**	0.70047	0.594687
12.00	0.634227	0.433731	**24.00**	0.671004	0.571243
12.75	0.607506	0.425979	**25.50**	0.644092	0.542965
13.50	0.558279	0.365928	**27.00**	0.607552	0.500503
14.25	0.55828	0.352084	**28.50**	0.588407	0.482413
15.00	0.524721	0.303056	**30.00**	0.565809	0.453363
15.75	0.522335	0.300777	**31.50**	0.537714	0.439248
16.50	0.499828	0.281322	**33.00**	0.522441	0.408946
17.25	0.463519	0.267935	**34.50**	0.487764	0.409043
18.00	0.452902	0.261405	**36.00**	0.477861	0.39345
18.75	0.383464	0.227096	**37.50**	0.462423	0.379022
19.50	0.383463	0.227097	**39.00**	0.44703	0.369647
20.25	0.35215	0.217425	**40.50**	0.427988	0.353942
21.00	0.336858	0.206675	**42.00**	0.413196	0.336166
21.75	0.330274	0.203382	**43.50**	0.397158	0.322804
22.50	0.277268	0.1209	**45.00**	0.380837	0.312804
23.25	0.277266	0.120901	**46.50**	0.380837	0.301041
24.00	0.26634	0.105385	**48.00**	0.375397	0.284694
24.75	0.25276	0.104563	**49.50**	0.375396	0.284721
25.50	0.251876	0.104475	**51.00**	0.375396	0.284721
26.25	0.25276	0.104562	**52.50**	0.375396	0.284485

27.00	0.252766	0.104559	**54.00**	0.375396	0.284721
27.75	0.251944	0.105402	**55.50**	0.375396	0.284721
28.50	0.25276	0.104563	**57.00**	0.375396	0.284721
29.25	0.252097	0.056282	**58.50**	0.374785	0
30.00	0.25276	0.052281	**60.00**	0.375396	0
30.75	0.252354	0.052281			
31.50	0.252766	0.052281			
32.25	0.25276	0.052281			
33.00	0.20291	0.053085			
33.75	0.202929	0			
34.50	0.202929	0			
35.25	0.202929	0			
36.00	0.202929	0			
36.75	0.203086	0			

Supplementary table 1: Extracted probabilities from KM

7.2 Comprehensive distribution and SE justification

Type	Distribution	Standard Errors	Sources
Health state utilities	Beta	Assumed 10% of mean, PD SD available; corrected with sample size	Nilsson, Gal (45) Chouaid, Agulnik (46), Nafees, Lloyd (47), Nafees, Stafford (48)
Health state disutilities	Gamma	SE available	Nafees, Stafford (48)
All costs	Gamma		
Adverse Event costs		Assumed 10% of mean	Wehler, Zhao (56), Campone, Yang (57)
Health Care Resource Usage costs		Assumed 10% of mean	Kanters, Bouwmans (52), Nederlandse Zorg authoriteit (54)
Chemotherapy administration costs		Assumed 10% of mean	Nederlandse Zorg authoriteit (50)
Post progression medication		Assumed 10% of mean	Zorginstituut Nederland (53)
End-of-life costs		Assumed 10% of mean, incidence of nursing days was varied using a Beta distribution with a calculated SE	Nederlandse Zorg authoriteit (54), Zorginstituut Nederland (62)
Travel costs and average distances		Assumed 10% of mean	Kanters, Bouwmans (52)
Productivity costs		Assumed 10% of mean	Kanters, Bouwmans (52)
Informal care costs		Assumed 10% of mean	Kanters, Bouwmans (52)
Best supportive care costs		Assumed 10% of mean	Nederlandse Zorg authoriteit (54)
Adverse Event incidences, proportions medication in PD state, incidence of BSC, incidences of resource use,	Beta	Calculated based on ARCHER 1050 trial supplementary file or van Pompen et al.	Mok, Cheng (24), Pompen, Gok (59)
Units of healthcare resource usage	Gamma	Calculated based on available data using the method as described in Wan et al.	Pompen, Gok (59), Wan, Wang (64)
Treatment options once progressed	Dirichlet	Calculated based on ARCHER 1050 trial 1050 trial supplementary file	Wu, Cheng (3), Zorginstituut Nederland (53)
Average Body Surface Area	Gamma	Assumed 10% of mean	te Biesebeek, Nijkamp (58)
Average duration of Adverse Events	Gamma	Assumed 10% of mean	National Institute for Health and Care Excellence (NICE) (49), Lab Test Online (50), Harvard Health Publishing (51)

Supplementary table 2: Supplementary table with distributions

7.3 Parameters used for calculations in PSA with value, SE, distribution and source

Parameter	Value	SE	Distribution	Source
body surface area	1.92	0.19	gamma	(58)
Utility of Daco	0.78	0.08	beta	(45)
Utility of Gefi	0.83	0.08		(45)
Utility of BSC	0.17	0.02		(47)
Utility of Prog 1	0.67	0.01		(46)
Utility of Prog 2	0.59	0.02		(46)
Utility of Prog 3+	0.46	0.02		(46)
Ratio of male/female in the trial	0.40	0.03		(3)
Disutility of Diarrhea	0.05	0.02	gamma	(48)
Disutility of Paronychia	0.03	0.01		(48)
Disutility of Dermatitis acneiforme	0.03	0.01		(48)
Disutility of ALT increased	0.09	0.02		(48)
Disutility of Hypokalemie	0.09	0.02		(48)
Incidence of PD treatment Daco 1	0.42	-	dirichlet	(3)
Incidence of PD treatment Daco 2	0.19	-		(3)
Incidence of PD treatment Daco 3	0.18	-		(3)
Incidence of PD treatment Daco >3	0.21	-		(3)
Incidence of PD treatment Gefi 1	0.47	-		(3)
Incidence of PD treatment Gefi 2	0.22	-		(3)
Incidence of PD treatment Gefi 3	0.14	-		(3)
Incidence of PD treatment Gefi >3	0.16	-		(3)
Incidence of Pemetrexed Daco	0.27	-		(3)
Incidence of Carboplatin Daco	0.13	-		(3)
Incidence of Cisplatin Daco	0.16	-		(3)
Incidence of Osimertinib Daco	0.18	-		(3)
Incidence of Docetaxel Daco	0.11	-		(3)
Incidence of Gefitinib Daco	0.08	-		(3)
Incidence of Erlotinib Daco	0.07	-		(3)
Incidence of Pemetrexed Gefi	0.26	-		(3)
Incidence of Carboplatin Gefi	0.15	-		(3)
Incidence of Cisplatin Gefi	0.16	-		(3)
Incidence of Osimertinib Gefi	0.19	-		(3)
Incidence of Docetaxel Gefi	0.06	-		(3)
Incidence of Gefitinib Gefi	0.09	-		(3)
Incidence of Erlotinib Gefi	0.08	-		(3)
Incidence of PD BSC versus MED DACO	0.43	0.03	beta	(3)
Incidence of PD BSC versus MED GEFI	0.35	0.03		(3)
Number of Outpatient visits	27.20	3.49	gamma	(59)
Number of Hospitalizations	5.50	0.93		(59)
Number of Total length stay	36.60	5.19		(59)
Number of Micro organisms	5.60	0.93		(59)
Number of Pathology	4.20	1.15		(59)

