IVI ✳ INNOVATION AND VALUE INITIATIVE

Open-Source Value Project: IVI-NSCLC

Public Comments on Initial Release of IVI-Non-Small Cell Lung Cancer (NSCLC) Modeling Platform

July 10, 2019

abbvie

Innovation and Value Initiative
11100 Santa Monica Blvd,
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March 28, 2019

RE: Innovation and Value Initiative (IVI) Non-Small Cell Lung Cancer (NSCLC) open-source value platform (OSVP) Model – Response to Request for Public Comments

Dear IVI-NSCLC Technical Expert Panel,

Thank you for the opportunity to provide inputs into the Non-Small Cell Lung Cancer (NSCLC) open-source value platform (OSVP) Model. We appreciate IVI for creating a very flexible and user-friendly model. The platform is easy to follow, and has sufficient description on the model structure, treatment options, model inputs and model outputs. The model is very convenient and it even allows the end-user to edit or modify values on the model. As a strategic advisor, we have reviewed the current version of the NSCLC open source model and have consolidated key feedback that we believe will further enhance this model. The feedback is organized into two key sections: model structure and model outputs.

Section1: Model Structure

1. The ability to select between a three-state or four-state model structure in the IVI-NSCLC model allows the user to choose the typical scenario of the disease progression they observe in their patient population. It would, however, be useful for the reader to clearly see the description of the model structure upfront or at least have an icon displayed on the top portion of the model platform about the model structure is being considered.
2. From a treatment perspective, 1st Line treatment is comprehensive of EGFR+ NSCLC, but at disease progression the current model only considers and evaluates treatment of symptomatic system disease with multiple lesions. It would be helpful to clarify that to the user and describe this approach upfront.
3. Although the reference icons were incorporated for most model inputs, references for a few model inputs (especially for patient population were missing). It would be nice to see all the references included in the model platform from where the input variables are being extracted.

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4. Since the user is not going to make any edits or changes to the Std. Dev. for patient population input parameters such as 'age' or to the Std. Error values for the different 'adverse events' under cost model input, we recommend to delete these from the main screen, but have those built-into the back-end of the model.

5. In the current model, patient characteristics such as ' ethnicity/race' or 'smoking status' were not included as input options. We believe those model parameters could have an effect on disease severity, progression, as well as on survival, and therefore we suggest to consider these parameters into the model.

6. In the current version, there is no ability to define population characteristics based on EGFR+ NSCLC cell type. The model presumably only applies to patients with EGFR+ adenocarcinoma NSCLC. We suggest that this should be specifically called out upfront in the initial description stating that the current model only applies to EGFR+ adenocarcinoma NSCLC patients. Alternatively, if the model provides ability to the user to input percentages of adenocarcinoma and squamous cell carcinoma as well as treatment sequences based on histology that will definitely increase the usefulness of the model across all EGFR+ NSCLC treatment options.

7. In the current model version, a limited number of drugs were considered. For example - only cisplatin was included as a platinum based therapy (page 40 and 41 of the model description), whereas carboplatin was not considered in the model. For the future version of the model, we suggest to at least include all NCCN category 2A treatment options so that the model can provide a more comprehensive overview on the cost effectiveness for the different treatment options. Even for EGFR+ adenocarcinoma NSCLC numerous NCCN category 1 recommended treatments and combination treatments were not included in the current model. For the model to be truly useful in examining cost effectiveness of new market entrants, all currently available evidence and treatments should be included. If this is not possible because of limited data to use in a NMA, at least stating that upfront would be very helpful for the reader.

8. We suggest providing background information on MCDA; how MCDA parameters were identified and considered for the model; and how to best to interpret the MCDA outputs to be included in the general setting section. This will definitely help users to get more clarity around MCDA.

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Section 2: Model Outputs:

1. In the current model version, average costs are provided across 1L, 2L, and 2L+. It would be nice to have information on total costs broken down by individual line of therapy (Costs associated with 1L; costs associated with 2L, etc.). This would allow user to see the costs for each line and then based on those comparisons, more easily define a sequence to compare to the standard sequences to compare overall costs.

