

An R-based open-source cost-effectiveness model for **EGFR+ non-small-cell lung cancer**

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Purpose

- > A flexible open-source simulation model that can be used to estimate the value of alternative sequential treatment strategies for patients with metastatic EGFR+ non-small-cell lung cancer (NSCLC)
- > Accessible to both technical and non-technical end-users
- > Evaluate the impact of
 - > uncertainty in clinical evidence
 - > alternative model structures
 - > decision framework
 - > inclusion of novel concepts of values
 - > perspective

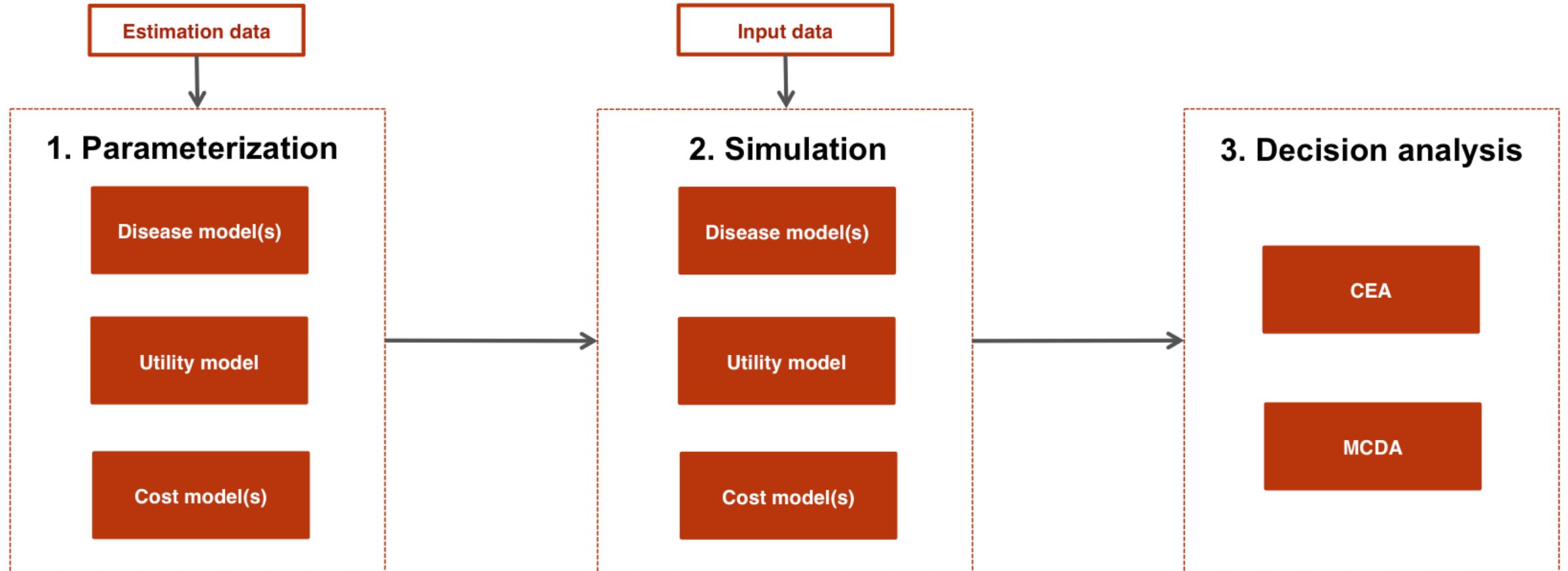
Model overview

- > Individual-level continuous-time state transition model (CTSTM)
- > Two model structures
 - > 3-state model
 - > 4-state model allowing for sequential treatment
- > Parameterized using multi-state (network) meta-analyses
 - > Weibull
 - > Gompertz
 - > 2nd order fractional polynomials
- > Novel element of value (i.e. value of hope)
- > Value of information

Model outcomes

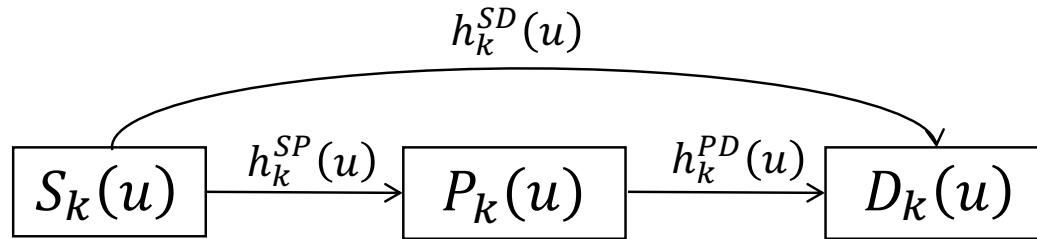
Category	Outcomes
Health outcomes	Health state probabilities; progression free survival & overall survival; quality-adjusted life-years
Adverse events	Diarrhea, dry skin, elevated alanine transaminase, elevated aspartate transaminase, eye problems, paronychia, pneumonitis, pruritus, rash, stomatitis
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

hesim



<http://hesim-dev.github.io/hesim/>

Preferred economic model structure: multi-state model



Common practice

Economic model

- Partitioned survival model

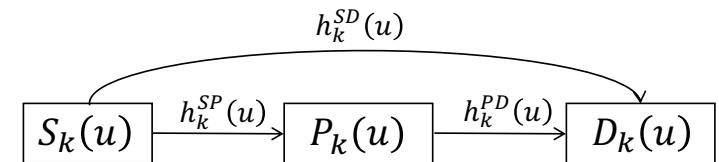


Evidence synthesis

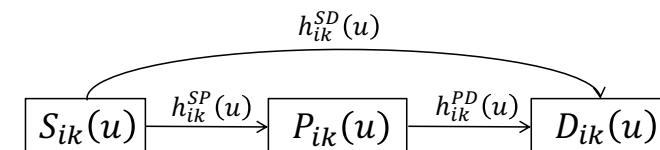
- Typical source data: KM curves, hazard ratios
- Meta-analysis of baseline hazard function for PFS and OS
- Network meta-analysis of (time-varying) hazard ratios for PFS and OS

Why not this?

Economic model



Evidence synthesis



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

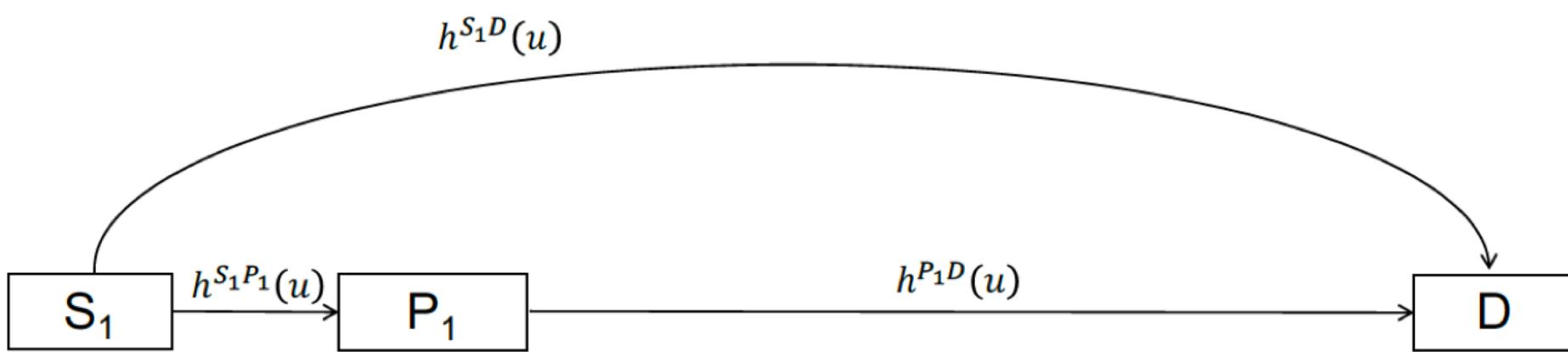
$$\ln(h_{ik}^{SD}(u)) = \alpha_{4ik}$$

$$\ln(h_{ik}^{PD}(u)) = \alpha_{5ik} + \alpha_{6ik}u^{p_1}$$

$$\begin{pmatrix} \alpha_{1ik} \\ \alpha_{2ik} \\ \alpha_{3ik} \\ \alpha_{4ik} \\ \alpha_{5ik} \\ \alpha_{6ik} \end{pmatrix} = \begin{pmatrix} \mu_{1ik} \\ \mu_{2ik} \\ \mu_{3ik} \\ \mu_{4ik} \\ \mu_{5ik} \\ \mu_{6ik} \end{pmatrix} + \begin{pmatrix} \delta_{1,ik} \\ d_{2,1t_{ik}} - d_{2,1t_{11}} \\ 0 \\ 0 \\ d_{3,1t_{ik}} - d_{3,1t_{11}} \\ 0 \end{pmatrix}$$