Number of Radiotherapy (mean number of courses/year)	5.50	1.47		(59)
Number of CT scan	7.20	1.06		(59)
Number of Bronchoscopy	1.20	0.18		(59)
Number of Lung function	1.20	0.10		(59)
Number of X-ray—thorax	12.70	2.87		(59)
Number of Xray abdominal	1.30	0.25		(59)
Number of Xray spine and hips	2.50	0.95		(59)
Number of MRI	2.00	0.58		(59)
Number of Ultrasound/Doppler sound	1.80	0.31		(59)
Number of Scintigraphy	1.60	0.19		(59)
Number of PET scan	1.10	0.15		(59)
Number of Outpatient visits PD	41.50	7.25		(59)
Number of Hospitalizations PD	7.00	0.87		(59)
Number of Total length stay PD	47.00	5.77		(59)
Number of Micro organisms PD	10.30	4.49		(59)
Number of Pathology PD	6.10	0.72		(59)
Number of Radiotherapy PD	12.80	1.44		(59)
Number of CT scan PD	6.60	0.64		(59)
Number of Bronchoscopy PD	2.30	0.35		(59)
Number of Lung function PD	1.70	0.21		(59)
Number of X-ray thorax PD	14.80	1.76		(59)
Number of Xray abdominal PD	3.00	0.34		(59)
Number of Xray spine and hips PD	4.60	0.99		(59)
Number of MRI PD	2.10	0.26		(59)
Number of Ultrasound/Doppler sound PD	4.00	0.72		(59)
Number of Scintigraphy PD	2.20	0.47		(59)
Number of PET scan PD	1.80	0.29		(59)
Incidence of Outpatient visits	1.00	fixed	fixed	(59)
Incidence of Hospitalizations	1.00	fixed		(59)
Incidence of Total length stay	1.00	fixed		(59)
Incidence of Micro organisms	0.68	0.09	beta	(59)
Incidence of Pathology	1.00	fixed	fixed	(59)
Incidence of Radiotherapy (mean number of courses/year)	0.43	0.09	beta	(59)
Incidence of CT scan	1.00	fixed	fixed	(59)
Incidence of Bronchoscopy	0.86	0.07	beta	(59)
Incidence of Lung function	0.64	0.09		(59)
Incidence of X-ray thorax	1.00	fixed	fixed	(59)
Incidence of Xray abdominal	0.32	0.09	beta	(59)
Incidence of Xray spine and hips	0.46	0.09		(59)
Incidence of MRI	0.43	0.09		(59)
Incidence of Ultrasound/Doppler	0.61	0.09		(59)
Incidence of Scintigraphy	0.82	0.07		(59)
Incidence of PET scan	0.36	0.09		(59)
Incidence of Outpatient visits PD	1.00	fixed	fixed	(59)
Incidence of Hospitalizations PD	1.00	fixed		(59)
Incidence of Total length stay PD	1.00	fixed		(59)
Incidence of Microorganisms PD	0.77	0.05	beta	(59)
Incidence of Pathology PD	1.00	fixed	fixed	(59)

Incidence of Radiotherapy PD	0.35	0.06	beta	(59)
Incidence of CT scan PD	0.85	0.04		(59)
Incidence of Bronchoscopy PD	0.73	0.05		(59)
Incidence of Lung function PD	0.53	0.06		(59)
Incidence of X-ray thorax PD	0.97	0.02		(59)
Incidence of Xray abdominal PD	0.26	0.05		(59)
Incidence of Xray spine and hips PD	0.32	0.05		(59)
Incidence of MRI PD	0.39	0.06		(59)
Incidence of Ultrasound/Doppler sound PD	0.46	0.06		(59)
Incidence of Scintigraphy PD	0.47	0.06		(59)
Incidence of PET scan PD	0.34	0.05		(59)
Cost of Diarrhea	€ 1,550.05	155.01	gamma	(56)
Cost of Paronychia	€ 1,877.95	187.79		(56)
Cost of Dermatitis acneiforme	€ 1,877.95	187.79		(56)
Cost of ALT increased	€ 1,389.30	138.93		(57)
Cost of Hypokalemie	€ 261.46	26.15		(57)
Cost of Dacomitinib	€ 98.09	fixed	Fixed	(27)
Cost of Gefitinib	€ 51.02	fixed		(53)
Cost of Pemetrexed	€ 1,130.42	113.04	gamma	(53)
Cost of Carboplatin	€ 200.16	20.02		(53)
Cost of Cisplatin	€ 4.53	0.45		(53)
Cost of Osimertinib	€ 205.01	20.50		(53)
Cost of Docetaxel	€ 90.37	9.04		(53)
Cost of Gefitinib	€ 51.02	5.10		(53)
Cost of Erlotinib	€ 69.90	6.99		(53)
Cost of administration IV	€ 139.56	13.96		(54)
Cost of Outpatient visits	€ 141.00	14.10		(52)
Cost of Hospitalizations	€ 667.00	66.70		(52)
Cost of Micro organisms	€ 49.61	4.96		(54)
Cost of Pathology	€ 64.11	6.41		(54)
Cost of Radiotherapy	€ 1,035.00	103.50		(54)
Cost of CT scan	€ 154.00	15.40		(52)
Cost of Bronchoscopy	€ 437.63	43.76		(54)
Cost of Lung function	€ 66.51	6.65		(54)
Cost of X-ray thorax	€ 44.54	4.45		(54)
Cost of Xray abdominal	€ 130.85	13.09		(54)
Cost of Xray spine and hips	€ 78.46	7.85		(54)
Cost of MRI	€ 244.00	24.40		(52)
Cost of Ultrasound/Doppler sound	€ 129.23	12.92		(54)
Cost of Scintigraphy	€ 256.05	25.60		(54)
Cost of PET scan	€ 1,123.15	112.31		(54)
Cost of bsc	€ 1,359.68	135.97		(54)
Incidence of Diarrhea Daco	0.08	0.01	beta	(3)
Incidence of Paronychia Daco	0.08	0.01		(3)
Incidence of Dermatitis acneiforme Daco	0.14	0.02		(3)
Incidence of ALT increased Daco	0.01	0.00		(3)
Incidence of Hypokalemie Daco	0.05	0.01		(3)
Incidence of Diarrhea Gefi	0.01	0.00		(3)
Incidence of Paronychia Gefi	0.01	0.01		(3)
Incidence of Dermatitis acneiforme Gefi	0.00	fixed		(3)