2. Additionally, in the current model costs are averaged for patients with and without T790M mutations. It would be nice if the model could pprovide separate cost outputs for patients who are T790M positive T790M negative patients. This will provide better evidence for evaluating treatment sequences for mutational status since mutational status is predictive of treatment choice.

Yours Sincerely,

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Sabina Gasper
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To,

Jennifer Bright
Executive Director
Innovation Value Initiative

As a science-led organization, AstraZeneca is committed to developing treatments that deliver long-term benefits to patients in lung cancer. We are encouraged by Innovation Value Initiative's (IVI) goal of creating a new, transparent, and more holistic approach to value assessment by considering multiple lines of therapy and incorporating the patient perspective. We support the overarching objectives of the organization and are committed to providing constructive feedback that will help in improving the model. We appreciate the opportunity to provide comment on the innovative IVI-NSCLC Value Tool.

AstraZeneca supports patient-centric value assessments that comprehensively measure available data, costs and budget impacts, taking into consideration personalized approaches to care delivery. We believe these tools need to be carefully constructed to ensure they do not restrict patient access to appropriate therapies and support continued innovation to address unmet medical needs. Generally, we are concerned about patient access to therapy being affected by misinterpretations of model results by decision-makers. We support patient access to all appropriate treatment options in EGFR mutation-positive (EGFRm+) metastatic non-small cell lung cancer (mNSCLC). Key stakeholders (e.g. physicians, institutions and insurance plans) may misinterpret results due to limited modeling expertise and may not understand the relationships between model inputs and model assumptions. Clarity in this regard is essential to ensure scientifically valid applications of model results to decision-making. It is important that value models do not restrict patient access to appropriate therapies, inhibit continued innovation to address unmet medical needs, or interfere with provider and patient autonomy in informed and shared decision-making.

Below we outline areas where we believe there may be gaps in methodology and potential for improvement.

Model and Methodology

1. External acceptance of the model would be enhanced with an explicit discussion of trial heterogeneity (including whether cross-over was allowed in each trial) and trial selection for the network meta-analysis (NMA). Similarly, given the need to adjust for heterogeneity across the set of first-line (1L) trials it would be helpful to provide clear instructions on how to enter one's own efficacy estimates across perhaps a different number of trials.

2. The technical NMA discussion could expand on reasons for variable and/or counterintuitive results. Lambert et al (2005)[1] show that apparently vague priors can make a large difference on final estimates, even in a simple random-effects model. Thus, greater justification for the vague priors chosen in the NMA should be provided. This issue can be addressed by showing robustness of the results under different sets of vague priors. This may be especially important when estimating between study variances in a random effects model since the choice of a prior distribution for this parameter can affect its estimate which, in turn, affects standard errors. When the NMA studies have different population sizes, the standard errors influence effect size estimates (relative to equal population sizes) through the weights attached to each study.

3. In addition, the report could include an expanded discussion of how NMA parameter estimates translate into OS/PFS curves, perhaps by being more explicit in linking the amount of information gleaned from the eleven 1L input trials to the number of parameters estimated in the NMA. This will let users better assess the effects of trial heterogeneity on estimated NMA parameters; in random-effects models these parameters include the between-study variance parameter or parameters.

4. The report could also include a validation section showing comparisons of estimated parameters (where possible) and survival curves to external sources (e.g. historical literature) and NMA consistency results, comparing relative indirect effects with direct effects. It is well known that head to head trials contain significantly more information in an NMA than information from indirect comparisons. However, some of the unusual results below, using mostly default inputs in the 4-state model, indicate that results do not conform with those expected from head to head trials.

   a) The projected median PFS and OS estimates for first-line erlotinib (15-20 months and 35-45 months respectively in Figures A39 - A42) are not supported by the available trial evidence. For example, the EURTAC and OPTIMAL study results show a 1L PFS of no more than 13 months.[2,3]

   b) Several published studies report similar/equal efficacy between erlotinib and gefitinib.[4,5] However, the model shows better efficacy of erlotinib versus gefitinib.

   c) The OS for erlotinib and osimertinib are ranked differently in 3-state vs 4-state health models. It is counterintuitive that the OS for a sequence starting with erlotinib would be greater than one starting with osimertinib.

   d) Sequences starting with EGFR TKIs that report higher AEs, down-dosing and higher discontinuation rates have lower adverse event costs.[6] An example is a sequence starting with dacomitinib vs starting with other first-generation or second-generation EGFR TKIs.

e) Several of the Kaplan Meier (KM) curves reported in the appendices have very long tails with little or no information for long periods of time (e.g. docetaxel, WJTOG3405).[7]

5. The authors critique traditional NMAs of hazard ratios (HRs) due to their assumption of proportional hazards (PH) (report page 59).[7] However, the PH assumption is not shown to be violated under the multi-state model for the NMA.

