A Description of the IVI-NSCLC Model v1.0

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*Innovation and Value Initiative

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1 Open Source Value Project

The continuing increase in U.S. healthcare costs has stimulated the introduction of initiatives to promote the use of high-value care. Cost-effectiveness analysis can inform efficient use of healthcare resources by formally computing costs and benefits to identify the most valuable treatment options for a given disease. In many countries, a single health technology assessment agency assesses the value of healthcare technology by means of cost-effectiveness analysis and recommends a utilization strategy. In the US, however, utilization decisions are decentralized and made by a variety of payers and provider organizations. Value frameworks are gaining prominence to guide utilization of therapies, but vary in perspective, the evidence considered, and approaches, thereby resulting in confusion and debate among stakeholders.

A thorough evidence-based analysis of the value of medical technology is resource intensive and complex. Typically, there is no empirical study with sufficient long-term follow-up that compares all treatments for a particular disease regarding relevant clinical outcomes and costs. Thus, cost-effectiveness analyses generally rely on mathematical models that integrate evidence on the course of disease, treatment effects, and the relationship between clinical outcomes and costs, from a variety of studies. The nature of these evaluations can lead to disputes in the scientific literature and community. Models are typically difficult to understand. Even modeling experts may not be able to fully understand a model-based cost-effectiveness analysis without public source code and detailed model documentation. This lack of transparency also poses problems for users whose perspective, local context, or patient population varies from that of the reported analysis. In the absence of public access to the actual model, updating the evaluation is cumbersome, if not impossible, for someone other than the original model developer. As a result, published cost-effectiveness findings risk immediate irrelevance to some stakeholders and growing irrelevance to all stakeholders as new clinical evidence emerges. Value assessment only has relevance for decision-making when it reflects the totality of the latest evidence, is transparent, deemed credible by different stakeholders, representative of the local context and patient population, and can be easily updated without duplication of effort.

With the Open-Source Value Project (OSVP), the Innovation and Value Initiative (IVI) aims to maximize both the relevance and credibility of value assessment in the context of the U.S. decentralized decision-making environment by developing and providing access to flexible open source decision models for value assessment. Refer to the IVI website here for a more detailed description regarding the objectives of these interactive models.

IVI conducted its most recent OSVP within oncology. When selecting the tumor type of interest, IVI considered criteria such as burden of disease, development of innovative treatment, alternative treatment strategies available, availability of clinical evidence, and engagement of patient organization(s) to actively contribute to the project.

Lung cancer is the leading cause of cancer related death worldwide (Jemal et al. 2011). Non-small lung cancer (NSCLC) accounts for an estimated 85% of lung cancer cases and comprises adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (D'addario et al. 2010). The five-year survival of stage IV NSCLC is less than 2% (Cetin et al. 2011). Given the rapid pace of development in NSCLC, the scope of the OSVP needed to be limited to a very specific sub-population in order to ensure a model could be developed in a reasonable time frame that allowed IVI to demonstrate the typical areas of uncertainty in value assessment in oncology. The selected target population of interest for the most recent OSVP is metastatic epidermal growth factor receptor positive (EGFR+) NSCLC. EGFR mutations are more commonly observed in tumors from female patients with adenocarcinomas without a history of smoking and with Asian ethnicity, but can occur in patients with prior smoking history and across all races and genders (Lynch et al. 2004). The evidence base for the treatments used for the EGFR+ population is more modest than the evidence base for treatments used for EGFR negative NSCLC, which makes development of a model reflective of the latest evidence base more manageable given the logistical constraints set for this project. Future activities may include expanding the model to other subpopulations of interest.

2 Purpose

2.1 Value assessment

The IVI-NSCLC (egfr+) model is designed to assess the value of multiple competing sequential treatment strategies for patients with metastatic EGFR+ NSCLC. Sequential treatment strategies of interest are outlined in Figure 1. The final treatment strategies–starting with 1st line treatment (1L), followed by 2nd line treatment (2L), and treatment beyond 2nd line (2L+)–that can be evaluated with version 1 of the model were informed by the available evidence base, guidelines, and clinician input. The model is primarily designed to evaluate sequences starting with 1L, but sequences starting with 2L were analyzed given a certain 1L treatment received.

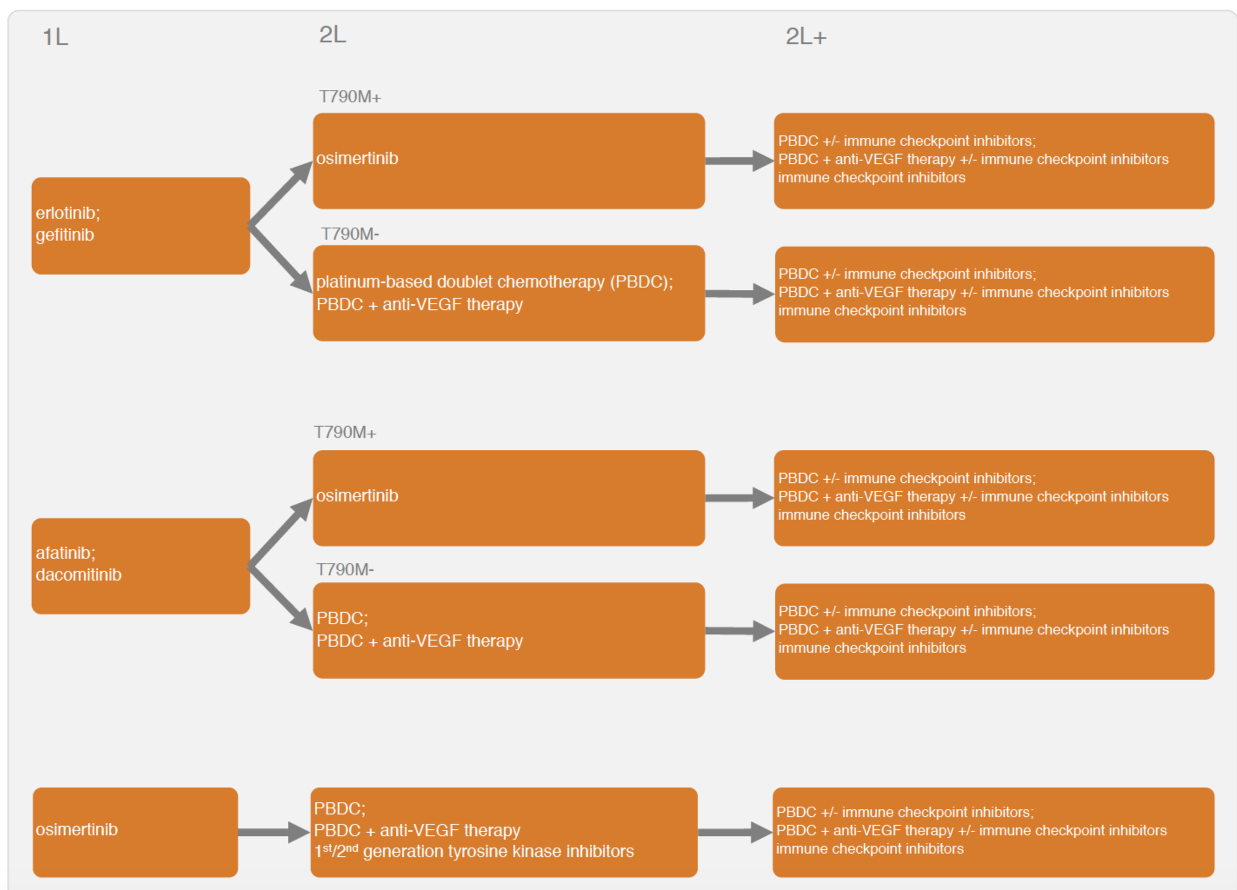


Figure 1: Sequential treatment strategies of interest to be compared with the model

The IVI-NSCLC(egfr+) model is suitable for informing decisions for specific (sub)populations, but is not suitable for making predictions at the individual level, nor should it replace the patient-physician shared decision-making process. Local decision makers can modify the model to perform analysis of value that reflect the local setting while accounting for all scientific uncertainty and help them understand the confidence with which they make decisions.