Incidence of ALT increased Gefi	0.08	0.01		(3)
Incidence of Hypokalemie Gefi	0.02	0.01		(3)
Duration of Diarrhea	5.53	0.28	gamma	(49)
Duration of Paronychia	7.00	0.70		(51)
Duration of Dermatitis acneiforme	28.00	2.80		a
Duration of ALT increased	45.00	4.50		(50)
Duration of Hypokalemie	28.00	2.80		a
average of nursingdays terminal care	10.10	1.01		(62)
Incidence of Requiring Nursing terminal care	0.38	0.02	beta	(62)
Cost of Nursing terminal care	1172.91	117.29	gamma	(62)
Friction Period	12.10	fixed	fixed	(52)
Cost of average of Prod	€ 36.99	3.70	gamma	(52)
Cost of average of Prodwomen	€ 33.64	3.36		(52)
Cost of average of Prodmen	€ 40.35	4.03		(52)
Cost of unpaid	€ 14.90	1.49		(52)
Hours per week Informal care PFS	8.00	0.80		b
Hours per week Informal care PD	12.00	1.20		c
Probability of working	0.61	0.02	beta	(61)
Probability of full-time	0.46	-	dirichlet	(61)
Probability of part-time	0.51	-		(61)
Probability of 0 to 12	0.14	fixed	fixed	(61)
Probability of 12 to 20	0.15	fixed		(61)
Probability of 20 to 28	0.33	fixed		(61)
Probability of 28 to 35	0.38	fixed		(61)
average of Distance to Hospital	7.00	0.70	gamma	(52)
average of Distance to GP	1.10	0.11		(52)
average of Distance to Pharmacy	1.30	0.13		(52)
Cost of Car	€ 0.20	€ 0.02		(52)
Cost of Parking	€ 3.19	€ 0.32		(52)
Cost of Public Transit	€ 0.20	€ 0.02		(52)
Cost of Taxi basic fare rate	€ 3.14	€ 0.31		(52)

Supplementary table 3: Parameter values, standard errors, distributions and sources. [a]assumed to be cycle length, [b]assumed to be 8 hours, [c]assumed to be 12 hours.

7.4 Univariate sensitivity analysis

	Value		Cost/QALY		Cost/LY	
	Lower	**Upper**	**Lower**	**Upper**	**Lower**	**Upper**
Average of nursingdays terminal	8.59	11.62	€ 181,603	€ 181,513	€ 84,409	€ 84,367
Average of Distance to Hospital	5.95	8.05	€ 181,538	€ 181,578	€ 84,378	€ 84,397
Average of Distance to Pharmacy	1.11	1.50	€ 181,554	€ 181,562	€ 84,386	€ 84,390
body surface area	1.63	2.21	€ 181,794	€ 181,322	€ 84,497	€ 84,278
Cost Discount Rate	0.03	0.05	€ 186,194	€ 177,128	€ 86,543	€ 82,329
Cost of administration IV	118.62	160.49	€ 181,422	€ 181,694	€ 84,325	€ 84,451
Cost of ALT increased	1180.90	1597.69	€ 181,600	€ 181,516	€ 84,408	€ 84,368
Cost of Average of Prod	31.45	42.54	€ 181,569	€ 181,547	€ 84,393	€ 84,383
Cost of Bronchoscopy	371.98	503.27	€ 181,401	€ 181,715	€ 84,315	€ 84,461
Cost of bsc	1155.73	1563.63	€ 180,217	€ 182,899	€ 83,765	€ 85,011
Cost of Car	0.17	0.23	€ 181,556	€ 181,560	€ 84,387	€ 84,389
Cost of Carboplatin	170.14	230.18	€ 181,935	€ 181,181	€ 84,563	€ 84,213
Cost of Cisplatin	3.85	5.21	€ 181,560	€ 181,556	€ 84,389	€ 84,387
Cost of CT scan	130.90	177.10	€ 181,341	€ 181,775	€ 84,287	€ 84,489
Cost of Daco	83.38	112.80	€ 158,516	€ 204,600	€ 73,678	€ 95,098
Cost of Dermatitis acneiforme	1596.26	2159.64	€ 181,455	€ 181,661	€ 84,340	€ 84,436
Cost of Diarrhea	1317.54	1782.56	€ 181,512	€ 181,604	€ 84,366	€ 84,410
Cost of Docetaxel	76.81	103.93	€ 181,374	€ 181,742	€ 84,302	€ 84,474
Cost of Erlotinib	59.42	80.39	€ 181,701	€ 181,415	€ 84,454	€ 84,321
Cost of Gefi	43.37	58.67	€ 189,910	€ 173,206	€ 88,270	€ 80,506
Cost of Gefitinib	43.37	58.67	€ 181,719	€ 181,397	€ 84,463	€ 84,313
Cost of Hospitalizations	566.95	767.05	€ 174,565	€ 188,551	€ 81,138	€ 87,638
Cost of Hypokalemie	222.24	300.68	€ 181,554	€ 181,562	€ 84,386	€ 84,390
Cost of Lung function	56.53	76.48	€ 181,544	€ 181,572	€ 84,382	€ 84,394
Cost of Micro organisms	42.17	57.05	€ 181,477	€ 181,639	€ 84,350	€ 84,426
Cost of MRI	207.40	280.60	€ 181,510	€ 181,606	€ 84,366	€ 84,410
Cost of Nursing terminal	996.97	1348.85	€ 181,603	€ 181,513	€ 84,409	€ 84,367
Cost of Osimertinib	174.26	235.76	€ 182,037	€ 181,079	€ 84,611	€ 84,165
Cost of Outpatient visits	119.85	162.15	€ 180,292	€ 182,824	€ 83,800	€ 84,976
Cost of Parking	2.71	3.67	€ 181,540	€ 181,576	€ 84,379	€ 84,397
Cost of Paronychia	1596.26	2159.64	€ 181,508	€ 181,608	€ 84,365	€ 84,411
Cost of Pathology	54.49	73.73	€ 181,473	€ 181,643	€ 84,348	€ 84,428
Cost of Pemetrexed	960.86	1299.98	€ 181,599	€ 181,517	€ 84,407	€ 84,369
Cost of PET scan	954.68	1291.62	€ 181,411	€ 181,705	€ 84,319	€ 84,456
Cost of PublicTransit	0.17	0.23	€ 181,556	€ 181,560	€ 84,387	€ 84,389
Cost of Radiotherapy	879.75	1190.25	€ 180,718	€ 182,397	€ 83,998	€ 84,778
Cost of Scintigraphy	217.64	294.45	€ 181,491	€ 181,625	€ 84,357	€ 84,419
Cost of Taxi basic fare rate	2.67	3.61	€ 181,528	€ 181,588	€ 84,374	€ 84,402
Cost of Ultrasound Doppler sound	109.85	148.62	€ 181,507	€ 181,609	€ 84,364	€ 84,411
Cost of unpaid labor	12.67	17.14	€ 179,788	€ 183,328	€ 83,565	€ 85,211