$$\delta_{1,ik} \sim N(d_{1,1t_{ik}} - d_{1,1t_{11}}, \sigma_{d_1}^2)$$

3-state model



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

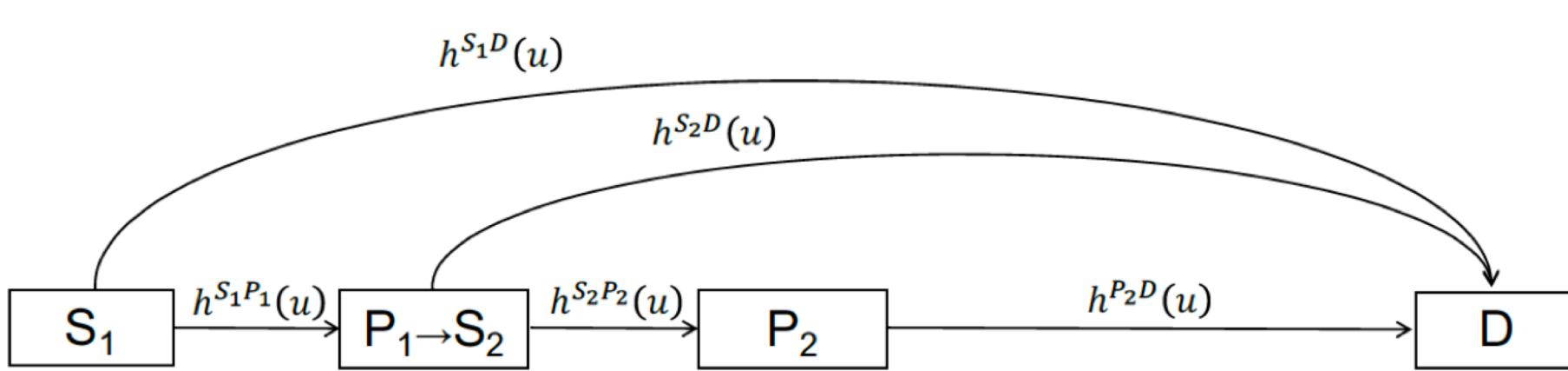
D = Dead

$h^{S_1P_1}(u)$ = 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

4-state model



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

$h^{S_1 P_1}(u)$ = hazard for transitioning from progression-free to progression with 1L treatment at time u

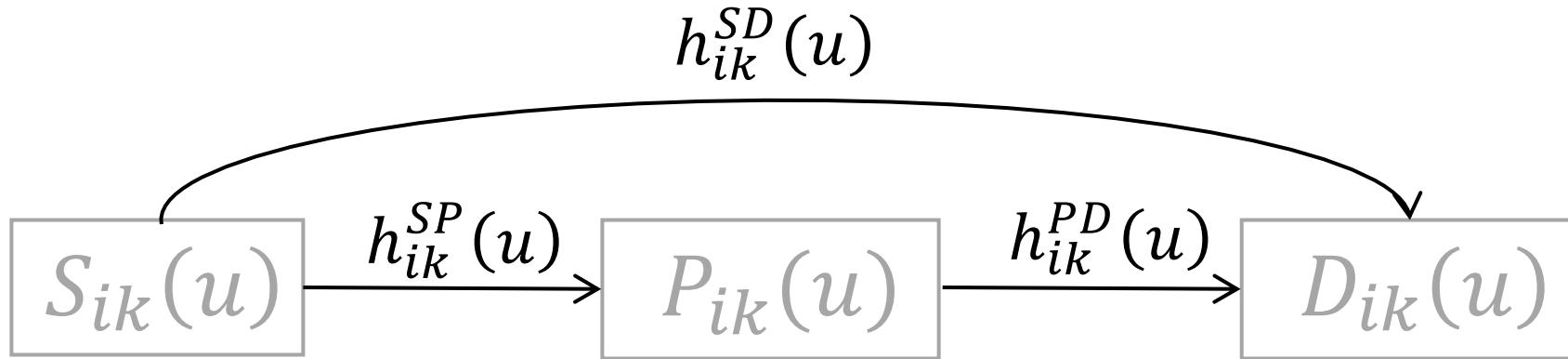
$h^{S_1 D}(u)$ = hazard for transitioning from progression-free to dead with 1L treatment at time u

$h^{S_2 P_2}(u)$ = hazard for transitioning from progression-free to progression with 2L treatment at time u

$h^{S_2 D}(u)$ = hazard for transitioning from progression-free to dead with 2L treatment at time u

$h^{P_2 D}(u)$ = hazard for transitioning from progression on 2L to dead at time u

Parameterization using multi-state (network) meta-analysis conducted separately by line (1L, 2L)



$S_{ik}(u)$ = progression -free (stable disease) in study i, treatment arm k at time u

$P_{ik}(u)$ = progressed disease in study i, treatment arm k at time u

$D_{ik}(u)$ = dead in study i, in treatment arm k at time u

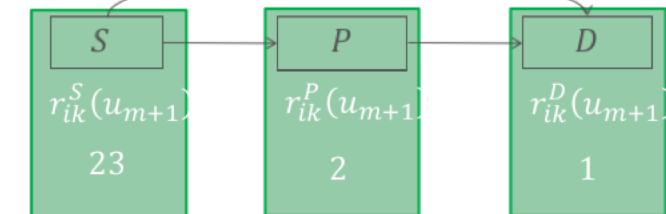
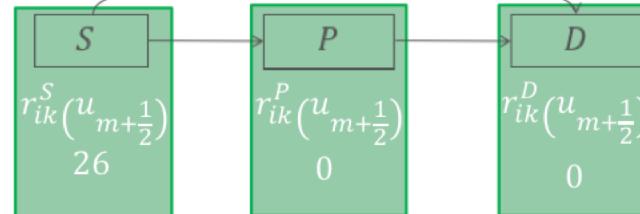
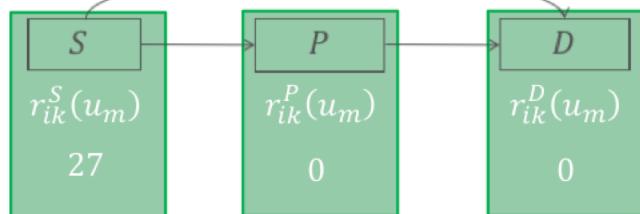
$h_{ik}^{SP}(u)$ = hazard rate for disease progression in study i, in treatment arm k at time u

$h_{ik}^{PD}(u)$ = hazard rate for dying post-progression in study i, in treatment arm k at time u

$h_{ik}^{SD}(u)$ = hazard rate for dying pre-progression in study i, in treatment arm k at time u