The IVI-NSCLC(egfr+) model is not a value assessment framework, but a model that simulates the costs, health outcomes, and risks associated with sequential treatment sequences for metastatic EGFR+ NSCLC. It can therefore be used with any value framework preferred by the user. Currently, two methodologies for decision analysis are supported by the model: CEA based on cost per quality adjusted life year (QALY) expressed as net-monetary benefit (NMB) and MCDA (Keeney and Raiffa 1993).

The MCDA was implemented according to Thokala et al. (2016) and based on the following criteria: progression free survival (PFS), overall survival (OS), adverse events, expected time on first, second, and third line treatment, utility/quality of life, health care sector costs, productivity losses, route of administration (oral/injection/infusion) and time the medication has been on the market. The assessment of value can be performed from a health care sector perspective by only incorporating health care sector costs, or from a (limited) societal perspective by including productivity losses in addition.

Garrison et al. (2017) suggest five concepts of value that researchers should consider adding to the standard cost per QALY based CEA: (i) a reduction in uncertainty from a diagnostic test; (ii) insurance value for healthy individuals due to reduction against physical risk; (iii) the value of hope for individuals who become risk-loving and would rather pay for a therapy with a long right survival tail than a therapy with a shorter right survival tail but an equivalent (or shorter) expected life-expectancy; (iv) real option value when a therapy allows an individual to benefit from future medical innovations; and (v) scientific spillovers when the benefits of an innovation cannot be entirely appropriated by the innovator.

The value of hope is most relevant for innovations that increase longevity and might be particularly well suited to the analyses of treatments for NSCLC. Traditionally, CEA focuses on maximizing expected QALYs; however, patients might be willing to take gambles (i.e., they become "risk lovers") and care about the variation in benefits and costs, not simply the means. If patients value hope, they may prefer the treatment with greater variability in survival over the treatment with less variability despite having the same expected survival. In contrast, if patients are risk-averse, they may prefer the latter to avoid an unlucky outcome. Either way, they have a preference for one intervention over its alternative that appear identical based on its average costs and benefits. Patients may place substantial value on a modest chance of a durable survival response, over and above average survival, and decision-makers acting on their behalf may want to consider this aspect when making population level decisions regarding the value of interventions.

The IVI-NSCLC(egfr+) model allows users to incorporate value of hope into their analyses, while noting that the approach is less well-established than conventional cost-effectiveness analysis. Future versions of the IVI-NSCLC(egfr+) may consider incorporating other value components.

2.2 Evaluation of scientific uncertainty

Decision models can be used to inform efficient use of health care resources, but often lead to scientific disagreements and mistrust among stakeholders. Model inputs are typically informed by a formal evidence synthesis to ensure all relevant evidence is considered. However, decisions regarding the mathematical structure relating model inputs to outputs are frequently made arbitrarily based on the idiosyncratic expertise of the model developer without evaluating the impact on findings. While robustness can be assessed by means of sensitivity analyses, these are typically limited to studying the impacts of varying model inputs. For any given disease, a variety of modeling approaches have typically been proposed in the literature. In order to evaluate the impact of these different approaches on estimates of value in a systematic way, we need flexible open-source models to not only capture the uncertainty in model input parameters (i.e. parameter uncertainty), but also capture alternative model structures (i.e. structural uncertainty). This flexibility facilitates demonstrating the implications of different areas of uncertainty and leads to a better understanding of the reasons why value estimates can vary.

3 Components

Version 1 of the IVI-NSCLC(egfr+) model is designed to provide a starting point for open debate. To facilitate transparency, understanding, debate and collaboration among diverse stakeholders, the IVI-lung model will consist of the following components available in the public domain:

Source code: R and C++ code for the model are available in an IVI GitHub repository. Modelers and programmers may adapt the source code for their own purposes or collaborate to improve the code.

R package: The model will be released as an R-package with documentation available online. Researchers can use the package to run the model for custom analyses. Use of the package is recommended when performing analyses for scientific research.

Detailed model documentation: This document provides extensive technical details on the model structure, statistical methods for parameter estimation, and source data.

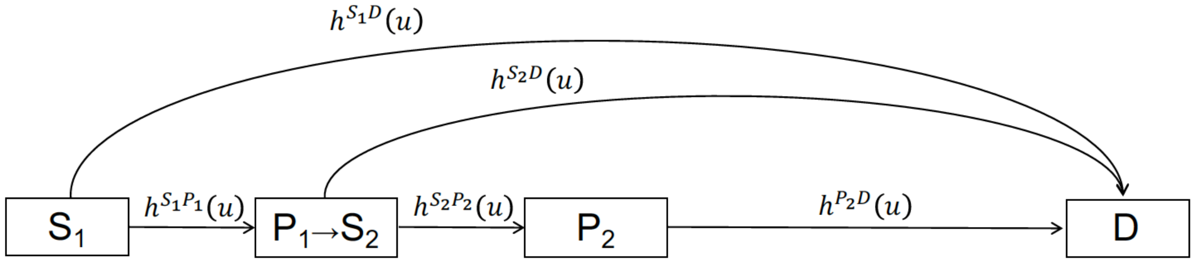
Model Interface: For users not well-versed in the programming language, a web application for running the model online is provided. The web application is designed for custom analyses and allows users full control over the treatments, patient population, model structures, parameter values, and simulation settings.

Value Tool: An important aim of OSVP is to obtain feedback from as many relevant stakeholders as possible. A general audience web-application has been developed, allowing those who are not experts in modeling or health economics, to interact with the model.

4 Model structure

4.1 Disease model

The IVI-NSCLC is an individual-level continuous-time state transition model (CTSTM) in which patients can either have stable disease, progressed disease, or have died. To model sequential treatment strategies, we assumed that patients move to the next treatment after disease progression. In other words, a patient with stable disease moves to the second treatment in a sequence after progression on the first treatment, to the third treatment after progression on the second treatment, and so on. A patient can die at any time. Figure 2 shows health state transitions for an example sequence of 3 treatments. Sequential treatment is incorporated into the CTSTM by expanding the number of health states according to the number of treatment lines. In the figure there are 3 treatment lines and 5 health states; more generally, there is one health state for each treatment line, a health state after progression on the final line, and a death state, so a model with n treatment lines will have n+2 health states.



S_1= Progression-free (stable disease) with 1L treatment

P_1= Progression with 1L treatment

S_2= Progression-free (stable disease) with 2L treatment

P_2= Progression with 2L treatment, captures the survival with 2L+ without making a distinction between a progression free and progression phase

D= Dead

$h^{S_1P_1}(u)$= hazard for transitioning from progression-free to progression with 1L treatment at time u

$h^{S_1D}(u)$= hazard for transitioning from progression-free to dead with 1L treatment at time u

$h^{S_2P_2}(u)$= hazard for transitioning from progression-free to progression with 2L treatment at time u

$h^{S_2D}(u)$= hazard for transitioning from progression-free to dead with 2L treatment at time u

$h^{P_2D}(u)$= hazard for transitioning from progression on 2L to dead at time u

Figure 2: Simplified model structure with 4 states describing development of disease over time for a sequence starting with 1L, followed by 2L and 2L+ treatment; 2L+ treatment is captured with the L2 progression state

The hazard rate, h^{qr} (u) for a transition from state q to state r at time u follows different parametric distributions including the exponential, Weibull, Gompertz, log-logistic, and fractional polynomial distributions as estimated with a multi-state network meta-analysis (NMA). In the individual-level model, time to each state r that can be entered from state q is sampled based on time-varying hazard rates and patients' transition to the state with the shortest sampled time.