Cost of X ray thorax	37.86	51.22	€ 181,411	€ 181,705	€ 84,320	€ 84,456
Cost of Xray abdominal	111.22	150.48	€ 181,537	€ 181,579	€ 84,378	€ 84,398
Cost of Xray spine and hips	66.69	90.23	€ 181,532	€ 181,584	€ 84,376	€ 84,400
Diagnostic tests	0.00	0.15	€ 181,558	€ 181,558	€ 84,388	€ 84,388
Disutility of ALT increased	0.08	0.10	€ 181,619	€ 181,497	€ 84,388	€ 84,388
Disutility of Dermatitis acneiforme	0.03	0.04	€ 181,533	€ 181,583	€ 84,388	€ 84,388
Disutility of Diarrhea	0.04	0.05	€ 181,554	€ 181,562	€ 84,388	€ 84,388
Disutility of Hypokalemie	0.08	0.10	€ 181,540	€ 181,576	€ 84,388	€ 84,388
Disutility of Paronychia	0.03	0.04	€ 181,555	€ 181,561	€ 84,388	€ 84,388
Duration of ALT increased	38.25	51.75	€ 181,619	€ 181,497	€ 84,388	€ 84,388
Duration of Dermatitis acneiforme	23.80	32.20	€ 181,533	€ 181,583	€ 84,388	€ 84,388
Duration of Diarrhea	4.70	6.36	€ 181,554	€ 181,562	€ 84,388	€ 84,388
Duration of Hypokalemie	23.80	32.20	€ 181,540	€ 181,576	€ 84,388	€ 84,388
Duration of Paronychia	5.95	8.05	€ 181,555	€ 181,561	€ 84,388	€ 84,388
Hours week Informal PD	10.20	13.80	€ 181,003	€ 182,113	€ 84,130	€ 84,646
Hours week Informal PFS	6.80	9.20	€ 180,343	€ 182,773	€ 83,823	€ 84,953
Incidence of ALT increased Daco	0.01	0.01	€ 181,546	€ 181,570	€ 84,386	€ 84,390
Incidence of ALT increased Gefi	0.07	0.10	€ 181,673	€ 181,443	€ 84,410	€ 84,366
Incidence of Bronchoscopy	0.73	0.99	€ 181,533	€ 181,583	€ 84,376	€ 84,399
Incidence of Bronchoscopy PD	0.62	0.84	€ 181,426	€ 181,690	€ 84,326	€ 84,450
Incidence of CT scan	0.85	1.00	€ 181,497	€ 181,558	€ 84,360	€ 84,388
Incidence of CT scan PD	0.72	0.98	€ 181,402	€ 181,714	€ 84,315	€ 84,461
Incidence of Dermatitis acneiforme Daco	0.12	0.16	€ 181,431	€ 181,685	€ 84,340	€ 84,436
Incidence of Dermatitis acneiforme Gefi	0.00	0.15	€ 181,558	€ 180,626	€ 84,388	€ 84,038
Incidence of Diarrhea Daco	0.07	0.10	€ 181,502	€ 181,614	€ 84,364	€ 84,412
Incidence of Diarrhea Gefi	0.01	0.01	€ 181,564	€ 181,552	€ 84,391	€ 84,385
Incidence of Hospitalizations	0.85	1.00	€ 181,558	€ 181,558	€ 84,388	€ 84,388
Incidence of Hospitalizations PD	0.85	1.00	€ 181,558	€ 181,558	€ 84,388	€ 84,388
Incidence of Hypokalemie Daco	0.04	0.06	€ 181,526	€ 181,590	€ 84,385	€ 84,391
Incidence of Hypokalemie Gefi	0.02	0.02	€ 181,569	€ 181,547	€ 84,389	€ 84,387
Incidence of Lung function	0.55	0.74	€ 181,555	€ 181,561	€ 84,387	€ 84,389
Incidence of Lung function PD	0.45	0.61	€ 181,547	€ 181,569	€ 84,383	€ 84,393
Incidence of Micro organisms	0.58	0.78	€ 181,548	€ 181,568	€ 84,383	€ 84,393
Incidence of Micro organisms PD	0.65	0.89	€ 181,487	€ 181,629	€ 84,355	€ 84,421
Incidence of MRI	0.36	0.49	€ 181,547	€ 181,569	€ 84,383	€ 84,393
Incidence of MRI PD	0.33	0.45	€ 181,522	€ 181,594	€ 84,371	€ 84,405
Incidence of Outpatient visits	0.85	1.00	€ 181,348	€ 181,558	€ 84,290	€ 84,388

Incidence of Outpatient visits PD	0.85	1.00	€ 180,503	€ 181,558	€ 83,897	€ 84,388
Incidence of Paronychia Daco	0.07	0.09	€ 181,495	€ 181,621	€ 84,360	€ 84,416
Incidence of Paronychia Gefi	0.01	0.02	€ 181,569	€ 181,547	€ 84,393	€ 84,383
Incidence of Pathology	0.85	1.00	€ 181,543	€ 181,558	€ 84,381	€ 84,388
Incidence of Pathology PD	0.85	1.00	€ 181,487	€ 181,558	€ 84,355	€ 84,388
Incidence of PD BSC DACO	0.36	0.49	€ 153,969	€ 219,229	€ 82,620	€ 86,156
Incidence of PD BSC GEFI	0.30	0.40	€ 207,331	€ 161,100	€ 85,287	€ 83,489
Incidence of PET scan	0.30	0.41	€ 181,534	€ 181,582	€ 84,377	€ 84,399
Incidence of PET scan PD	0.29	0.39	€ 181,435	€ 181,681	€ 84,331	€ 84,445
Incidence of Radiotherapy PD	0.30	0.40	€ 180,718	€ 182,397	€ 83,998	€ 84,778
Incidence of RequireNursing terminal	0.32	0.44	€ 181,603	€ 181,513	€ 84,409	€ 84,367
Incidence of Scintigraphy	0.70	0.94	€ 181,540	€ 181,576	€ 84,379	€ 84,397
Incidence of Scintigraphy PD	0.40	0.54	€ 181,510	€ 181,606	€ 84,366	€ 84,410
Incidence of Total length stay	0.85	1.00	€ 180,219	€ 181,558	€ 83,765	€ 84,388
Incidence of Total length stay PD	0.85	1.00	€ 175,904	€ 181,558	€ 81,760	€ 84,388
Incidence of Ultrasound Doppler	0.52	0.70	€ 181,550	€ 181,566	€ 84,384	€ 84,392
Incidence of Ultrasound Doppler sound PD	0.39	0.53	€ 181,515	€ 181,601	€ 84,368	€ 84,408
Incidence of X ray thorax	0.85	1.00	€ 181,527	€ 181,558	€ 84,374	€ 84,388
Incidence of X ray thorax PD	0.83	1.12	€ 181,442	€ 181,674	€ 84,334	€ 84,442
Incidence of Xray abdominal	0.27	0.37	€ 181,555	€ 181,561	€ 84,387	€ 84,389
Incidence of Xray abdominal PD	0.22	0.30	€ 181,540	€ 181,576	€ 84,380	€ 84,396
Incidence of Xray spine and hips	0.39	0.53	€ 181,553	€ 181,563	€ 84,386	€ 84,390
Incidence of Xray spine and hips PD	0.28	0.37	€ 181,537	€ 181,579	€ 84,378	€ 84,398
Laboratory tests	0.00	0.15	€ 181,558	€ 181,558	€ 84,388	€ 84,388
Number of Bronchoscopy	1.02	1.38	€ 181,533	€ 181,583	€ 84,376	€ 84,399
Number of Bronchoscopy PD	1.96	2.65	€ 181,426	€ 181,690	€ 84,326	€ 84,450
Number of CT scan	6.12	8.28	€ 181,497	€ 181,619	€ 84,360	€ 84,416
Number of CT scan PD	5.61	7.59	€ 181,402	€ 181,714	€ 84,315	€ 84,461
Number of Hospitalizations	4.68	6.33	€ 181,548	€ 181,568	€ 84,383	€ 84,393
Number of Lung function	1.02	1.38	€ 181,555	€ 181,561	€ 84,387	€ 84,389
Number of Lung function PD	1.45	1.96	€ 181,547	€ 181,569	€ 84,383	€ 84,393
Number of Micro organisms	4.76	6.44	€ 181,548	€ 181,568	€ 84,383	€ 84,393
Number of Micro organisms PD	8.76	11.85	€ 181,487	€ 181,629	€ 84,355	€ 84,421
Number of MRI	1.70	2.30	€ 181,547	€ 181,569	€ 84,383	€ 84,393
Number of MRI PD	1.79	2.42	€ 181,522	€ 181,594	€ 84,371	€ 84,405
Number of Outpatient visits	23.12	31.28	€ 181,335	€ 181,781	€ 84,284	€ 84,492
Number of Outpatient visits PD	35.28	47.73	€ 180,497	€ 182,619	€ 83,895	€ 84,881