6. Second-line (2L) treatment effectiveness is estimated and extrapolated based on a synthesis of absolute effects, effectively producing a naïve comparison of osimertinib against PBDC. We disagree with the assumption that the effectiveness of all therapies other than osimertinib in 2L is equal to chemotherapy.[8] A discussion of population similarities and differences across the relevant trials is appropriate in this situation.

7. The post-progression evidence base could include an exploratory analysis of post-progression FLAURA endpoints (Time to First Subsequent Treatment, Time to Second Subsequent Treatment, and PFS for the 2L treatments).[9]

8. The model should allow for patient attrition after each line since some patients may not continue therapy after progression, for a variety of reasons [10,11,12]. Such patients may receive palliative or supportive care. It was observed in the FLAURA trial that 29% of patients in the osimertinib arm and 47% of patients in the EGFR TKI comparator arm went on to receive a first subsequent anti-cancer therapy.[13] Moreover, in a study by Chiang et al, using the Flatiron Health Electronic Health Record database, 30% of patients treated with a first or second-generation EGFR TKI died before receiving a subsequent therapy (Figure 1).[14]

9. The assumption that all patients treated with a first or second-generation EGFR TKI will be tested for the T790M resistance mutation upon progression may not hold in practice. In Chiang et al, 37.6% of patients received a second-line treatment and of this population only 30% were tested for T790M (Figure 1).[14] As not all patients are tested for T790M, consider including in the model an option for T790M unknown status.[14]

   a) Users are able to set the T790M mutation probability between 0-100%. The default value of 52% is taken from Ma et al (2011) who indicate that T790M accounts for about 52% of all acquired resistant patients (i.e. it is implausible for all patients who progress on 1L TKI to acquire the T790M resistance mutation). This matches values from other literature that indicate a T790M mutation prevalence of approximately 50%.[15-19]

   b) The report should note that it is also important to consider the sensitivity and quality of the testing performed. In the Flatiron data, only 25 patients of the 88 patients (28.4%) tested for T790M were positive (Figure 1).[14]

10. Mean surface area is used to calculate the cisplatin dose. However, the average cisplatin dose should be calculated from an average of individual doses. This

requires individual patient surface areas. The same concept also applies to bevacizumab, where individual weights are needed to estimate the average, rather than the dose associated with the mean weight.

11. The technical report could mention that caregiver cost data are unavailable. For EGFR TKIs, where grade 1 or 2 adverse events could be substantial, including caregiver costs would give a more complete picture of total treatment costs.

12. Nausea, vomiting and immune-mediated AEs do not appear to be included in adverse event costs. Moreover, failure to incorporate adverse events in 2L underestimates the costs associated with adverse events.

13. Consider updating the Wholesale Acquisition Costs (WACs) as some appear incorrect.[20]

14. The default utility values are noted to be lower than values previously used in NSCLC analyses. Further, the adverse event disutilities seem high and may not align with other values in the literature.[21]

15. The model would benefit from greater granularity in the results. For example, there is no breakdown of QALYs by health state and outcome (e.g. adverse events). This applies to the R model and the web application. Providing this information would enable the user to identify what drives QALY differences.