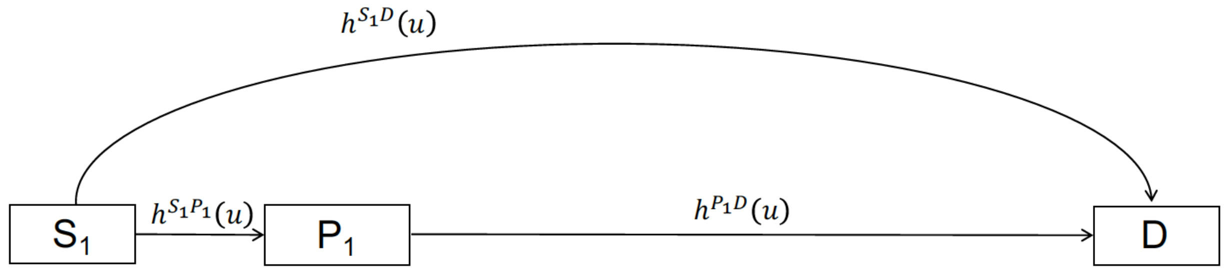
The parameterization of transitions between health states allows incorporating potentially relevant prognostic factors or effect-modifiers. This would also facilitate including carry-over effects from one line of treatment to the next, once such data becomes available.

4.2 Adverse events

The model includes multiple distinct adverse events associated with oncology treatment by treatment line. More precisely, for each treatment line and each patient, the model samples whether each adverse event occurs from a binomial distribution.

4.3 Cost and utility

All non-death health states are associated with utility and cost values. Cost values are separated into distinct categories (e.g., drug acquisition and administration costs, costs due to inpatient hos-



S_1= Progression-free (stable disease) with 1L treatment

P_1= Progression with 1L treatment, captures the survival with 2L and 2L+ without making a distinction between progression free and progression phases

D= Dead

$h^{S_1P_1}(u)$= hazard for transitioning from progression-free to progression with 1L treatment at time u

$h^{S_1D}(u)$= hazard for transitioning from progression-free to dead with 1L treatment at time u

$h^{P_1D}(u)$= hazard for transitioning from progression on 1L to dead at time u

Figure 3: Simplified model structure with 3 states describing development of disease over time for a treatment sequence starting with 1L until death; 2L and 2L+ treatment is captured with the progression state

pitalizations, etc.). Because we did not find strong evidence to the contrary, we assumed that utility and cost values remain constant over time within a given health state, but the model is also flexible enough to estimate utility and cost values that vary over time in a general manner. Adverse events cause utility decrements and more serious adverse events–such as those that require hospitalizations–increase health care costs.

Drug acquisition and administration related costs are modeled based on standard clinical practice. For example, consider a case in which a therapy is dosed daily. Then costs will accrue each day until disease progression and the patient switches to the next treatment in the sequence. Another possible scenario is that dosing is based on fixed cycles. In these cases, costs will accrue until the end of a cycle or until the patient switches treatment due to disease progression. Other scenarios will be considered as required.

The value of hope is illustrated with the model assuming representative relationships between utility values for each of the health states as a function of time reflecting risk-seeking and risk-averse behavior.

Adverse events cause utility decrements and more serious adverse events–such as those that require hospitalizations–increase health care costs.

4.4 Patient heterogeneity

The model is sufficiently flexible so that all model parameters (i.e., the parameters of probability distributions characterizing health state transitions, adverse event rates, costs, and utility) can depend on patient characteristics. In other words, we modeled input parameters as a function of covariates so that they can vary across individuals and treatments. That is, a given parameter,

a_{jt}, for individual j using treatment t is modeled as $\alpha_{jt} = g^{-1}(X_{jt}\beta)$ where g^{-1} (.) is an inverse transformation function. However, the extent heterogeneity can be modeled depends on the level of detail in the available evidence. We modeled heterogeneity based off of the level of evidence available.

4.5 Rationale for individual-level simulation

Our primary motivation for using an individual-level model relates to the distinction between "clock forward" and "clock reset" approaches to parameter estimation. In the "clock reset" approach, time u in h^{qr} (u) resets to 0 after each transition whereas in the "clock forward" approach, time u refers to time since the start of the model. If a "clock forward" approach is used, then health state probabilities can be calculated analytically using the Aalen and Johansen (1978) estimator and a cohort CTSTM can be used; conversely, if a "clock reset" approach is taken, then individual-level simulation-based approaches must be used to estimate health state probabilities (Putter et al. 2007), (de Wreede et al. 2011), (Jackson 2016). In our case, each line specific multi-state NMA is a "clock-forward" model; however, when modeling sequential treatment multiple multi-state NMAs are used so the disease model is a mixture between the two: a "clock forward" model is used for each treatment but time u resets each time a patient begins a new treatment. To accommodate a mixture of "clock reset" and "clock forward" approaches, we use an individual-level model.

5 Model outcomes

The model simulates the health outcomes, risks, and costs associated with alternative treatment strategies in oncology. The model's time horizon can be selected by the user and will default to a lifetime horizon. The health outcomes, risks, and costs will be combined to assess value using two frameworks: CEA and MCDA. Both disaggregated model outcomes and value estimates will be based on mean values (i.e., averages across all simulated patients). An overview of all model outcomes is shown in Table 1. Additional details are provided in the text below.

Table 1: Model outcomes

Category	Outcomes
Health outcomes	Health state probabilities; progression free survival & overall survival; quality-adjusted life-years
Risks	Adverse events (diarrhea, dry skin, elevated alanine transaminase, elevated aspartate transaminase, eye problems, paronychia, pneumonitis, pruritus, rash, stomatitis)
Health care sector costs	Drug acquisition and administration costs; adverse event costs; costs from inpatient hospital stays; costs from hospital outpatient or doctor office visits
Non-health care sector costs	Productivity losses
Value assessment	Cost-effectiveness analysis; multi-criteria decision analysis

5.1 Health outcomes

The primary health outcome is the probability that a patient is in a given health state at a given point in time following treatment initiation. A survival curve was generated from the health state probabilities as one minus the probability that a patient has died. Since the model is an individual patient simulation, life expectancy is just the average time of death across simulated patients. Life-years was calculated as age at death minus age at treatment initiation. QALYs are weighted life-years, with weights equal to the utility values assigned to states. Discounted QALYs were also calculated using a default discount rate of 3 percent.

5.2 Risks

The model calculates the expected number of adverse events per patient as the mean number of adverse events experienced by patients during the simulation. To improve interpretability, this number is reported as the expected number of adverse events per 1,000 patients. Both the expected number of total adverse events and the expected number of adverse events by type are reported.

5.3 Costs

osts are calculated for multiple categories and separated into health care sector and non-heath care sector costs as recommended by the Sanders et al. (2016). Health care sector cost categories included drug acquisition and administration costs, adverse events costs, the costs of inpatient hospital stays, and costs from hospital outpatient and doctor office visits. Non-health care sector costs include productivity losses. We used both human-capital approach and friction-cost approach to estimate productivity losses associated with the different treatment sequences. The level of detail regarding productivity related cost estimates that were incorporated is based on the available data in the literature.

5.4 Value assessment

Value can be assessed using two frameworks: CEA and MCDA. If CEA is used for value assessment, then the value of treatment is estimated using the NMB. CEA from a societal perspective includes productivity losses while analyses from a health care sector perspective do not.

With MCDA, the value of each treatment strategy is based on a "total value" score. The score is calculated in three steps. First, a number of distinct criteria are assigned values on a common scale, for instance, ranging from 0 to 100. Second, each criterion is assigned points, say, ranging from 0 to 10, which is, in turn, used to calculate a weight by dividing each criterion's points by the sum of points across all criteria. For example, if there were 3 criteria and each criterion was given a score of 5, then each criterion would receive a weight of 1/3. If, on the other hand, the three criteria were given scores of 2.5, 5, and 7.5, then they would be given weights of 0.167, 0.33, and 0.5, respectively. Third, to aggregate results, we multiplied the value of each criterion on the common scale by its weight and sum the weighted scores across criteria. Future iterations of the model will consider using the Patient Experience Study to inform the baseline weights across attributes.