Data structure

r1	r2	r3	r4	r5	r6	r7	r8	r9	z1	z2	z3	dt1	dt2	time	study	arm	pfs	os	study_intervention	
27	0	0	26	0	0	23	2	1	27	26	26	1	2	1	1	1	2	1	1	Yang_2014 Pemetrexed+Cisplatin (EGFR+).xlsx
23	2	1	23	1	2	22	2	2	26	26	26	1	2	3	1	2	0.88	0.922	Yang_2014 Pemetrexed+Cisplatin (EGFR+).xlsx	
22	2	2	21	3	2	21	2	3	26	26	26	1	2	5	1	2	0.8	0.922	Yang_2014 Pemetrexed+Cisplatin (EGFR+).xlsx	
21	2	3	20	3	3	20	1	5	26	26	26	1	2	7	1	2	0.768	0.884	Yang_2014 Pemetrexed+Cisplatin (EGFR+).xlsx	
20	1	5	17	4	5	15	6	5	26	26	26	1	2	9	1	2	0.667	0.806	Yang_2014 Pemetrexed+Cisplatin (EGFR+).xlsx	
15	6	5	15	6	5	13	8	5	26	26	26	1	2	11	1	2	0.562	0.806	Yang_2014 Pemetrexed+Cisplatin (EGFR+).xlsx	
13	8	5	12	9	5	12	8	6	26	26	26	1	2	13	1	2	0.469	0.806	Yang_2014 Pemetrexed+Cisplatin (EGFR+).xlsx	
12	8	6	12	8	6	12	7	7	26	26	26	1	2	15	1	2	0.469	0.769	Yang_2014 Pemetrexed+Cisplatin (EGFR+).xlsx	
12	7	7	12	7	7	12	7	7	26	26	26	1	2	17	1	2	0.467	0.73	Yang_2014 Pemetrexed+Cisplatin (EGFR+).xlsx	
12	7	7	12	6	8	12	6	8	26	26	26	1	2	19	1	2	0.467	0.695	Yang_2014 Pemetrexed+Cisplatin (EGFR+).xlsx	
12	6	8	12	6	8	10	8	8	26	26	26	1	2	21	1	2	0.467	0.689	Yang_2014 Pemetrexed+Cisplatin (EGFR+).xlsx	
10	8	8	10	8	8	10	8	8	26	26	26	1	2	23	1	2	0.391	0.689	Yang_2014 Pemetrexed+Cisplatin (EGFR+).xlsx	
10	8	8	10	8	8	10	6	10	26	26	26	1	2	25	1	2	0.39	0.689	Yang_2014 Pemetrexed+Cisplatin (EGFR+).xlsx	
10	6	10	10	5	10	9	5	10	26	25	24	1	2	27	1	2	0.39	0.598	Yang_2014 Pemetrexed+Cisplatin (EGFR+).xlsx	
9	5	10	9	4	11	7	6	11	24	24	24	1	2	29	1	2	0.39	0.546	Yang_2014 Pemetrexed+Cisplatin (EGFR+).xlsx	
7	6	11	7	6	11	5	8	11	24	24	24	1	2	31	1	2	0.291	0.535	Yang_2014 Pemetrexed+Cisplatin (EGFR+).xlsx	

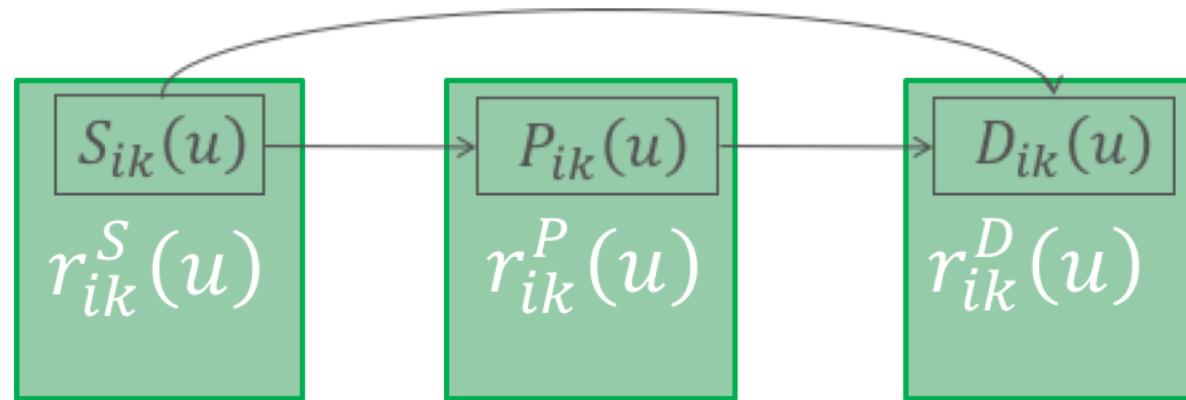


Data at the beginning of interval m

Data at the midpoint of interval m

Data at the end of interval m

Likelihood



$$(r_{ik}^S(u), r_{ik}^P(u), r_{ik}^D(u)) \sim \text{multinomial}(S_{ik}(u), P_{ik}(u), D_{ik}(u), n_{ik}(u))$$

where $n_{ik}(u) = r_{ik}^S(u) + r_{ik}^P(u) + r_{ik}^D(u)$ and $S_{ik}(u) + P_{ik}(u) + D_{ik}(u) = 1$

Interval specific hazard rates

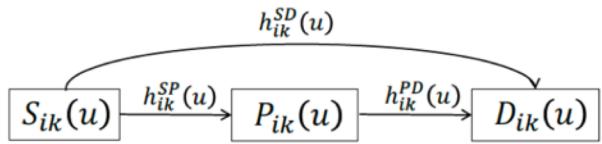
- Assuming constant hazards for each interval m and with information regarding S , P , and D at the beginning (u_m), middle ($u_{m+\frac{1}{2}}$) and end point (u_{m+1}) of the interval we can estimate the interval-specific hazards h_{ikm}^{SP} , h_{ikm}^{SD} , and h_{ikm}^{PD} according to:

$$S_{ik}(u) = S_{ik}(u_m) e^{-(h_{ikm}^{SP} + h_{ikm}^{SD})(u - u_m)}$$

$$P_{ik}(u) = P_{ik}(u_m) e^{-h_{ikm}^{PD}(u - u_m)} + \frac{S(u_m) h_{ikm}^{SP} (e^{-(h_{ikm}^{SP} + h_{ikm}^{SD})(u - u_m)} - e^{-h_{ikm}^{PD}(u - u_m)})}{h_{ikm}^{PD} - h_{ikm}^{SP} - h_{ikm}^{SD}}$$

$$D_{ik}(u) = 1 - S_{ik}(u) - P_{ik}(u)$$

Multi-state network meta-analysis model



$S_{ik}(u)$ = progression -free (stable disease) in study i, treatment arm k at time u

$P_{ik}(u)$ = progressed disease in study i, treatment arm k at time u

$D_{ik}(u)$ = dead in study i, in treatment arm k at time u

$h_{ik}^{SP}(u)$ = hazard rate for disease progression in study i, in treatment arm k at time u

$h_{ik}^{PD}(u)$ = hazard rate for dying post-progression in study i, in treatment arm k at time u

$h_{ik}^{SD}(u)$ = hazard rate for dying pre-progression in study i, in treatment arm k at time u