Value Scores/Perspectives on Value

1. It would be beneficial if the technical report either indicated that the MCDA variables and weights were arbitrarily chosen or that they were derived using established methodology (e.g. recommendations of the ISPOR MCDA Task Force).[22] In addition, the variables appear to not include the National Comprehensive Cancer Network® (NCCN®) guidelines for preferred treatment status.[23] Without an additional discussion of MCDA methodology and how variables are selected, users not versed in MCDA or the NCCN guidelines for preferred status may misinterpret model results.

    a) The default value weights are rather high (50%) for 2L PFS and post-progression. Considering that several patients die in 1L and may not get an opportunity to receive 2L treatment, more weightage should be given to 1L PFS.[10,11,12] In addition, earlier generation TKIs will be a priori favored by high weights on 2L PFS and post-progression since effective 2L treatments are not used in 1L. The example below illustrates this bias against effective 2L treatments:

2L: PDC\Osmimertinib 3L: PDC + Pembro	MCDA Preferences								1L Treatments				
	1L PFS	2L PFS	Post-Progression Survival	Health Care Costs	Oral	Years Since Approval	Loss of Income	AE Weight	Gefitinib Value Score	Erlotinib Value Score	Afatinib Value Score	Dacomitinib Value Score	Osimertinib Value Score
Default	25%	25%	25%	13%	0	0	0	13%	45	48	46	47	42

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b) IVI could consider adding an expanded discussion of MCDA interpretations when the value score conflicts with calculated ICERs. The example below uses the default MCDA weights. Keeping 2L and 3L options constant, the osimertinib sequence has a lower overall cost and a better ICER than the one starting with dacomitinib. However, the model gives the dacomitinib sequence a higher value score compared to osimertinib.

	Cost, ICER, and Value Score				
	gefitinib	**erlotinib**	**afatinib**	**dacomitinib**	**osimertinib**
2L: Osimertinib/PDC 3L: PDC + Pembro Default Settings 100/100	$633,564 Reference 43	$706,115 $124,052 48	$648,475 $65,866 45	$756,172 $227,646 47	$738,238 $201,638 42

2. We are not sure if the value scores adequately reflect osimertinib's efficacy relative to other drugs. For example, a 100% weight for 1L PFS gives a value score of 19 for gefitinib and 44 for erlotinib compared to 52 for osimertinib. Osimertinib has superior efficacy data than both the drugs that were in the same (control) group of the FLAURA trial. Based on the trial it can be argued that erlotinib and gefitinib should receive a similar score.[13]

3. Our understanding is that IVI would like to include the value of innovation in its assessment. The report could discuss different ways of capturing this (e.g. days since FDA approval for newer generation treatments).

4. Of the 19 NSCLC patients included in the "Patients Perspectives on the Value in the Treatment of NSCLC" technical report, which was conducted to support the development of the model, only nine had EGFRm+ NSCLC.[24] The model can use patient preferences work entitled "Patient preferences for tyrosine kinase inhibitor treatments for EGFR mutation-positive metastatic NSCLC".[25]

5. An expanded discussion of the value of hope would be useful, especially how to interpret a negative value of hope (e.g. comparing sequences starting with any EGFR TKI to a sequence starting with erlotinib).

Model interface and functionality

1. The following are model settings which cannot be altered by the user (some were mentioned above):

a) Users may want to adjust for trial heterogeneity on their own. Providing a clear path to users on changing PFS and OS would be useful in this regard.

b) Relative treatment effectiveness choices appear restricted to fixed-effects Weibull and fractional polynomial models. A random effects Weibull model cannot be selected, and no other modifications to relative treatment effectiveness can be made, e.g. equal OS and PFS between gefitinib and erlotinib.

c) The model does not allow for IO + Chemo in the 2L setting.

d) We recommend an easier way to add individual adverse events without using the 'locks' and consider labelling sequences while showing cost and effectiveness data for easier understanding of the results.

2. The model does not allow for palliative or supportive care.

The enclosed information should in no way be construed as a recommendation for the use of osimertinib in any manner other than as approved by the Food and Drug Administration (FDA) and as described in the prescribing information for TAGRISSO. Prescribing information for FDA approved AstraZeneca products may be obtained from www.astrazeneca-us.com or by calling the Information Center at AstraZeneca at 1-800-236-9933. For medical information requests, please contact AstraZeneca at 1-877-893-1510.