6 Source data and parameter estimation

Key parameters for the model relate to: (i) transition probabilities; (ii) adverse events; (iii) utilities; (iv) healthcare resource use; and (v) productivity. Parameter estimates are based on currently available published evidence identified by means of a systematic literature review (SLR) and synthesized with meta-analysis techniques where appropriate. Additional information regarding the SLR (Appendix A) and NMA (Appendix B) are provided in the Appendix.

6.1 Transition probabilities

Traditional NMAs in oncology are based on separate analyses for OS and PFS, with relative treatment effects estimated using hazard ratios (HR). There are two limitations of this approach. First, HR estimates rely on the proportional hazard assumption, which is implausible if the hazard functions of the competing interventions cross (Dias et al. 2018). Second, separate analyses of OS and PFS ignore the structural relationship between stable disease, progression, and death and implicitly assume that transition probabilities for stable to death and progression to death are equal.

We overcome these limitations by using a multi-state NMA that explicitly estimates each possible transition in a 3-state model—stable to progression, stable to death, and progression to death–and modeling time-varying hazard rates and relative treatment effects with known parametric survival functions or fractional polynomials. Our approach is illustrated in Figure 4 and expressed mathematically in Equation 1,

$$\ln\left(h_{ik}^{SP}(u)\right) = \begin{cases} \alpha_{1ik} + \alpha_{2ik}u^{p_1} + \alpha_{3ik}u^{p_2} & \text{if } p_1 \neq p_2 \\ \alpha_{1ik} + \alpha_{2ik}u^{p} + \alpha_{3ik}u^{p}\ln(u) & \text{if } p_1 = p_2 = p \end{cases}$$

$$\ln\left(h_{ik}^{SD}(u)\right) = \begin{cases} \alpha_{4ik} + \alpha_{5ik}u^{p_1} + \alpha_{6ik}u^{p_2} & \text{if } p_1 \neq p_2 \\ \alpha_{4ik} + \alpha_{5ik}u^{p} + \alpha_{6ik}u^{p}\ln(u) & \text{if } p_1 = p_2 = p \end{cases}$$

$$\ln\left(h_{ik}^{PD}(u)\right) = \begin{cases} \alpha_{7ik} + \alpha_{8ik}u^{p_1} + \alpha_{9ik}u^{p_2} & \text{if } p_1 \neq p_2 \\ \alpha_{7ik} + \alpha_{8ik}u^{p} + \alpha_{9ik}u^{p}\ln(u) & \text{if } p_1 = p_2 = p \end{cases}$$

$$\begin{pmatrix} \alpha_{1ik} \\ \alpha_{2ik} \\ \alpha_{3ik} \\ \alpha_{4ik} \\ \alpha_{5ik} \\ \alpha_{6ik} \\ \alpha_{7ik} \\ \alpha_{8ik} \\ \alpha_{9ik} \end{pmatrix} = \begin{pmatrix} \mu_{1ik} \\ \mu_{2ik} \\ \mu_{3ik} \\ \mu_{4ik} \\ \mu_{5ik} \\ \mu_{6ik} \\ \mu_{7ik} \\ \mu_{8ik} \\ \mu_{9ik} \end{pmatrix} + \begin{pmatrix} \lambda_{1,ik} \\ d_{2,t_{ik}} - d_{2,t_{i1}} \\ 0 \\ 0 \\ 0 \\ 0 \\ d_{7,t_{ik}} - d_{7,t_{i1}} \\ 0 \\ 0 \end{pmatrix} \tag{1}$$

$$\lambda_{1,ik} \sim N(d_{1,t_{ik}} - d_{1,t_{i1}}, \sigma^2)$$

where $t^0 = \ln(u)$.

The $\alpha_{\cdot ik}$ are regression coefficients that represent the scale and shape parameters of the log hazard function in study i for treatment arm k. The $\mu_{\cdot i}$ reflect the study effects regarding the scale and shape parameters in each study i. The $\delta_{0,ik}$ are the study specific true underlying relative treatment effects regarding the scale of the log hazard function for the transition from stable to progression, which are described by a normal distribution with an average effect for treatment t relative to

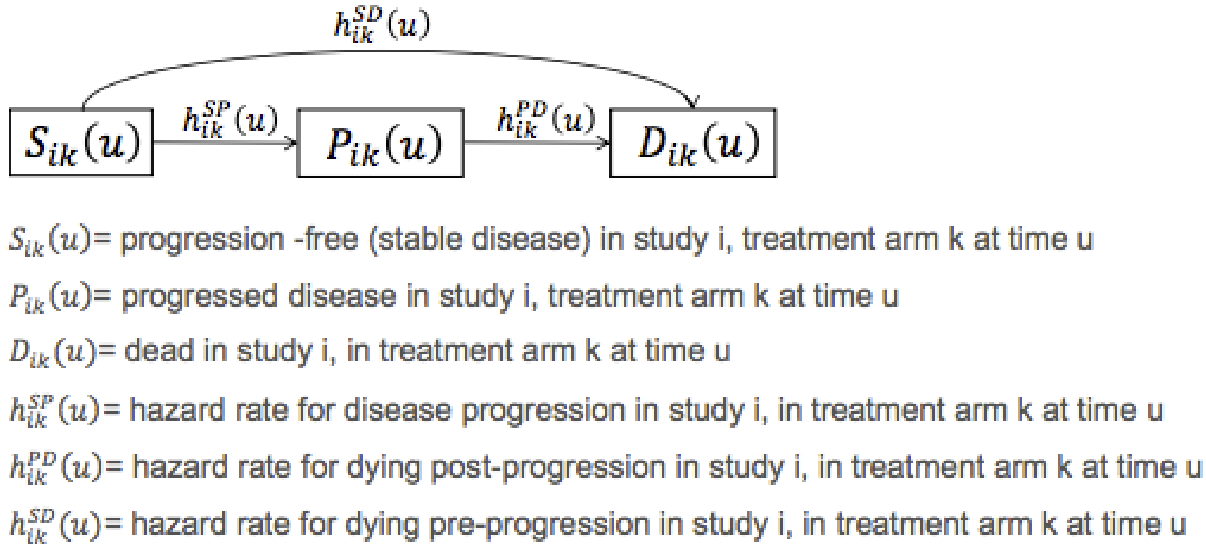


Figure 4: Relationship between stable disease (S), progression (P) and death (D) as used in the multi-state network meta-analysis model

reference treatment 1 ($d_{0,1t}$) and between study heterogeneity σ_0^2. The treatment effect for the first shape parameter for the transition from stable to progression ($d_{2,1t}$) and the scale parameter for the transition from progression to death ($d_{7,1t}$) are assumed to be fixed by treatment.

Weibull ($p_1 = 0$), Gompertz ($p_1 = 1$), and two second order fractional polynomial models $\{(p_0, p_1) = (0,0), (0,1)\}$ were fit. The estimated 2nd order fractional polynomial models are extensions of the Weibull and Gompertz model and allow arc- and bathtub shaped hazard functions. To facilitate parameter estimation, we assume that treatment only has an impact on the time-varying transition rates from stable to progression; we assume that transition rates between stable disease and death are independent of treatment. In addition, we assume that treatment has no effect on the 2nd shape parameter in the transition from stable to progression or on either shape parameter in the transition from progression to death.

The model parameters were estimated based on the number of patients in each of the three health states over time obtained from the published Kaplan-Meier (KM) curves for each arm of each trial included in the NMA. Accordingly, we will use a multinomial likelihood for the proportion of patients in each of the three health states at any point in time. These proportions are related to the time-varying hazards $h_{ik}^{SP}(u)$, $h_{ik}^{SD}(u)$, $h_{ik}^{PD}(u)$ according to a set of differential equations (Jansen and Trikalinos 2013).