Number of Pathology	3.57	4.83	€ 181,543	€ 181,573	€ 84,381	€ 84,395
Number of Pathology PD	5.19	7.02	€ 181,487	€ 181,629	€ 84,355	€ 84,421
Number of PET scan	0.94	1.27	€ 181,534	€ 181,582	€ 84,377	€ 84,399
Number of PET scan PD	1.53	2.07	€ 181,435	€ 181,681	€ 84,331	€ 84,445
Number of Radiotherapy PD	10.88	14.72	€ 180,718	€ 182,397	€ 83,998	€ 84,778
Number of Scintigraphy	1.36	1.84	€ 181,540	€ 181,576	€ 84,379	€ 84,397
Number of Scintigraphy PD	1.87	2.53	€ 181,510	€ 181,606	€ 84,366	€ 84,410
Number of Total length stay	31.11	42.09	€ 180,219	€ 182,897	€ 83,765	€ 85,010
Number of Total length stay PD	39.95	54.05	€ 175,904	€ 187,212	€ 81,760	€ 87,016
Number of Ultrasound Doppler sound	1.53	2.07	€ 181,550	€ 181,566	€ 84,384	€ 84,392
Number of Ultrasound Doppler sound PD	3.40	4.60	€ 181,515	€ 181,601	€ 84,368	€ 84,408
Number of X ray thorax PD	12.58	17.02	€ 181,442	€ 181,674	€ 84,334	€ 84,442
Number of X ray thorax	10.80	14.61	€ 181,527	€ 181,589	€ 84,374	€ 84,402
Number of Xray abdominal	1.11	1.50	€ 181,555	€ 181,561	€ 84,387	€ 84,389
Number of Xray abdominal PD	2.55	3.45	€ 181,540	€ 181,576	€ 84,380	€ 84,396
Number of Xray spine and hips	2.13	2.88	€ 181,553	€ 181,563	€ 84,386	€ 84,390
Number of Xray spine and hips PD	3.91	5.29	€ 181,537	€ 181,579	€ 84,378	€ 84,398
Outcome Discount Rate	0.01	0.02	€ 179,338	€ 183,793	€ 84,388	€ 84,388
OS dist choice	4.00	3.00	€ 171,894	€ 167,228	€ 70,085	€ 66,475
Probability of 0 to 12	0.12	0.16	€ 181,558	€ 181,558	€ 84,388	€ 84,388
Probability of 12 to 20	0.13	0.17	€ 181,558	€ 181,558	€ 84,388	€ 84,388
Probability of 20 to 28	0.28	0.38	€ 181,560	€ 181,556	€ 84,389	€ 84,387
Probability of 28 to 35	0.32	0.44	€ 181,560	€ 181,556	€ 84,389	€ 84,387
Probability of full time	0.39	0.53	€ 181,564	€ 181,552	€ 84,391	€ 84,385
Probability of part time	0.44	0.59	€ 181,562	€ 181,554	€ 84,390	€ 84,386
Probability of working	0.52	0.70	€ 181,558	€ 181,558	€ 84,388	€ 84,388
PFS dist choice	4.00	3.00	€ 140,467	€ 136,360	€ 89,609	€ 88,566
Utility of BSC	0.14	0.19	€ 184,353	€ 178,847	€ 84,388	€ 84,388
Utility of Daco	0.66	0.90	€ 368,827	€ 120,417	€ 84,388	€ 84,388
Utility of Gefi	0.70	0.95	€ 132,835	€ 286,729	€ 84,388	€ 84,388
Utility of Prog	0.54	0.73	€ 181,558	€ 181,558	€ 84,388	€ 84,388
Utility of Prog 1	0.57	0.77	€ 178,956	€ 184,236	€ 84,388	€ 84,388
Utility of Prog 2	0.50	0.68	€ 181,878	€ 181,239	€ 84,388	€ 84,388
Utility of Prog 3	0.39	0.53	€ 182,766	€ 180,366	€ 84,388	€ 84,388