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

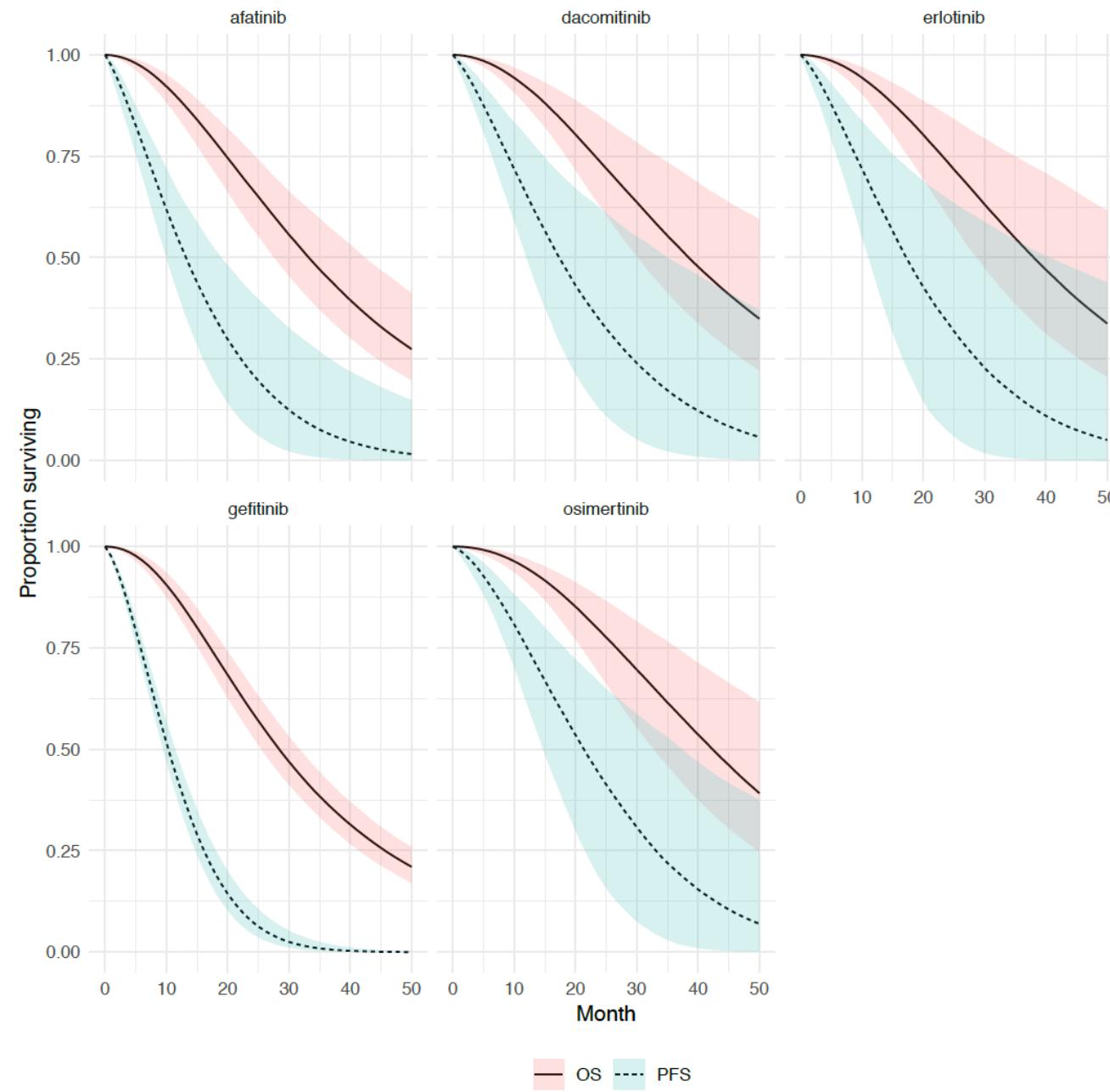
$$\ln(h_{ik}^{SD}(u)) = \alpha_{4ik}$$

$$\ln(h_{ik}^{PD}(u)) = \alpha_{5ik} + \alpha_{6ik}u^{p_1}$$

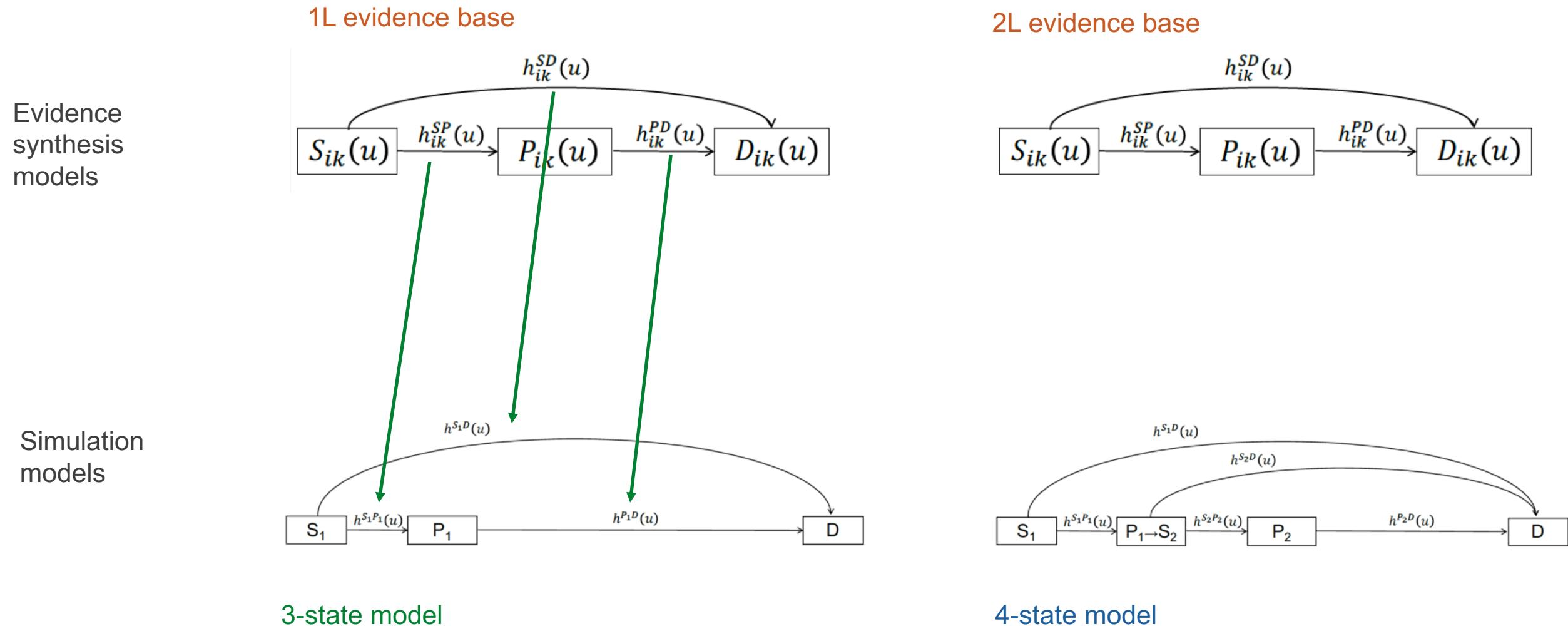
$$\begin{pmatrix} \alpha_{1ik} \\ \alpha_{2ik} \\ \alpha_{3ik} \\ \alpha_{4ik} \\ \alpha_{5ik} \\ \alpha_{6ik} \end{pmatrix} = \begin{pmatrix} \mu_{1ik} \\ \mu_{2ik} \\ \mu_{3ik} \\ \mu_{4ik} \\ \mu_{5ik} \\ \mu_{6ik} \end{pmatrix} + \begin{pmatrix} \delta_{1,ik} \\ d_{2,1t_{ik}} - d_{2,1t_{i1}} \\ 0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

$$\delta_{1,ik} \sim N(d_{1,1t_{ik}} - d_{1,1t_{i1}}, \sigma_{d_1}^2)$$

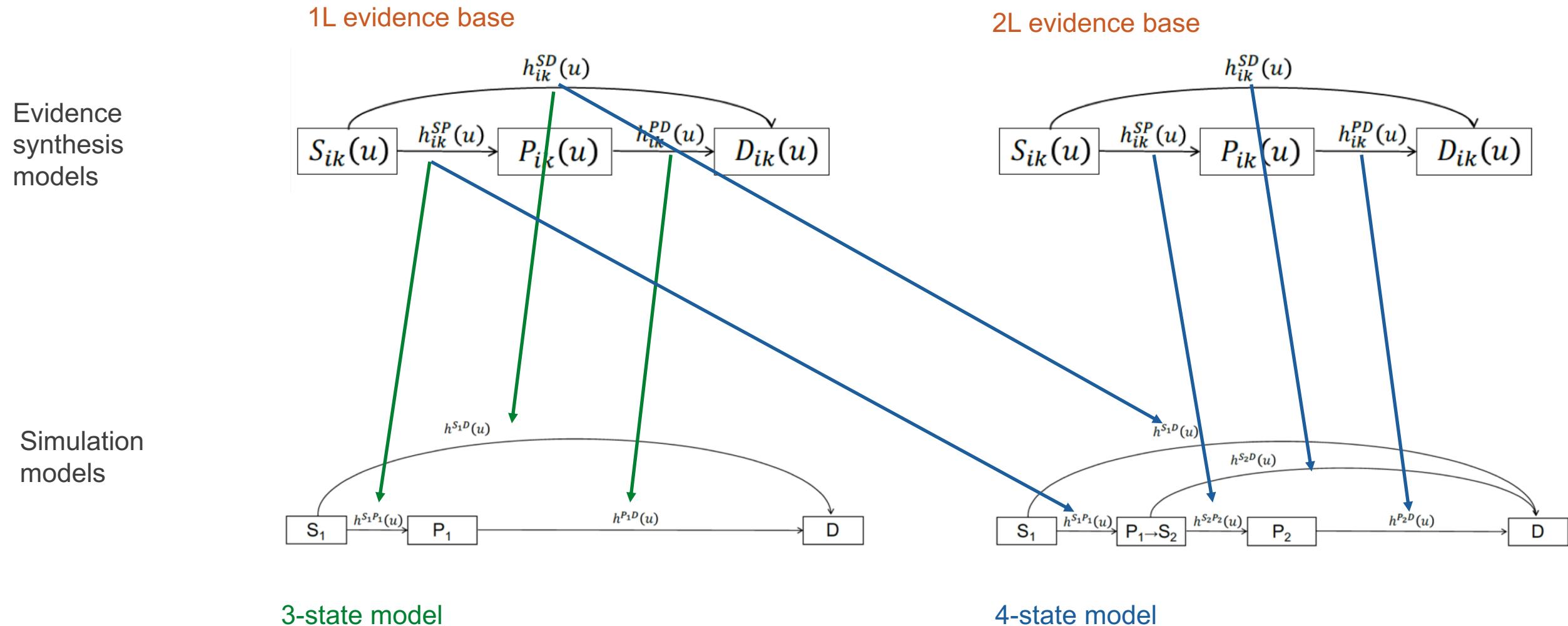
where $u^0 = \ln(u)$ and $d_{1,11} = 0$, $d_{2,11} = 0$, and $d_{3,11} = 0$