Separate analyses were performed by line of treatment (i.e., 1L and 2L) conditional upon prior treatment (class) when relevant, based on data extracted from the studies identified with the SLR in a Bayesian framework using both fixed and random effects. We use the random effects by default in the model, which accounts for heterogeneity across studies. However, since few RCTs were available, heterogeneity estimation became unreliable and the use of conventional "non-informative priors" resulted in artificially wide uncertainty intervals. Need to add details about the priors. The prior distributions are displayed in Equation 2:

$$
\begin{aligned}
&\begin{pmatrix} \mu_{1i} \\ \vdots \\ \mu_{9i} \end{pmatrix} \sim MVN\left(\begin{pmatrix} 0 \\ \vdots \\ 0 \end{pmatrix}, T_\mu\right) \qquad T_\mu = \begin{pmatrix} 10^4 & \cdots & 10^4 \\ \vdots & \ddots & \vdots \\ 10^4 & \cdots & 10^4 \end{pmatrix} \\
&\begin{pmatrix} d_{1,1t} \\ d_{2,1t} \\ d_{7,1t} \end{pmatrix} \sim MVN\left(\begin{pmatrix} 0 \\ \vdots \\ 0 \end{pmatrix}, T_d\right) \qquad T_d = \begin{pmatrix} 10^4 & \cdots & 10^4 \\ \vdots & \ddots & \vdots \\ 10^4 & \cdots & 10^4 \end{pmatrix}
\end{aligned}
\tag{2}
$$

Absolute effects at 1L, the $\mu_{\cdot i}$, were estimated with a multi-state meta-analysis of gefitinib and the relative treatment effects, the $d_{\cdot,1t}$, were estimated using Equation 1. The simulated posterior distribution of the parameter estimates were then used to simulate a posterior distribution for PFS and OS. Figure 6 reports mean estimates of PFS and OS by month for each 1L treatment and each fitted model.

Figure 5: Absolute effects for 1L with reference treatment

When a 3-state economic model is used, the 1L NMA is used to directly simulate disease progression. However, if a 4-state model is used, then both 1L and 2L estimates are incorporated. In particular, the 1L results are used to simulate the transition from S_1 to $P_1 \rightarrow S_2$ and the 2L results are used to simulate the transition from $P_1 \rightarrow S_2$ to P_2, P_2 to D, and $P_1 \rightarrow S_2$ to D (see Figure 2). Furthermore, recall that second line treatment depend on whether a patient has a T790M mutation. Separate 2L multi-state meta-analyses were consequently conducted to parameterize transitions among T790M positive and T790M negative patients. For T790M positive patients, we performed a meta-analysis of osimertinib. Among possible treatments for T790M negative patients, there was only trial data available for PBDC, so we performed a meta-analysis of PBDC (estimates for other 2L treatment options including PBDC + anti-VEGF therapy and 1st/2nd genration TKIs are assumed to be equivalent to PBDC in the economic model). Since T790M mutation status was not a prognostic factor or an effect modifier, the PBDC meta-analysis was conducted using an all-comer population. Mean estimates of PFS and OS by month for the 2L treatments are displayed in Figure 7a.

6.2 Adverse events

Since adverse events in nearly all clinical trials were reported as the number of patients experiencing the event, the NMA was performed on the proportion of patients experiencing the event of interest with a binomial likelihood and logit link (Dias et al. 2018, Chapter 2). Add details about pooling and the priors...

Table 2: **Utility by health state**

Health state	Mean	Standard error	Reference
S1	0.7540	0.0000	Nafees et al. (2017)
P1/S2	0.6532	0.0222	Nafees et al. (2008)
P2	0.4734	0.0311	Nafees et al. (2008)

Table 3: **Disutility due to adverse events**

Adverse event	Mean	Standard error	Reference
Elevated alanine transaminase	0.0735	0.0185	Nafees et al. (2008)
Elevated aspartate transaminase	0.0735	0.0185	Nafees et al. (2008)
Diarrhea	0.0468	0.0155	Nafees et al. (2008)
Dry skin	0.0325	0.0117	Nafees et al. (2008)
Eye problems	0.0449	0.0148	Nafees et al. (2008)
Paronychia	0.0325	0.0117	Nafees et al. (2008)
Pneumonitis	0.0500	0.0120	Doyle et al. (2008)
Pruritus	0.0325	0.0117	Nafees et al. (2008)
Rash	0.0325	0.0117	Nafees et al. (2008)
Stomatitis	0.0325	0.0117	Nafees et al. (2008)

6.3 Utilities

6.4 Health care sector costs

6.4.1 Treatment costs

Treatment costs are a function of drug acquisition and drug administration costs. Dosage for each drug based on Federal Drug Administration (FDA) labels is presented in Table 4. Patients using PBDC are, by default, assumed to use a combination of cisplatin and pemetrexed, although this can be adjusted in the **R** package. At a given treatment line, patients continue to take a drug until disease progression or the end of a treatment cycle. For example, a patient using erlotinib at 1L would take a 150 mg tablet each day until disease progression, at which point they would begin to use the 2L drug. Conversely, a patient using PBDC at 2L would discontinue cisplatin and pemetrexed after completing 6 21-day cycles.

In some cases, patients might be required to use multiple dosage forms to obtain the recommended dosage. In these cases, we assume that patients use the cheapest possible combination of dosage forms. For instance, dosage for nivolumab is 240 mg every 2 weeks, so patients are assumed to use 2 100mg vials and 1 40mg vials.

Dosing with cisplatin depends on body weight. The mean body surface area (BSA) in the United States is $1.6m^2$ for women and $1.9m^2$ for men, which implies a dose of of 120 mg for women of and 142.5 mg for men. The model assumes that there is no vial sharing, so patients use 1 100mg vial and 1 50 mg vial of cisplatin.

Wholesale acquisition costs (WACs) are shown in Table 5. Drug acquisition costs in the model are equal to the WACs adjusted for discounts and rebates. These discounts can be applied to uniquely

Table 4: **Drug dosage**

Drug	Dosage
erlotinib	150 mg orally, once daily
gefitinib	250 mg orally, daily
afatinib	40 mg orally, once daily
dacomitinib	45 mg orally, once daily
osimertinib	80 mg orally, once daily
cisplatin	75mg/m2, 1x/cycle, 6 21-day cycles
pemetrexed	500 mg, 1x/cycle, 6 21-day cycles
bevacizumab	15mg/kg IV every 3 weeks with carboplatin/paclitaxel
nivolumab	240 mg every 2 weeks or 480 mg every 4 weeks
pembrolizumab	200 mg every 3 weeks
atezolizumab	1200 mg as an IV infusion over 60 min every 3 weeks

to each drug in the **R** package, but are, by default, assumed to range from 20% to 30%. When historical data was available, we used the most recently available WAC from either ProspectoRx or AnalySource. There was no historical data for dacomitinib, so we used the publicly announced WAC of $12,400 per month.

Table 5: Wholesale acquisition costs

Drug	Strength	Acquisition cost
erlotinib	150mg tablet	281.71
gefitinib	250mg tablet	257.06
afatinib	40mg tablet	235.05
dacomitinib	45mg tablet	407.39
osimertinib	80mg tablet	487.22
cisplatin	50mg/50ml vial	14.51
cisplatin	100mg/100ml vial	35.00
cisplatin	200mg/200ml vial	100.00
pemetrexed	100mg vial	676.52
pemetrexed	500mg vial	3382.60
bevacizumab	100mg/4ml vial	199.24
bevacizumab	400mg/16ml vial	199.24
nivolumab	100mg/10ml vial	262.21
nivolumab	40mg/4ml vial	262.21
pembrolizumab	100mg/4ml vial	1162.41
atezolizumab	1200mg/20ml vial	444.03

Table 6 reports drug administration costs. Drug administration costs are based on US Current Procedures Terminology (CPT) codes and accrued each time a patient takes a drug.