We hope these comments offer constructive feedback and help in improving the model. Please let us know if there are any questions.
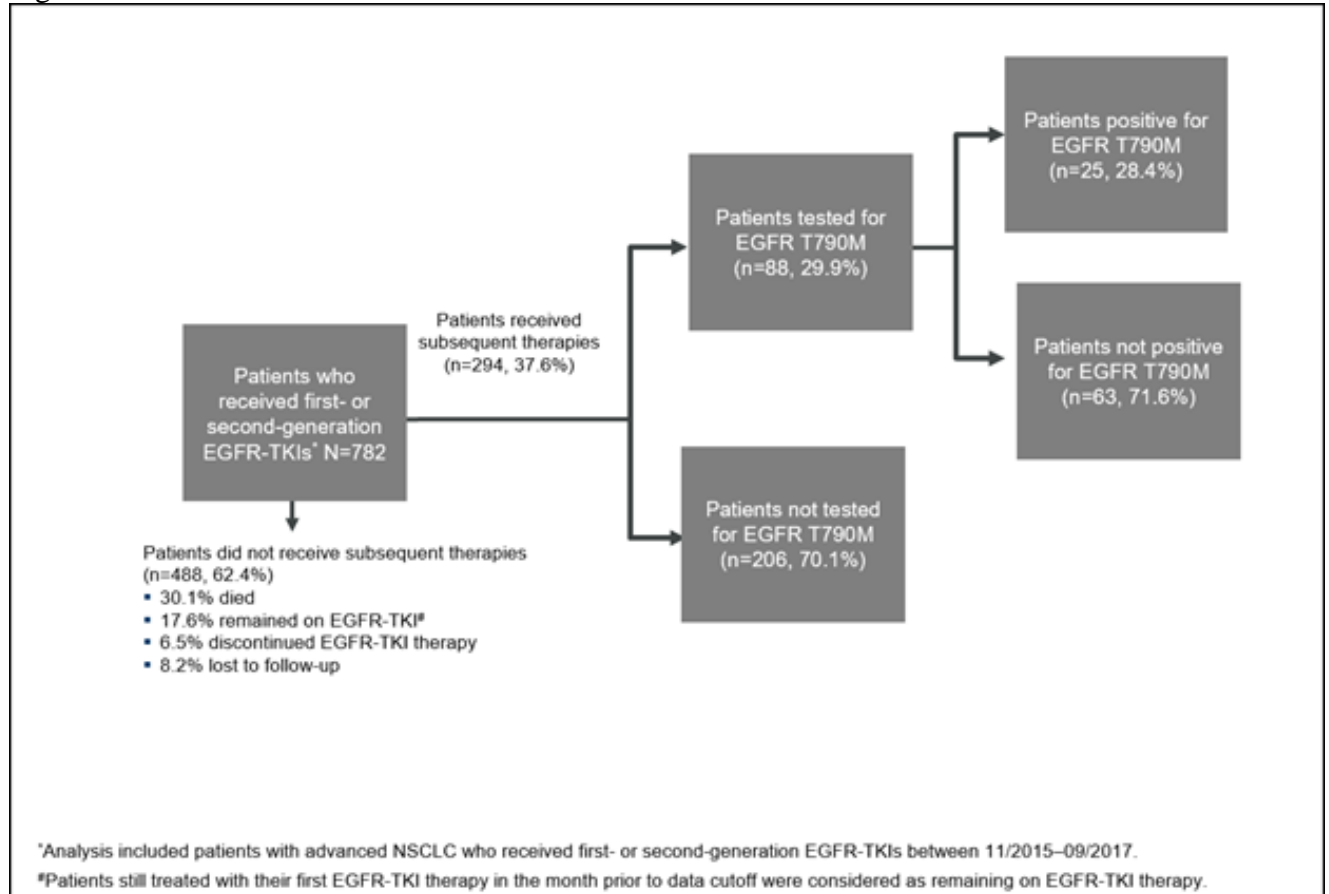
Sincerely,

Rahul Shenolikar, PhD.
Director, US HEOR, AstraZeneca

Bjorn Bolinder, MBA
Executive Director, US HEOR, AstraZeneca

Figures

Figure 1

Patients who received first- or second-generation EGFR-TKIs* N=782

Patients did not receive subsequent therapies (n=488, 62.4%)
- 30.1% died
- 17.6% remained on EGFR-TKI#
- 6.5% discontinued EGFR-TKI therapy
- 8.2% lost to follow-up

Patients received subsequent therapies (n=294, 37.6%)

Patients tested for EGFR T790M (n=88, 29.9%)

Patients not tested for EGFR T790M (n=206, 70.1%)

Patients positive for EGFR T790M (n=25, 28.4%)

Patients not positive for EGFR T790M (n=63, 71.6%)

*Analysis included patients with advanced NSCLC who received first- or second-generation EGFR-TKIs between 11/2015–09/2017.