Incorporation of treatment effect parameters in CE model



Incorporation of treatment effect parameters in CE model



IVI-NSCLC architecture



IVI-NSCLC Basic Value Tool



IVI-NSCLC Advanced Value Tool



IVI-NSCLC R-software package



R source code (GitHub)

<https://innovationvalueinitiative.github.io/IVI-NSCLC/>

Source code available on GitHub

The screenshot shows the GitHub repository page for `InnovationValueInitiative / IVI-NSCLC`. The page includes a navigation bar with links to Pull requests, Issues, Marketplace, and Explore. Below the header, there are tabs for Code, Issues (1), Pull requests (0), Projects (0), Wiki, and Insights. A message at the top states, "The IVI-NSCLC simulation model <https://innovationvalueinitiative.git...>". Below this, there is a tag cloud with the term "open-source-models". Key statistics are displayed: 349 commits, 1 branch, 0 releases, 1 environment, and 4 contributors. A dropdown menu shows the current branch is "master". There are buttons for "New pull request", "Create new file", "Upload files", "Find File", and a prominent green "Clone or download" button. The main content area lists recent commits by user "dinceriti", with the latest commit being "Remove unneeded tmp object from tutorial" (commit b66d50f, 5 days ago). Other commits include updates to R scripts, data files, and documentation, along with merges and Travis CI configuration changes.

Commit	Description	Time Ago
b66d50f	Remove unneeded tmp object from tutorial	5 days ago
R	A third update to hesim links	14 days ago
data-raw	Update params_mstate_nma object to specify random_method element in ...	3 months ago
data	Update params_mstate_nma object to specify random_method element in ...	3 months ago
docs	Remove unneeded tmp object from tutorial	5 days ago
man	A third update to hesim links	14 days ago
pkgdown	Update package website.	3 months ago
tests	Fix for treatment costs and T790M mutation status. Unit tests added.	3 months ago
vignettes	Remove unneeded tmp object from tutorial	5 days ago
.Rbuildignore	New functions to create treatment sequences	9 months ago
.gitignore	Merge branch 'master' of https://github.com/InnovationValueInitiative...	4 months ago
.travis.yml	Run travis on R 3.6	16 days ago
DESCRIPTION	Update hesim links	14 days ago
NAMESPACE	New function summarize_outcomes to summarize clinical and economic ou...	4 months ago
README.md	Fix typo on package home page.	3 months ago
README.md		

IVI-NSCLC technical web page

iviNSCLC **1.0.0.9000** API Tutorial PDF documentation Source data Web apps ▾



IVI-NSCLC

iviNSCLC is an R package that runs the [Innovation and Value Initiative's \(IVI's\)](#) non-small cell lung cancer (NSCLC) simulation model (the IVI-NSCLC model). The model simulates the costs, health outcomes, and risks associated with sequences of treatment including EGFR Tyrosine Kinase Inhibitors (TKIs), platinum-based doublet chemotherapy (PBDC), anti-vascular endothelial growth factor (anti-VEGF) therapy, and immune checkpoint inhibitors for patients with epidermal growth factor receptor (EGFR) positive NSCLC.

Installation

```
# Install the development version from GitHub:  
# install.packages("devtools")  
devtools::install_github("InnovationValueInitiative/IVI-NSCLC")
```

Links

Browse source code at
[https://github.com/
InnovationValueInitiative/IVI-NSCLC](https://github.com/InnovationValueInitiative/IVI-NSCLC)

Report a bug at
[https://github.com/
InnovationValueInitiative/IVI-NSCLC/issues](https://github.com/InnovationValueInitiative/IVI-NSCLC/issues)

License

GPL-3

Developers

Devin Incerti
Author, maintainer

Jeroen P. Jansen
Author

Dev status

build passing

codecov 96%

<https://innovationvalueinitiative.github.io/IVI-NSCLC/>

Reference

Parameter estimates

params_mstate_nma	Multi-state network meta-analysis parameters
mstate_nma_pfs mstate_nma_os	Progression-free survival and overall survival from network meta-analysis
mstate_nma_hazard	Hazard functions from network meta-analysis
mstate_nma_hr	Hazard ratios from network meta-analysis
mstate_nma_coef	Coefficients from network meta-analysis
mstate_ma_coef	Coefficients from meta-analyses
adverse_events	Adverse events
params_ae_nma	Adverse event network meta-analysis parameters
params_utility	Utility parameters
params_costs_tx	Treatment cost parameters
annualized_tx_costs()	Annualized treatment costs
params_costs_op	Outpatient cost parameters
params_costs_inpt	Inpatient cost parameters
params_costs_ae	Adverse event cost parameters
params_costs_prod	Productivity cost parameters

Patient population

age_dist	Patient age
create_patients()	Create patient data table

Treatment sequences

treatments	Treatments
tx_1L()	First line treatment options
tx_2L()	Second line treatment options
tx_2LP()	Second line plus treatment options
txseq()	A single treatment sequence
txseq_list()	A list of treatment sequences

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- [Treatment sequences](#)
- [Model structure](#)
- [Economic model](#)
- [Multi criteria decision analysis](#)
- [Value of hope](#)

R package tutorial - Increasing transparency with reproducible scripts

3 Economic model

We provide an example a four-state model for 1L treatment, while also showing how a three-state model could be specified. Importantly, different modeling approaches are used for the three-state and four-state approaches. Since a “clock-forward” multi-state NMA was conducted separately by line of treatment, the four-state model is a mixture of clock-forward and “clock-reset” models. In the clock-reset approach, time u in $h^s(u)$ resets after each transition whereas in the clock-forward approach time u refers to time since the start of the model (see the tutorial [here](#) for a more detailed discussion). In the four-state model, the clock resets when entering state S1. Conversely, in the three-state model (either starting at 1L or 2L), the transition rates are always estimated using a NMA of treatments within a single line, so a clock-forward multi-state model must be used.

An individual-level simulation is required to simulate clock-reset and mixtures of clock-forward and clock-reset models, and can also be used to simulate clock-forward models. The individual-level model is simulated in R using the `IndivCtstm` class from the `hesim` package.

3.1 Set up

3.1.1 Patient population

The first step in the analysis is to define the target population. In the individual-level model, a sufficient number of patients must be simulated so that expected (i.e., mean) outcomes are stable across simulations. In this example, we simulate 1,000 patients.

```
pats <- create_patients(n = 1000)
```

3.1.2 Treatment sequences

Since T790M mutation status is unknown in the 1L four-state case, a treatment sequence consists of a 1L treatment and treatment options for both the T790M+ and T790M- cases at 2L and 2L+. Multiple treatment sequences are combined into a “txseq_list” object using `txseq_list()`. We specify that the model begins at first line treatment with the argument `start_line = "first"` at which time the T790M mutation status is unknown; however, note that the evidence base is currently too limited to reliably simulate disease progression when starting at second line.

```
txseq1 <- txseq(first = "gefitinib",
                  second = c("osimertinib", "PBDC"),
                  second_plus = c("PBDC + bevacizumab", "PBDC + bevacizumab"))
txseq2 <- txseq(first = "erlotinib",
                  second = c("osimertinib", "PBDC"),
                  second_plus = c("PBDC + bevacizumab", "PBDC + bevacizumab"))
txseqs <- txseq_list("Sequence 1" = txseq1, "Sequence 2" = txseq2,
                      start_line = "first",
                      mutation = "unknown")
```

It is also useful to write a short convenience function for creating informative names for treatment strategies (i.e., treatment sequences), which can be used for plotting.

```
# Convenience function to add factor names to data table
# for plotting
strategy_factor <- function(x, rev = FALSE){
```

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4 Decision analysis

Decision analysis can be performed using either a cost-effectiveness analysis (CEA) or a multi criteria decision analysis (MCDA) framework.