Table 6: Drug administration costs

Drug	Administration cost	Source
erlotinib	0.00	N/A
gefitinib	0.00	N/A
afatinib	0.00	N/A
dacomitinib	0.00	N/A
osimertinib	0.00	N/A
cisplatin	91.72	CPT 96417, 96415
pemetrexed	136.15	CPT 96413
bevacizumab	91.72	CPT 96413, 96415, 96417
nivolumab	136.15	CPT 96413
pembrolizumab	136.15	CPT 96413
atezolizumab	136.15	CPT 96413

Table 7: Inpatient medical costs

Health state	Mean	Standard error	Reference
S1	7,699	0	None
P1/S2	7,699	0	Skinner et al. (2018)
P2	12,577	0	Skinner et al. (2018)

Table 8: Outpatient medical costs

Health state	Mean	Standard error	Reference
S1	127,860	0	None
P1/S2	127,860	0	Skinner et al. (2018)
P2	127,728	0	Skinner et al. (2018)

6.4.2 Inpatient and outpatient costs

6.4.3 Adverse event costs

6.5 Productivity

Missed days of work to temporary disability = 151 (range = 120.8 - 181.2)

Reduction in hours worked due to permanent disability = 4 (range = 3 - 5)

6.6 Value of hope

To be added.

Table 9: Costs of adverse events

Adverse event	Mean	Lower	Upper	Reference
Diarrhea	6,462	5,169	7,754	DRG 391
Dry skin	940	752	1,128	Wong et al. (2018)
Elevated alanine transaminase	3,900	3,120	4,680	Latremouille-Viau et al. (2017)
Elevated aspartate transaminase	3,900	3,120	4,680	Latremouille-Viau et al. (2017)
Eye problems	2,737	2,189	3,284	Wong et al. (2018)
Paronychia	7,788	6,230	9,345	DRG 602
Pneumonitis	7,728	6,182	9,273	DRG 193
Pruritus	1,184	947	1,420	Wong et al. (2018)
Rash	940	752	1,128	Wong et al. (2018)
Stomatitis	8,101	6,480	9,721	DRG 157

Table 10: Weekly wages by gender and employment status

Gender	Employment status	Percentage	Weekly wage
Female	Full-time	72.4%	$796
Female	Part-time	23.3%	$326
Female	Unemployed	4.3%	$0
Male	Full-time	84.1%	$973
Male	Part-time	11.5%	$321
Male	Unemployed	4.4%	$0

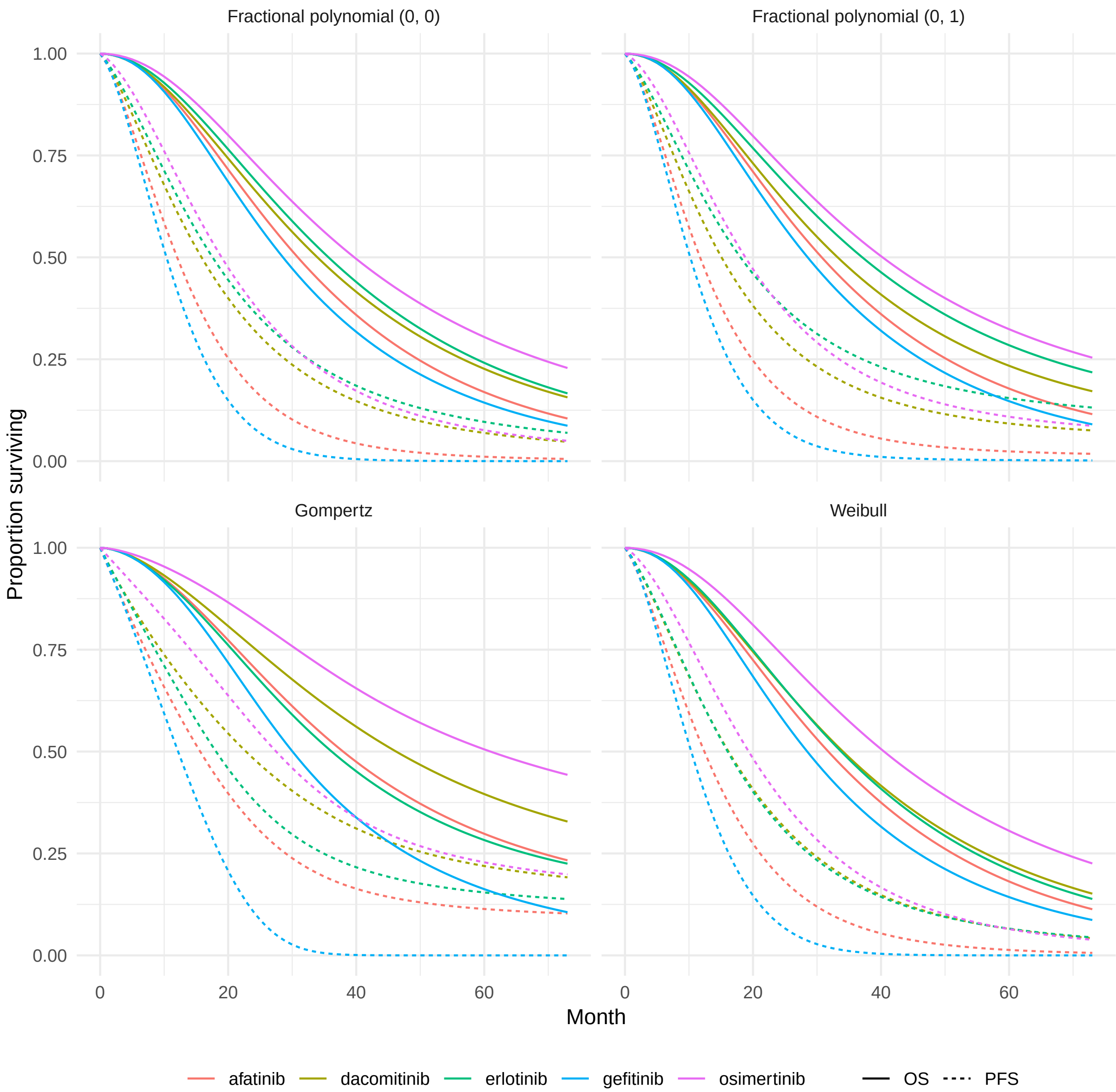
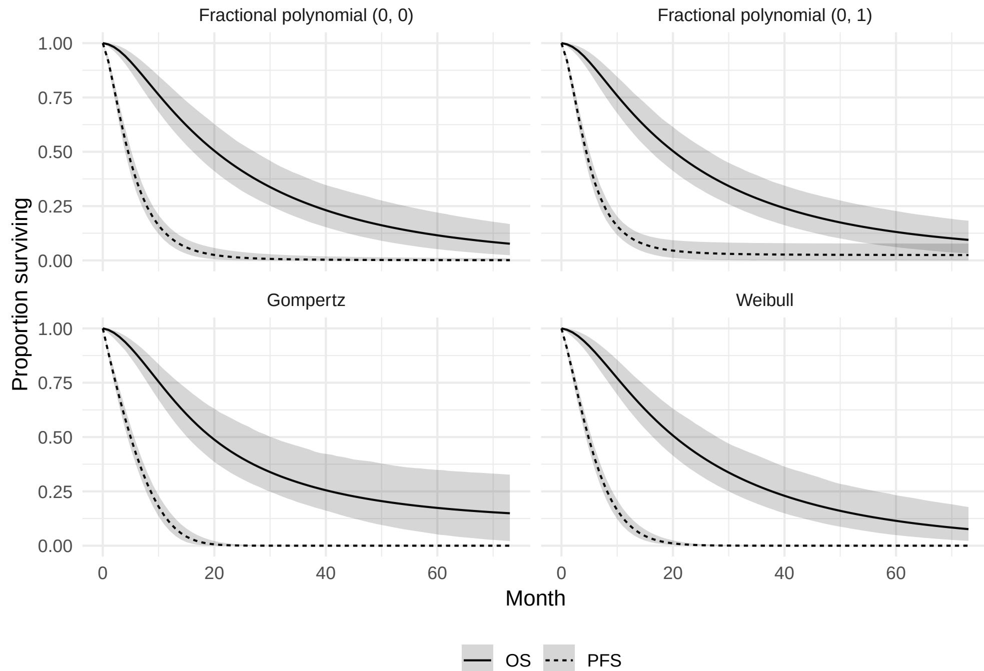
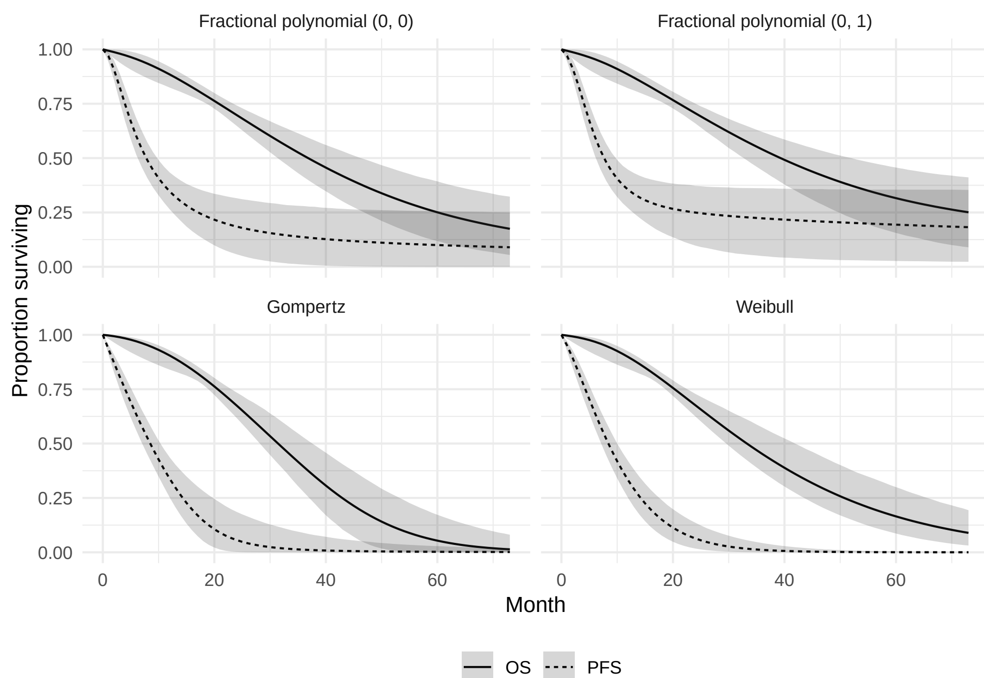