Supplementary table 4: Univariate sensitivity analysis

7.5 Multiway sensitivity analysis

Multiway deterministic analysis	Incremental Costs	Incremental QALY's	Cost/QALY	Cost/LY
Utilities +10%	€ 68,001	0.41	€ 165,059	€ 84,388
Utilities +20%	€ 68,001	0.45	€ 151,309	€ 84,388
Utilities -10%	€ 68,001	0.34	€ 201,721	€ 84,388
Utilities -20%	€ 68,001	0.30	€ 226,923	€ 84,388
Disutilties +10%	€ 68,001	0.37	€ 181,550	€ 84,388
Disutilties +20%	€ 68,001	0.37	€ 181,542	€ 84,388
Disutilties -10%	€ 68,001	0.37	€ 181,566	€ 84,388
Disutilties -20%	€ 68,001	0.37	€ 181,574	€ 84,388
Medication Costs +10% (excl. Daco and Gefi)	€ 67,747	0.37	€ 180,879	€ 84,072
Medication Costs +20% (excl. Daco and Gefi)	€ 67,493	0.37	€ 180,201	€ 83,757
Medication Costs -10% (excl. Daco and Gefi)	€ 68,256	0.37	€ 182,237	€ 84,703
Medication Costs -20% (excl. Daco and Gefi)	€ 68,510	0.37	€ 182,915	€ 85,019
Dacomitinib Price +10%; Gefi +0%	€ 73,755	0.37	€ 196,919	€ 91,528
Dacomitinib Price +20%; Gefi +0%	€ 79,508	0.37	€ 212,280	€ 98,668
Dacomitinib Price -10%; Gefi +0%	€ 62,248	0.37	€ 166,197	€ 77,248
Dacomitinib Price -20%; Gefi +0%	€ 56,495	0.37	€ 150,836	€ 70,108
Gefitinib Price +10%; Daco +0%	€ 65,916	0.37	€ 175,990	€ 81,800
Gefitinib Price +20%; Daco +0%	€ 63,830	0.37	€ 170,422	€ 79,212
Gefitinib Price -10%; Daco +0%	€ 70,087	0.37	€ 187,126	€ 86,976
Gefitinib Price -20%; Daco +0%	€ 72,172	0.37	€ 192,694	€ 89,564
AE Costs +10%	€ 68,041	0.37	€ 181,665	€ 84,438
AE Costs +20%	€ 68,081	0.37	€ 181,772	€ 84,487
AE Costs -10%	€ 67,961	0.37	€ 181,451	€ 84,338
AE Costs -20%	€ 67,921	0.37	€ 181,344	€ 84,289
Healthcare Costs +10%	€ 70,538	0.37	€ 188,331	€ 87,536
Healthcare Costs +20%	€ 73,075	0.37	€ 195,103	€ 90,684
Healthcare Costs -10%	€ 65,465	0.37	€ 174,785	€ 81,240
Healthcare Costs -20%	€ 62,928	0.37	€ 168,013	€ 78,092
Travel costs +10%	€ 68,015	0.37	€ 181,593	€ 84,404
Travel costs +20%	€ 68,028	0.37	€ 181,628	€ 84,421
Travel costs -10%	€ 67,988	0.37	€ 181,523	€ 84,372
Travel costs -20%	€ 67,975	0.37	€ 181,488	€ 84,355

Supplementary table 5: Multiway sensitivity analysis

7.6 Scenario analysis

Scenario analysis	Incremental Costs	Incremental QALY's	Cost/QALY	Cost/LY
Time Horizon 15 years	€ 67,656	0.37	€ 182,031	€ 84,869
Time Horizon 12 years	€ 66,395	0.36	€ 183,395	€ 86,286
Time Horizon 9 years	€ 61,729	0.33	€ 187,672	€ 91,085
Time Horizon 6 years	€ 48,740	0.24	€ 200,860	€ 108,830
Time Horizon 3 years	€ 27,632	0.09	€ 321,653	€ 245,720
Time Horizon 1 years	€ 14,149	-0.02	-€ 585,750	€16,665,212
When OS curve uses loglogistic, both arms	€ 86,739	0.50	€ 171,894	€ 70,085
Both arms exponential	€ 72,316	0.42	€ 172,836	€ 81,765
Both arms lognormal	€ 97,632	0.71	€ 137,022	€ 68,849
Both arms loglogistic	€ 90,946	0.64	€ 141,193	€ 73,484
Utility PFS set to 0.65 and Utility PD set to 0.47 (Nafees 2008)	€ 68,001	0.44	€ 154,636	€ 84,388
Utility PFS set to 0.784 and Utility PD set to 0.707 (Pembrolizumab)	€ 68,001	0.56	€ 121,258	€ 84,388
Utility PFS set to 0.883 and Utility PD set to 0.166 (Nafees 2017)	€ 68,001	0.49	€ 137,453	€ 84,388
Excluding wastage cost	€ 67,355	0.37	€ 179,831	€ 83,585
Excluding Informal care cost	€ 63,582	0.37	€ 169,758	€ 78,903
Gender pay gap with reported Proportions from ARCHER 1050	€ 68,006	0.37	€ 181,632	€ 80,549
Travel Cost if singular visits	€ 68,320	0.37	€ 182,408	€ 84,783

Supplementary table 6: Scenario analysis

7.7 Tech-ver

Verification Stage 1: Model Input/Pre-Analysis Calculations

Completeness check:

Survival extrapolation data is in the extrapolation sheet. The AIC and Cholesky matrix parameters as outputted by R are also located here. **The calculations from R are not provided.**

Input transition probabilities: patients transition probabilities can be found in the "Dacomitinib+" and "Gefitinib+" sheets.

Input costs: The input calculations based on the inputs in the "parameters" sheet for costs of first-line treatment with Dacomitinib/Gefitinib, PD treatment, AE, BSC, end of life, travel costs, informal care, productivity loss, wastage and heathcare resource use and cost can be found in the "Costs" sheet.

Input utilities: Calculations of utilities based on input parameters in the "Parameters" sheet for progressed disease utility and AE disutility are presented in the "Utilities" sheet.

The extrapolation methods for OS and PFS are mentioned and the correct ones are used. The formulae are inputted correctly (for Weibull: $S(t) = \exp(-\lambda t^{\gamma})$)

Summary of the Inquire output:

Summary

C:\Users\nilsd\Documents\Thesis HEPL\model\Nils Thesis Markov Model Dacomitinib 2021.xl

Item	Value
Creation Date	donderdag 12 maart 2009 13:46:58
Modified Date	maandag 21 juni 2021 13:11:06
File Size (bytes)	2,913,162
Title	
Author	ICT
Linked Workbooks	1
DDE Links	0
Data Connections	0
Visible Sheets	21
Hidden Sheets	0
Very Hidden Sheets	0
Formulas	38,143
Array Formulas	272
Formulas With Errors	3
Formulas With Logical Values	0
Formulas With Numeric Values	36,798
Formulas With Date/Time Values	0
Formulas With Textual Values	1,342
Formulas With Numeric Constants	18,542
Formulas With Textual Constants	354
Formulas With Nested IF Statements	0
Formulas Without Cell References	35
Formulas Referencing Blank Cells	1,142
Formulas Referencing Hidden Cells	0
Formulas Referencing Text Cells	994
Formulas Referencing External Workbo	0
Formulas Formatted As Text	0
Positive Formulas	9,031
Negative Formulas	5
Unique Formulas	37,342
Duplicate Formulas	801
Inconsistent Formulas	27
Cells With Dependents	41,906
Cells With Textual Constants	6,156
Cells With Numeric Constants	11,659
Cells With Comments	0
Cells With Validation Criteria	1
Cells With Conditional Formatting	19
Cells With Numerics Stored As Text	116
Invisible Cells	17
Used Input Cells	8,787
Unused Input Cells	9,028
Occupied Cells	55,958
Merged Cells	78
Blank Cells	102,054
Blank Referenced Cells	3,259
Unlocked Cells	2
Hidden Rows and Columns	0
Named Items	423
Named Items With Errors	48
Warnings	5

There are no hidden sheets, rows or columns. There are some named values and formulas with errors. Some items, such as days in the week, were hardcoded in the formulas.

No replication testing was done, since no changes were made.