4.1 Cost-effectiveness analysis

Before performing the CEA, we will first summarize relevant health and economic outcomes.

```
outcomes <- summarize_outcomes(econmod = econmod, prod_costs = prodcosts,
                                 dr_qalys = .03, dr_costs = .03,
                                 strategy_names = names(txseqs))
knitr::kable(outcomes)
```

Outcome	Sequence 1	Sequence 2
Life-years	3.55 (3.24, 4.07)	4.37 (3.46, 6.90)
QALYs	2.08 (1.88, 2.34)	2.71 (2.05, 4.68)
Drug acquisition costs	237,087 (214,427, 266,784)	307,991 (238,834, 509,227)
Drug administration costs	11,488 (9,837, 14,380)	11,027 (8,473, 13,871)
Outpatient medical costs	42,901 (35,144, 53,478)	41,912 (33,632, 51,968)
Inpatient medical costs	245,810 (200,136, 310,183)	257,532 (207,928, 321,675)
Adverse event costs	4,395 (2,048, 8,387)	4,086 (1,487, 9,210)
Health care sector costs	541,681 (475,980, 644,177)	622,548 (516,494, 846,604)
Productivity costs	61,995 (57,107, 66,719)	56,259 (43,722, 64,120)
Societal costs	603,676 (540,506, 701,460)	678,807 (577,991, 891,518)
Net monetary benefit	-291,455 (-360,398, -240,413)	-271,665 (-345,978, -179,196)

CEA can be [performed using](#) `hesim` with the functions `icea()` and `icea_pw()`. For this analysis, we used the first treatment sequence as the comparator and assume a willingness to pay per QALY of \$150,000.

```
icea <- hesim::icea(ce_sim, dr_qalys = .03, dr_costs = .03)
icea_pw <- hesim::icea_pw(ce_sim, comparator = 1, dr_qalys = .03, dr_costs = .03)
```

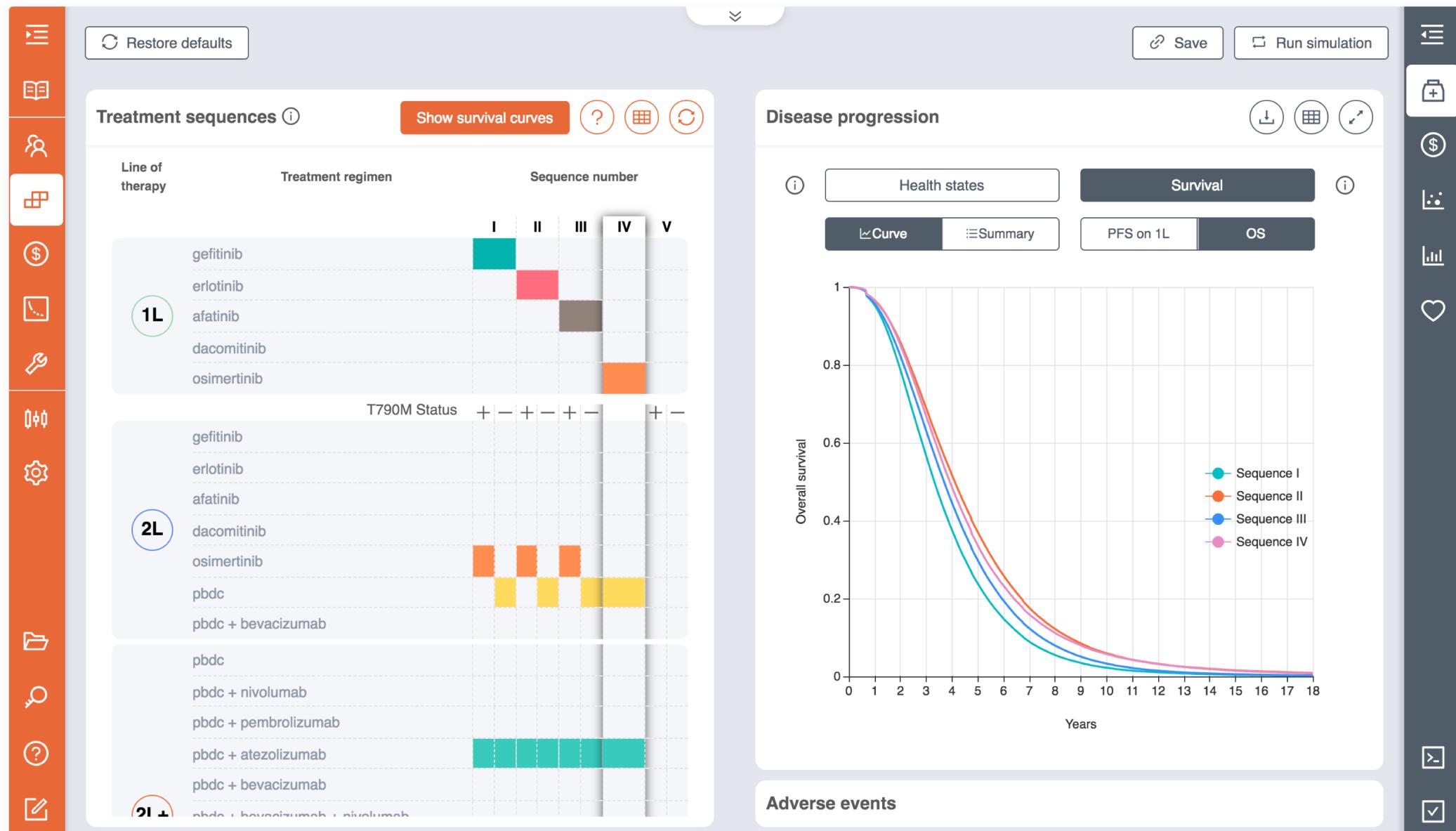
We report [incremental cost-effective ratios \(ICERs\)](#)—a commonly used measure for summarizing the cost-effectiveness of interventions—as well as the incremental net monetary benefit (NMB). The incremental NMB is defined as incremental QALYs multiplied by a willingness to pay threshold (\$150,000 in this example) less incremental costs.

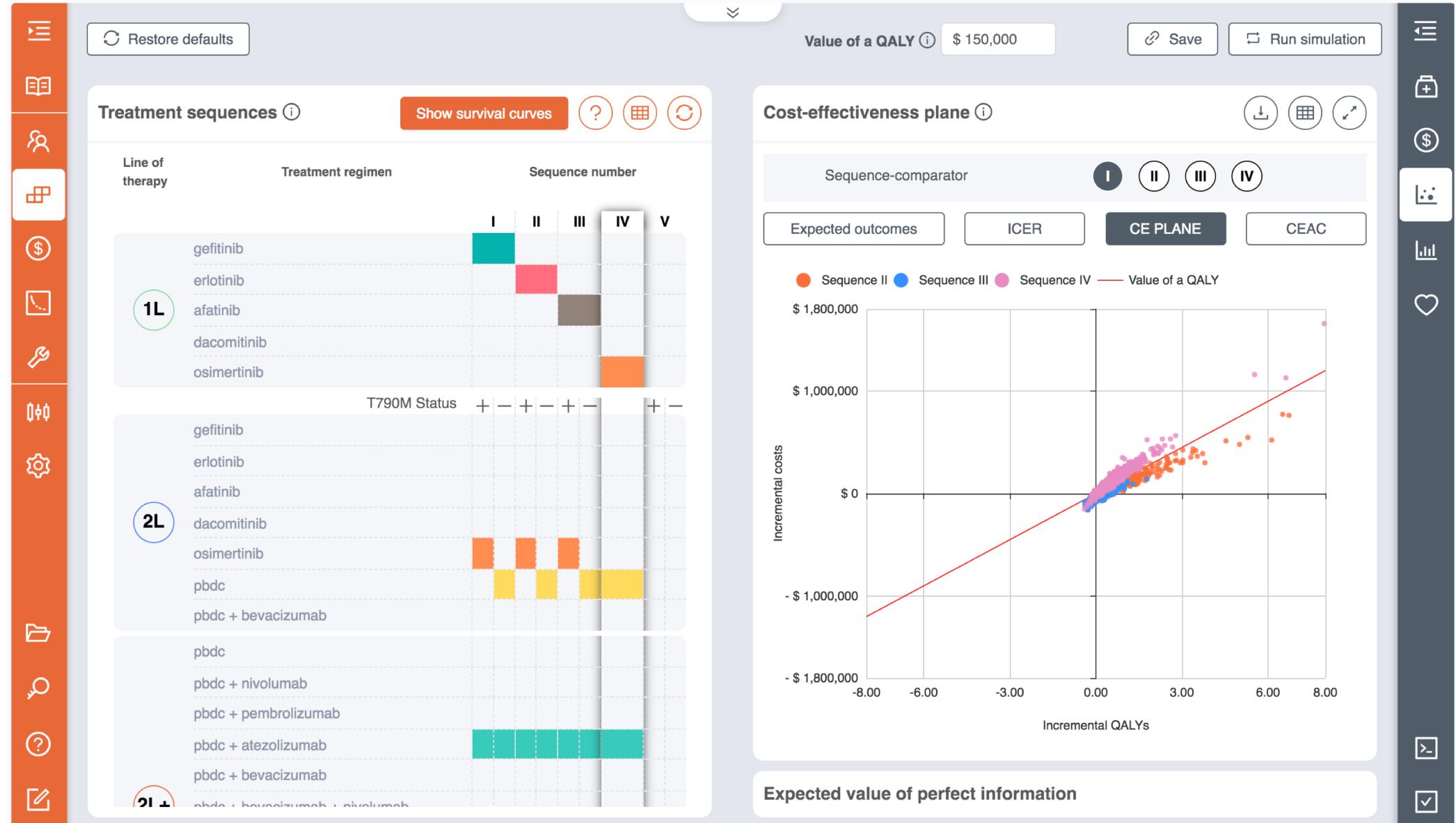
```
icer <- hesim::icer_tbl(icea_pw,
                        k = 150000, # WTP per QALY
```