Figure 6: First line estimates of mean progression-free survival and overall survival from the multi-state network meta-analysis

Notes: The simulated posterior distribution of the parameters of the Bayesian multi-state NMA was used to simulate a distribution of progression-free survival and overall survival curves. The curves in the figure are posterior means. Curves with credible intervals are shown in the appendix.



(a) Platinum based doublet therapy



(b) Osimertinib among T790M positive patients

Figure 7: Second line estimates of mean progression-free survival and overall survival from the multi-state network meta-analysis

Notes: The simulated posterior distribution of the parameters of the Bayesian multi-state NMA was used to simulate a distribution of progression-free survival and overall survival curves. The solid lines are posterior means and the shaded region denotes the 95 percent credible interval.

7 Simulation and uncertainty analysis

7.1 Parameter uncertainty

Parameter uncertainty is quantified using probabilistic sensitivity analysis (PSA), which propagates uncertainty in the model input parameters throughout the model by randomly sampling the input parameters from suitable probability distributions (Baio and Dawid 2015), (Claxton et al. 2005).Probability distributions are determined according to the distributional properties of the statistical estimates, which, in turn, depend on the statistical techniques used, and the distributions of the underlying data. Table 11 displays the probability distribution that we used for the model parameters. When conducting a CEA, the results of the PSA are summarized using standard measures from the literature including cost-effectiveness planes, cost-effectiveness acceptability curves, and estimates of the expected value of perfect information (Black 1990), (Van Hout et al. 1994), (Briggs 1999). Furthermore, all point estimates from a CEA or MCDA are reported along with 95 percent confidence intervals.

Table 11: Probability distributions for probabilistic sensitivity analysis

Parameter(s)	Distribution
Health state transitions	
Bayesian multi-state NMA	Simulated posterior distribution
Adverse events	
Bayesian NMA for adverse events	Simulated posterior distribution
Utility	
Health state utility	Normal
Adverse event disutilities	Normal
Health care sector costs	
Drug acquisition and administration cost	Fixed
Discounts and rebates applied to drug acquisition cost	Uniform
Inpatient costs	Gamma
Outpatient costs	Gamma
Adverse event costs	Normal
Productivity costs	
Missed work days	Uniform
Reduction in hours worked	Uniform

7.2 Structural uncertainty

Health state probabilities are typically very sensitive to the parametric distributions used in a survival models. We explore this sensitivity by providing options to choose from a number of different distributions. As discussed in Section 6.1 these included the Weibull, Gompertz, and two second order fractional polynomial models $\{(p_0, p_1) = (0, 0), (0, 1)\}$. Furthermore, both 4-state (Figure 2) and 3-state (Figure 3) model structures can be used. [Need to add detail.]

7.3 Implementation

The individual-level CTSTM was implemented using the R package **hesim** developed by IVI. The package provides a general framework for integrating parameter estimates from a statistical model with different types of simulation models for economic evaluation. Parameter uncertainty is propagated throughout *hesim* models using PSA. Specifically, we randomly drew all input parameters as described in Section 7.1 and simulated the CTSTM for each randomly sampled parameter set. All computationally intensive steps in **hesim** simulation models are written in C++ so the simulations are fast enough to be run with a PSA in web applications.

Appendices

A Systematic Literature Review

A.1 Treatment effects

The systematic literature reviews of treatment effects focused on randomized controlled trials (RCTs) evaluating the efficacy of relevant competing interventions for the treatment of metastatic EGFR+ non-squamous NSCLC by line of treatment, i.e. 1L, 2L, and 2L+. Primary outcomes of interest were OS, PFS and time to progression (TTP). Details regarding eligibility criteria defining the scope of the studies considered relevant are outlined in Table A1, Table A2, and Table A3. The identified evidence was used to estimate the relative treatment effects for each intervention versus a defined intervention of reference by line of treatment conditional upon the prior treatment (class), as well as to estimate the absolute treatment effects with the corresponding reference treatments.

A.2 Utilities

Health state utility values (EQ-5d, HUI2, HUI-3, SF-6D) for the different health states were used in the model as well as disutility estimates associated with adverse events identified by focusing on review or overview studies. Furthermore, published mapping algorithms that allow a non-preference-based measure (generic or disease-specific measure) to be mapped onto a generic preference-based measure are of interest, as well as mapping algorithms between different generic preference-based health state utility values (e.g. between SF-6D and EQ5D) will be searched for. See Appendix Table 4 for study selection criteria.

A.3 Resource use, productivity, and cost

Relevant evidence regarding resource use, productivity and cost estimates were identified by means of a review of published CEA modelling studies in NSCLC relevant for the US setting. See Appendix Table 5 for study selection criteria.

Table A1: PICOS criteria for review of treatment effects (metastatic 1L population)

PICOS	Criteria
Population	Adult patients with metastatic non-squamous NSCLC who are EGFR positive and without prior treatment for their disease.
Interventions	The following drugs as monotherapy or in combination with other drugs • erlotinib • afatinib • gefitinib • osimertinib • dacomitinib
Comparators	• placebo • best supportive care (BSC), defined as whichever therapy was judged to be appropriate by the treating physician. • any intervention of interest • any treatment that facilitates an indirect comparison
Outcomes	• OS • PFS • TTP
Study design	RCTs
Other	English language

Note: Trials where the overall study population is an all-comer population, but subgroup results are reported for the target population of interest are included. A trial or subgroup where the study population is a mixture of non-squamous and squamous patients is included if over 90% is non-squamous.

A.4 Study identification

Relevant studies were identified by searching the following databases using predefined search strategies: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), and Cochrane Central Register of Controlled Trials. The study design filters recommended by the Scottish Intercollegiate Guidelines Network (SIGN) for MEDLINE and EM-

BASE were used to identify clinical trials. The search included terms related to the generic and brand name of the interventions of interest. The US National Institutes of Health Clinical Trial Registry and EU Clinical Trials Registry were also searched to identify completed clinical trials not yet published to identify any completed or ongoing trials that meet the criteria with results available.