Black-Box testing:

Pre-analysis calculations	
Does the technology (drug/device, etc.) acquisition cost increase with higher prices?	Yes
Does the drug acquisition cost increase for higher weight or body surface area?	Only for PD, as intended
Does the probability of an event, derived from an OR/RR/HR and baseline probability, increase with higher OR/RR/HR?	NA (not applicable), separate models were fitted.
In a partitioned survival model, does the progression-free survival curve or the time on treatment curve cross the overall survival curve?	No
If survival parametric distributions are used in the extrapolations or time-to-event calculations, can the formulae used for the Weibull (generalized gamma) distribution generate the values obtained from the exponential (Weibull or Gamma) distribution(s) after replacing/transforming some of the parameters?	Yes, by changing the values in the cells of the Weibull distribution to match the values generated with the formula for the exponential extrapolation in the "extrapolation"sheet.
Is the HR calculated from Cox proportional hazards model applied on top of the parametric distribution extrapolation found from the survival regression?	NA
For the treatment effect inputs, if the model uses outputs from WINBUGS, are the OR, HR, and RR values all within plausible ranges? (Should all be non-negative and the average of these WINBUGS outputs should give the mean treatment effect)	NA

White-box testing:

Input lines for the costs and utilities were checked, no issues were found.

No replication testing was done, since no changes were made.

Verification Stage 2: Event state calculations

Completeness check:

The calculation of the distribution of cohorts among different health states at a given cycle in a state transition model:

Columns G:H:I in sheets "Dacomitinib+" and "Gefitinib+". G is PFS, H is PD and I is Death. PD is calculated by substracting the PFS and Death cohort patients from the base number.

The assignment of costs/QALYs/other health outcomes to the relevant states or events in the electronic model:

Costs are assigned in columns L:Y in the sheet "Gefitinib+" and columns L:Z in "Dacomitinib+". These costs are half-cycle corrected and discounted correctly.

Qaly's are calculated in AF:AH in in the sheet for Dacomitinib and life years in AC:AD.

Qaly's are calculated in AD:AF in in the sheet for Gefitinib and life years in AA:AC.

Black-Box testing:

Calculate the sum of the number of patients at each health state	Should add up to the cohort size
Check if all probabilities and number of patients in a state are greater than or equal to 0	All patient numbers are smaller than 1000, and larger than or equal to zero
Check if all probabilities are smaller than or equal to 1	All transition probabilities are smaller than one, and larger than or equal to zero
Compare the number of dead (or any absorbing state) patients in a period with the number of dead (or any absorbing state) patients in the previous periods?	Is always larger
In case of lifetime horizon, check if all patients are dead at the end of the time horizon	All patients are dead in the Gefitinib arm and less than 0.1 percent of patients is still alive after 20 years in the Dacomitinib arm.
Discrete event simulation specific: Sample one of the 'time to event' types used in the simulation from the specified distribution. Plot the samples and compare the mean and the variance from the sample	NA
Set all utilities to 1	Qalys are slightly lower due to discounting. If corrected for accrued LY and QALY's are equal
Set all utilities to 0	No utilities are accumulated in the model
Decrease all state utilities simultaneously (but keep event-based utility decrements constant)	Lower utilities will be accumulated each time
Set all costs to 0	No costs are accrued if all costs in the "costs"sheet in column Total are set to zero
Put mortality rates to 0	If OS is set to one, no patients transition to the Death cohort.
Put mortality rate at extremely high	If OS is set to zero in the second cycle and this is done consistently over all consequent cycles, patients are all dead
Set the effectiveness-, utility-, and safety-related model inputs for all treatment options equal	Same life-years and QALYs are accumulated for all treatment at any time. The effectiveness was made equal to the effectiveness of gefitinib, and utilities were also set to those of Gefitinib.
In addition to the inputs above, set cost-related model inputs for all treatment options equal	Same costs, life-years, and QALYs are accumulated for all treatment at any time. All costs were set to the cost of Gefitinib in the total column of the sheet "costs".
Change around the effectiveness-, utility- and safety-related model inputs between two treatment options	Accumulated life-years and QALYs in the model at any time are reversed
Check if the number of alive patients estimated at any cycle is in line with general population life-table statistics	The percentage of population alive is always lower than the base amount.

Check if the QALY estimate at any cycle is in line with general population utility estimates	No general population utility estimate is found. The expected remaining QALY's at this age are 19.59, Dacomitinib had an estimated expected remaining QALY's of 2.11 and Gefitinib 1.74. This is lower and in line with the expectation.
Set the inflation rate for the previous year higher	The costs (which are based on a reference from previous years) assigned at each time will be higher **NO**, the costs of medication was copied manually after indexation in the ïndex"sheet.
Calculate the sum of all ingoing and outgoing transition probabilities of a state in a given cycle	Difference of ingoing and outgoing probabilities at a cycle in a state times the cohort size yields the change in the number of patients at that state in that cycle
Calculate the number of patients entering and leaving a tunnel state throughout the time horizon	NA
Check if the time conversions for probabilities were conducted correctly.	Yes, they are conducted correctly
Decision tree specific: Calculate the sum of the expected probabilities of the terminal nodes	NA
Patient-level model specific: Check if common random numbers are maintained for sampling for the treatment arms	NA
Patient-level model specific: Check if correlation in patient characteristics is taken into account when determining starting population	NA
Increase the treatment acquisition cost	Yes, Increasing the cost of Dacomitinib also increases the accumulated costs.
Population model specific: Set the mortality and incidence rates to 0	Prevalence is constant in time

White-Box tests:

Columns G:H:I in sheets "Dacomitinib+" and "Gefitinib+" were checked on the distribution of cohorts among different health states at a given cycle in a state transition model (e.g. Markov trace).

The assignment of costs to the relevant states or events in the electronic model are checked from L:Y for Dacomitinib and L:Z for Gefitinib. The calculations of Qaly's are checked in AF:AH in in the sheet for Dacomitinib and life years in AC:AD.

Similarly, the calculations of Qaly's are checked in AD:AF in in the sheet for Gefitinib and life years in AA:AC.

No replication testing was done, since no changes were made.

Verification Stage 3: Result Calculations

Completeness check:

The calculation and interpretation of the incremental results and ICER(s) is done in the "Analysis", "simulation", "tornado diagram" and "tables" sheets. Total costs are calculated in the "Dacomitinib+" and "Gefitinib+" sheets.
Half cycle correction is done in all costs. Discount rates are applied to all costs and benefits. Disaggregated results can be found in the "Analysis", "simulation", "tornado diagram" and "tables" sheets. Total costs are calculated in the "Dacomitinib+" and "Gefitinib+" sheets.