2 user interfaces targeted at different end users

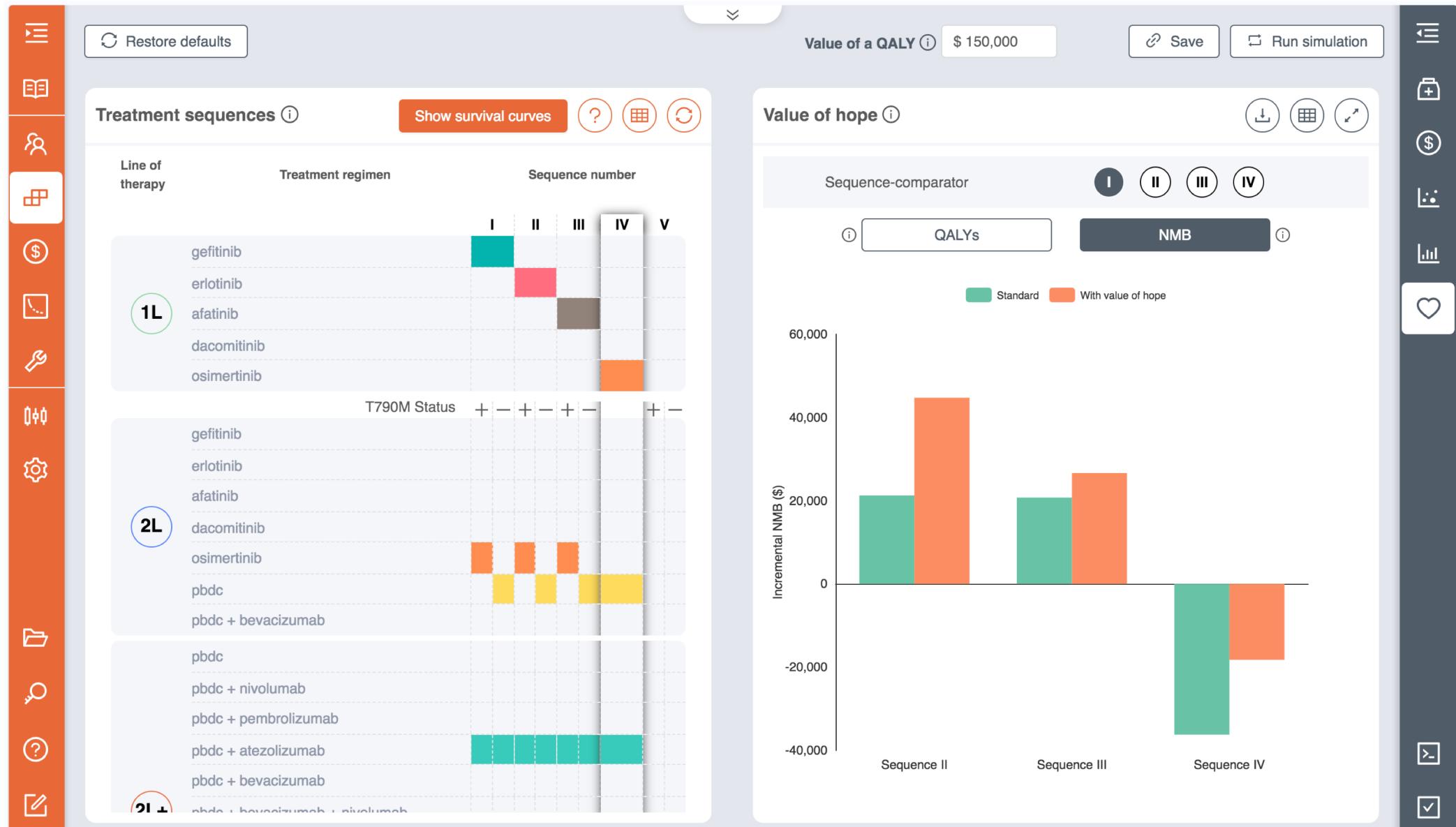
The image displays two side-by-side screenshots of the IVI-NSCLC Value Tools. The left screenshot shows the 'IVI-NSCLC Basic Value Tool' with a dark-themed interface. A central modal window titled 'Welcome to the IVI-NSCLC Basic Value Tool' contains descriptive text about the tool's purpose and usage, along with 'Take the tour' and 'Skip the tour' buttons. The right screenshot shows the 'IVI-NSCLC Advanced Value Tool' with a light-themed interface. It also features a central modal window titled 'Welcome to the IVI-NSCLC Advanced Value Tool' with similar descriptive text and 'Take the tour' and 'Skip the tour' buttons. Both interfaces have a consistent layout with a sidebar on the left containing icons for About IVI, Technical documentation, Feedback, and other tools, and a main content area on the right.

<https://innovationvalueinitiative.github.io/IVI-NSCLC/>





<https://innovationvalueinitiative.github.io/IVI-NSCLC/>



<https://innovationvalueinitiative.github.io/IVI-NSCLC/>

[Restore defaults](#)

[Save](#) [Run simulation](#)

MCDA preferences ⓘ

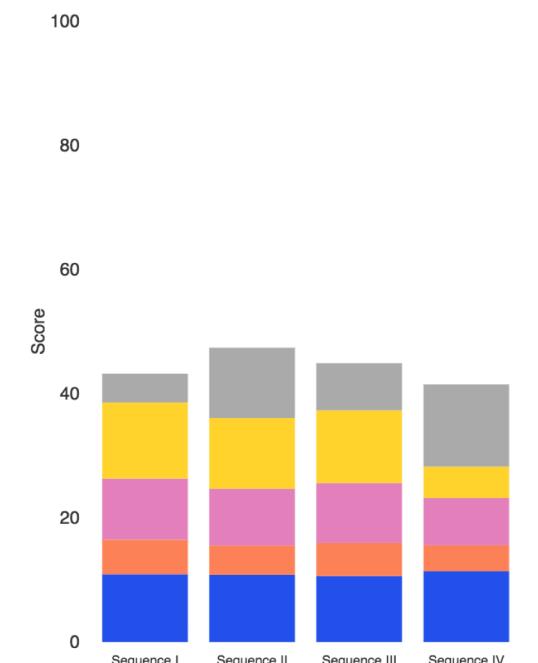
- PFS with 1L treatment ⓘ 25 % calculated
- PFS with 2L treatment ⓘ 25 % calculated
- Post-progression survival ⓘ 25 % calculated
- Total health care costs ⓘ 13 % calculated
- Administered orally ⓘ 0 % calculated
- Years since FDA approval ⓘ 0 % calculated
- Loss of income ⓘ 0 % calculated