For utility studies, and CEA studies providing evidence on healthcare utilization and costs, the following additional databases were searched in addition: NHS Economic Evaluation Database (NHS EED), Health Economic Evaluations Database (HEED), THe Health Economics Research Centre-maintained mapping algorithm database, and The University of Sheffield's ScHARRHUD database of health utilities' evidence.

Where there were gaps in the identified evidence, the search was expanded to include the grey literature, such as reports published by NICE.

A.5 Study selection

Two reviewers, working independently, reviewed all abstracts and proceedings identified in each of the searches according to the selection criteria, with the exception of outcome criteria in the efficacy and safety searches, which were only applied during the screening of full-text publications. All studies identified as eligible studies during abstract screening were then screened at a full-text stage by the same two reviewers. The full-text studies identified at this stage were included for data extraction. Following reconciliation between the two investigators, a third reviewer was included to reach consensus for any remaining discrepancies. The process of study identification and selection is summarized with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagrams (including reasons for exclusion at both the abstract and full text screening stage).

A.6 Data collection

For the clinical studies, two reviewers, working independently, extracted data on study characteristics, interventions, patient characteristics, and outcomes for the final list of included studies. Following reconciliation between the two reviewers, a third reviewer was included to reach consensus on any remaining discrepancies. For all outcomes of interest, information regarding point estimates, variability and uncertainty was obtained. For PFS and OS, hazard ratios and associated information regarding uncertainty were extracted. If results were reported as forest plots, the point estimate and 95$ percent confidence interval were extracted using DigitizeIt software version 2.1.4 (Bormisoft - Informer Technologies, Inc.). Kaplan Meier curves will also be digitzed using DigitizeIt and the proportion of patients free of the event over time will be extracted and the number of patients at risk over time. Adverse events were collected, if reported. Data collected included number and percent of patients with: any grade 3 or 4 adverse event, any grade 3 or 4 treatment related adverse event, any serious adverse event, any treatment related serious adverse event, and death within 30 days of last treatment. The duration over which safety outcomes were reported were also captured. Discontinuation due to adverse events were also examined.

For utility and cost-effectiveness studies, relevant information for the model was extracted from the source publications and checked by a second-reviewer.

A.7 Limitations

Despite the strengths of the proposed SLR, some limitations are applicable to all SLRs that should be acknowledged. As the evidence base is continually growing, any trials published after the search date will not be captured. Further, any trials that are published close to the search date but are not yet indexed in the databases at the time of the search will not be captured by the search of MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials. As with any literature review, this SLR is limited by the use of published data. There is a risk of publication bias as some clinical studies fail to be published while others are published only in abstract form, which presents limited information. Finally, the search and selection were restricted to trials published in English.

Table A2: PICOS criteria for review of treatment effects (metastatic 2L population)

PICOS	Criteria
Population	Adult patients with metastatic non-squamous NSCLC who are EGFR+ positive and who have experienced progression after one line of prior treatment.
Interventions	The following drugs as monotherapy or in combination with other drugs • erlotinib • afatinib • gefitinib • osimertinib • dacomitinib • nivolumab • pembrolizumab • atezolizumab • bevacizumab • platinum-based doublet therapy
Comparators	• placebo • best supportive care (BSC), defined as whichever therapy was judged to be appropriate by the treating physician. • any intervention of interest • any treatment that facilitates an indirect comparison
Outcomes	• OS • PFS • TTP
Study design	RCTs
Other	English language

Note: Trials where the overall study population is an all-comer population, but subgroup results are reported for the target population of interest are included. A trial or subgroup where the study population is a mixture of non-squamous and squamous patients is included if over 90% is non-squamous.

Table A3: PICOS criteria for review of treatment effects (metastatic 2L+ population)

PICOS	Criteria
Population	Adult patients with metastatic non-squamous NSCLC who are EGFR+ positive and who have experienced progression after two or more prior prior treatments.
Interventions	The following drugs as monotherapy or in combination with other drugs • nivolumab • pembrolizumab • atezolizumab • bevacizumab • platinum-based doublet therapy
Comparators	• placebo • best supportive care (BSC), defined as whichever therapy was judged to be appropriate by the treating physician. • any intervention of interest • any treatment that facilitates an indirect comparison
Outcomes	• OS • PFS • TTP
Study design	RCTs
Other	English language

Note: Trials where the overall study population is an all-comer population, but subgroup results are reported for the target population of interest are included. A trial or subgroup where the study population is a mixture of non-squamous and squamous patients is included if over 90% is non-squamous.

B Network meta-analysis

B.1 Feasibility assessment

With an NMA, interest centers on the comparison of the treatment effects of interventions that have not been studied in a head-to-head fashion. In order to ensure that these indirect comparisons of interventions are not affected by differences in study effects (i.e. known and unknown prognostic factors) between studies, we only considered the treatment effects of each trial. This consideration implied that all interventions indirectly compared have to be part of one network of trials where each trial has at least one intervention (active or placebo) in common with another trial. For interventions of interest that were not part of the same network, then it was not possible to perform an indirect comparison of treatment effects of these interventions without a substantial risk of bias (Jansen et al. 2014; Dias et al. 2018).

In combining direct and indirect evidence in an NMA, trials must be reasonably similar. Patients are randomized only within trials, not across trials, so there is a risk that patients participating in different trials differ with respect to demographic, disease or other characteristics. In addition, features of the trials themselves may differ. If these trial or patient characteristics are effect modifiers, i.e. they affect the treatment effects of an intervention versus a control, then there are systematic differences in treatment effects across trials. Systematic differences in known and unknown effect-modifiers among studies comparing the same interventions in direct fashion result in between-study heterogeneity. An imbalance in the distribution of effect modifiers between studies comparing different interventions will result in transitivity or consistency violations and therefore biased indirect comparisons (Jansen et al. 2012; Jansen and Trikalinos 2013).

In order to gauge the appropriateness of proceeding with an NMA, IVI's feasibility assessment included: (i) an assessment of whether the RCT evidence for the interventions of interest formed one evidence network for each outcome by line of treatment conditional upon prior treatment (class); and (ii) an assessment of the distribution of study and patient characteristics that may have had relative treatment effects across the direct comparisons of the evidence networks.

B.2 Evaluation of consistency between direct and indirect comparisons

Prior to the actual NMA, the consistency between direct and indirect comparisons were evaluated for networks that include closed loops. For comparisons (i.e., contrasts) that are part of a closed loop made up of more than 1 RCT connecting different interventions, we assessed the consistency by comparing the relative treatment effect for one contrast of this loop based on direct information with the corresponding estimates based on indirect information (Dias et al. 2018).

B.3 Estimation of the relative treatment effects under the assumption of consistency

Based on the findings of the feasibility assessment, the results of the RCTs that are part of one evidence network and deemed sufficiently similar were synthesized by means of NMAs by outcome of interest. Under the assumption of consistency, the NMA model relates the data from the individual studies to basic parameters reflecting the (pooled) relative treatment effect of each intervention compared to an overall treatment of reference. The NMA models were extended by incorporating covariates (i.e., meta-regression analysis) only if there was an imbalance in treatment potential effect modifiers across trials in the network (Dias et al. 2018).

B.4 Model selection

The deviance information criterion (DIC) can be used to compare the goodness-of-fit of competing evidence synthesis models (Dias et al. 2018). DIC provides a measure of model fit that penalizes model complexity. In general, a more complex model results in a better fit to the data, demonstrating a smaller residual deviance. The model with the better trade-off between fit and parsimony has a lower DIC. A difference in DIC of about 10 points can be considered meaningful.

B.5 Software

The parameters of the different models were estimated using a Markov Chain Monte Carlo (MCMC) method implemented in the JAGS software package. All JAGS analyses were run using R statistical software (R Core Team 2014).

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