Black-Box tests:

Check the incremental life-years and QALYs gained results. Are they in line with the comparative clinical effectiveness evidence of the treatments involved?	Yes, longer survival and more accrued QALY's
Check the incremental cost results. Are they in line with the treatment costs?	Yes, higher costs for Dacomitinib
Total life years greater than the total QALYs	Yes
Undiscounted results greater than the discounted results	Undiscounted results are not disclosed, setting discount rates to zero does confirm this.
Divide undiscounted total QALYs by undiscounted life years	Yes
Subgroup analysis results: How do the outcomes change if the characteristics of the baseline change?	NA
Could you generate all the results in the report from the model (including the uncertainty analysis results)?	Yes
Do the total life-years, QALYs, and costs decrease if a shorter time horizon is selected?	Yes
Is the reporting and contextualization of the incremental results correct?	Yes
Are the reported ICERs in the fully incremental analysis non-decreasing?	NA
If disentangled results are presented, do they sum up to the total results (e.g. different cost types sum up to the total costs estimate)?	Yes
Check if half-cycle correction is implemented correctly (total life-years with half-cycle correction should be lower than without)	Yes, drug acquisition costs are half-cycle corrected because pills are taken daily.
Check the discounted value of costs/QALYs after 2 years	Discounted value = undiscounted/(1 + r)2 Yes, after two years the value is ^2
Set discount rates to 0	NA not reported separately
Set mortality rate to 0	Yes. The undiscounted total life-years per patient is equal to the length of the time horizon

Put the consequence of adverse event/discontinuation to 0 (0 costs and 0 mortality/utility decrements)	Yes Incidence zero: € 180,567 Costs and utility zero: € 180,567
Divide total undiscounted treatment acquisition costs by the average duration on treatment	Average life years accrued in Dacomitinib were about 1.66 years. Dividing the undiscounted total cost per patient (€ 59,240) by this number yielded € 2,692.71, which is only slightly lower than the cycle cost of Dacomitinib of €2,746.52.
Set discount rates to a higher value	Yes. Total discounted results decrease
Set discount rates of costs/effects to an extremely high value	Yes. Total discounted results are more or less the same as the discounted results accrued in the first cycles
Put adverse event/discontinuation rates to 0 and then to an extremely high level	Yes, costs decrease and increase accordingly
Double the difference in efficacy and safety between the new intervention and comparator, and report the incremental results	NA, PFS and OS are independently modeled and treatment effect is not determined like a Hazard ratio.
Do the same for a scenario in which the difference in efficacy and safety is halved	NA, PFS and OS are independently modeled and treatment effect is not determined like a Hazard ratio.

White-Box tests:

The half-cycle correction, discounting and result calculations were thoroughly checked.
No replication testing was done, since no changes were made.

Verification Stage 4: Uncertainty Analysis Calculations

Completeness check:

PSA calculations are located in the "Parameters" sheet. These are found in column C. in the "Simulation" sheet the 1000 iterations are presented. The "CEAC", "EVPI" and "CE-Plane" sheets contain their respective analyses as performed by Excel VBA macro's.

Black-Box tests:

Are all necessary parameters subject to uncertainty included in the One way sensitivity analysis (OWSA)?	Yes, only parameters that need multiway variation and extrapolation and Cholesky matrix parameters are not varied.
Check if the OWSA includes any parameters associated with joint uncertainty (e.g. parts of a utility regression equation, survival curves with multiple parameters)	No, these were not varied
Are the upper and lower bounds used in the one-way sensitivity analysis using confidence intervals based on the statistical distribution assumed for that parameter?	No, a 15% variation was used
Are the resulting ICER, incremental costs/QALYs with upper and lower bound of a parameter plausible and in line with a priori expectations?	Yes, if the upper and lower bound are replaced with upper and lower 15%
Check that all parameters used in the sensitivity analysis have appropriate associated distributions –	Yes, distributions are based on recommendations by the literature.

upper and lower bounds should surround the deterministic value (i.e. upper bound ≥ mean ≥ lower bound)	
Standard error and not standard deviation used in sampling	Yes
Lognormal/gamma distribution for HRs and costs/resource use	Yes
Beta for utilities and proportions/probabilities	Yes
Dirichlet for multinomial	Yes
Multivariate normal for correlated inputs (e.g. survival curve or regression parameters)	Yes
Normal for other variables as long as samples do not violate the requirement to remain positive when appropriate	NA
Check PSA output mean costs, QALYs, and ICER compared with the deterministic results. Is there a large discrepancy?	No, example: incremental cost deterministic is € 68,001 versus € 67,921 for the PSA
If you take new PSA runs from the Microsoft Excel model do you get similar results?	Yes, although the extremes do differ sometimes (dividing by almost zero incremental qaly's)
Is(are) the CEAC line(s) in line with the CE scatter plots and the efficient frontier?	Yes, at a threshold of 80.000 euros and 1% of cost effectiveness about 10 iterations fall below the cost effectiveness threshold line in the CE-plane
Does the PSA cloud demonstrate an unexpected behavior or have an unusual shape?	No, it is ellipse shaped
Is the sum of all CEAC lines equal to 1 for all WTP values?	Yes, it always sums to one
Do the explored scenario analyses provide a balanced view on the structural uncertainty (i.e. not always looking at more optimistic scenarios)?	Not all sources of methodological uncertainty is investigated. It gives an insight in some basic alterations
Are the scenario analysis results plausible and in line with a priori expectations?	Yes, decreasing time horizon increases the ICER. Using other forms of extrapolation or other utility values decreases the ICER.
Check the correlation between two PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator)	Very low
If a certain seed is used for random number generation (or previously generated random numbers are used), check if they are scattered evenly between 0 and 1 when they are plotted	NA
Compare the mean of the parameter samples generated by the model against the point estimate for that parameter; use graphical methods to examine distributions, functions	The sample means and the point estimates are relatively similar

Check if sensitivity analyses include any parameters associated with methodological/structural uncertainty (e.g. annual discount rates, time horizon)	No, they are not included in the PSA
Value of information analysis if applicable: Was this implemented correctly?	Yes
Which types of analysis? Were aggregated parameters used? Which parameters are grouped together? Does it match the write-up's suggestions?	EVPI and popEVPI, all parameters varied in the PSA were used
Is EVPI larger than all individual EVPPIs?	NA
Is EVPPI for a (group of) parameters larger than the EVSI of that (group) of parameter(s)?	NA
Are the results from EVPPI in line with OWSA or other parameter importance analysis (e.g. ANCOVA)?	NA
Did the electronic model pass the black-box tests of the previous verification stages in all PSA iterations and in all scenario analysis settings? (Additional macro can be embedded to the PSA code, which stops the PSA when an error such as negative transition probability is detected)	Yes
Check if all sampled input parameters in the PSA are correctly linked to the corresponding event/state calculations	Yes

Verification Stage 5: Overall Validation/Other Supplementary Tests

The univariate deterministic sensitivity analysis Excel VBA is not efficient, and it could be structured in a loop rather than using repetitions.

The median OS was 34.1 months for Dacomitinib and 27.0 months for Gefitinib in the clinical trial. Using the Weibull data extrapolation method similar results of a median OS of 36.92 months for Dacomitinib and 30.46 months for Gefitinib. The median PFS was 14.7 months in the Dacomitinib group, and 9.2 months in the Gefitinib group. The model resulted in a median PFS of 16.05 months for Dacomitinib and 11.65 months for Gefitinib.