+ Adverse events (13%)

Overall value ⓘ AEs combined

Detailed by category

Category	Score
PFS with 1L treatment	100
Post-progression survival	80
Total health care costs	60
Administered orally	80
Years since FDA approval	60
Loss of income	60
PFS with 2L treatment	60
AEs combined	60



Probability of ranking

Mapping from original scale to common scale

Value of a QALY ⓘ \$ 150,000

Save Run simulation

Model inputs used in the simulation

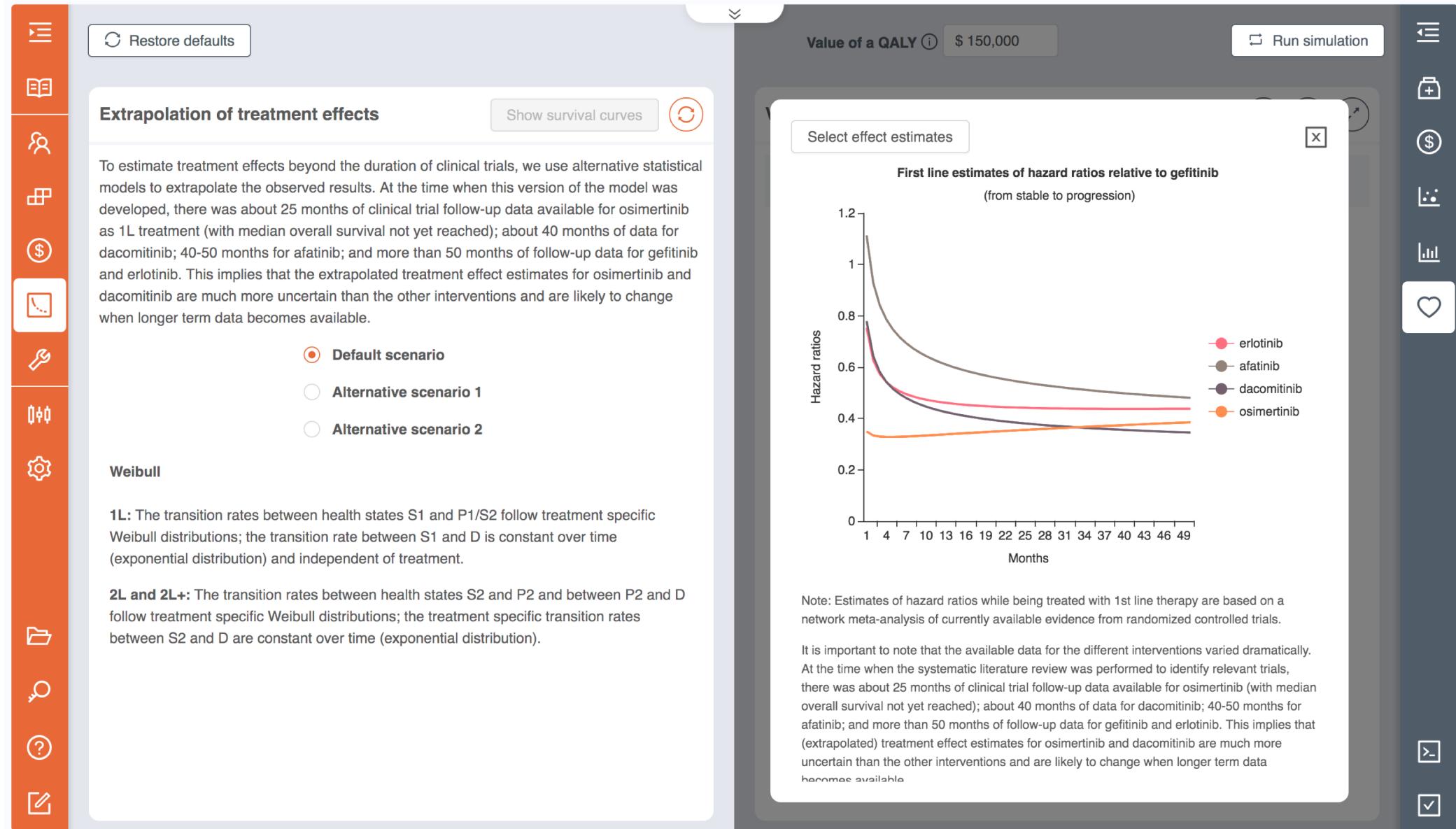
Search parameter Show only modified values

Parameter	Applied Inputs	Default Settings
+ Population		
- Treatment sequences		
Sequence 1	gefitinib osimertinib / PBDC PBDC + atezolizumab / PBDC + atezolizumab	gefitinib osimertinib / PBDC PBDC + atezolizumab / PBDC + atezolizumab
Sequence 2	erlotinib osimertinib / PBDC PBDC + atezolizumab / PBDC + atezolizumab	erlotinib osimertinib / PBDC PBDC + atezolizumab / PBDC + atezolizumab
Sequence 3	afatinib osimertinib / PBDC PBDC + atezolizumab / PBDC + atezolizumab	afatinib osimertinib / PBDC PBDC + atezolizumab / PBDC + atezolizumab
Sequence 4	osimertinib PBDC / PBDC PBDC + atezolizumab / PBDC + atezolizumab	

- + Efficacy
- + Utility
- + Treatment cost
- + Adverse events cost
- + Costs by health state
- + MCDA
- + General settings

pbdc + bevacizumab

Sequence II Sequence III Sequence IV



The screenshot shows a software interface for generating R code for a clinical trial simulation. The main area is a code editor titled "R Code" containing 49 lines of R script. The interface includes a toolbar on the left with various icons for file operations, a status bar at the bottom, and a header with simulation parameters.

R Code

```
1 pats <- create_patients(n = 100)
2
3
4
5 txseq1 <- txseq(
6   first = c("gefitinib"),
7   second = c("osimertinib", "PBDC"),
8   second_plus = c("PBDC + atezolizumab", "PBDC + atezolizumab")
9 )
10
11
12 txseq2 <- txseq(
13   first = c("erlotinib"),
14   second = c("osimertinib", "PBDC"),
15   second_plus = c("PBDC + atezolizumab", "PBDC + atezolizumab")
16 )
17
18
19 txseq3 <- txseq(
20   first = c("afatinib"),
21   second = c("osimertinib", "PBDC"),
22   second_plus = c("PBDC + atezolizumab", "PBDC + atezolizumab")
23 )
24
25
26 txseq4 <- txseq(
27   first = c("osimertinib"),
28   second = c("PBDC", "PBDC"),
29   second_plus = c("PBDC + atezolizumab", "PBDC + atezolizumab")
```

Value of a QALY ⓘ \$ 150,000

Save **Run simulation**

pbdc + bevacizumab

pbdc + bevacizumab + nivolumab

Model documentation

A Description of the IVI-NSCLC Model v1.0 *†

Devin Incerti‡ Jeroen P. Jansen‡

May 6, 2019

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*We would like to thank Mark Linthicum, Jason Shafrin, Lauren Zhao, Ina Zhang, Shivani Mehta, Florence Wilson, Rohan Shirali, Oscar Correa, Evgeniya Correa, Vladimir Bandarov, and Sergio Zapatel for their contribution to the development of the IVI-NSCLC model.

†This report should be referenced as follows: Incerti D, Jansen JP. A Description of the IVI-NSCLC Model v1.0; last updated January 31, 2019; available from <https://innovationvalueinitiative.github.io/IVI-NSCLC/model-doc/model-doc.pdf>. This report may be updated on a regular basis. It is recommended to access the report at the website to ensure you have the latest copy.

‡Innovation and Value Initiative

Summary of the IVI-NSCLC model

- > The IVI-NSCLC model is an open-source individual-level continuous-time state transition model to estimate clinical and economic outcomes and the value of alternative treatment sequences for patients with metastatic EGFR+ NSCLC
- > Allows evaluating the impact of uncertainty in clinical evidence, alternative model structures, the decision framework of choice (CEA or MCDA), the inclusion of value of hope, and perspective (healthcare or limited societal) on estimates of value
- > The model may be used to perform custom analyses to help inform population-level decision-making by local decision-makers
- > Accessible to both technical and non-technical end-users; Model can be run with R package or using web interfaces
- > Open source code base for iterative model development

Thank you

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