#Patients still treated with their first EGFR-TKI therapy in the month prior to data cutoff were considered as remaining on EGFR-TKI therapy.

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April 1, 2019

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BY ELECTRONIC DELIVERY

Re: Study Protocol: Open-Source Value Project - Sequential treatment strategies for patients with metastatic EGFR+ non-small cell lung cancer

Dear Dr. Lakdawalla and Dr. Shafrin:

As a leader in immuno-oncology research, Bristol-Myers Squibb (BMS) acknowledges the importance of understanding and fully characterizing the value that innovative therapies provide to patients, and appreciates the opportunity to comment on the Innovation and Value Initiative (IVI) Open Source Value Project (OSVP) - Sequential Treatment Strategies for patients with Metastatic EGFR+ Non-Small Cell Lung Cancer (NSCLC). BMS is dedicated to advancing the science of immuno-oncology and to disseminating the results of our research to ensure that our work can benefit the widest range of patients.

We have reviewed the open source value tools and believe the IVI-NSCLC model could benefit from the following feedback in guiding its development.

General Comments

Refine with HLC's Principles of Value Frameworks

BMS agrees with IVI's patient centric and transparent approach to developing the current version of the IVI-NSCLC model. For example, the patient focus groups conducted initially were a key resource in developing the model. As IVI looks to refine the NSCLC model further, we recommend referring to a set of principles on value frameworks developed by the Healthcare Leadership Council (HLC), a coalition of chief executives from all disciplines within American healthcare. In 2017, HLC released the following set of principles that should guide the creation of value frameworks being used to determine the cost-effectiveness of new healthcare innovations[i]. These align also with our own company's principles on value frameworks.

1. Collect patient and provider input on what "value" should be measured in a treatment option in order to measure outcomes that matter to patients and providers (such subjective data as discomfort during or after treatment).

2. A diverse group of disease area experts should participate in both the development of methodology and assessments before these are submitted through a peer review process to ensure scientific rigor.
3. During and after the review process, provide full transparency of evaluation criteria, including any models and data used – allowing for research to be analyzed and results replicated by others.
4. Assess and reassess value over time (recognizing that prices can vary over time), to capture appropriately the value of curative or preventative treatments whose full value may not be realized until after the initial approval.
5. Define value to society broadly – this includes outcomes values such as productivity, opportunity costs, and avoided long-term costs.
6. Incorporate real-world evidence and adjust evaluation techniques to capture actual patient outcomes and preference for treatment, recognizing some data may be difficult to obtain for pragmatic or ethical reasons.
7. Treatments should accurately reflect real-world usage.
8. Consider variations in treatment setting, technique, and provider when evaluating a new product or technique.

IVI has already adhered to many of these principles in developing open source value tools. As IVI seeks to refine the NSCLC model, we recommend continued robust patient and provider engagement, as well as increasing the incorporation of real world evidence.

Specific Comments

1. Elements of Value

Feedback: Incorporate additional elements of value

We recommend that IVI continue to incorporate important elements of value that are typically not captured in standard cost-effectiveness analyses (CEA). We are encouraged to see that IVI has incorporated value of hope into the current IVI-NSCLC model, and recommend prioritizing the development and incorporation of additional value elements such as real-option value, value of insurance, etc. Given that T790M status is part of the IVI-NSCLC model, IVI should consider incorporating the value of reduction in uncertainty from a diagnostic test. Not only will this help advance the methodology for developing and incorporating additional elements of value, but it will more fully capture value to patients and society.

2. Input parameters

Feedback: Ensure accuracy and consistency of cost inputs

In reviewing the cost input files we recommend ensuring these inputs are up to date and accurate.

3. Interface refinements

   A. *Feedback: The sequential treatment strategies compared in the model should mention radiation and surgery may be options.*

We encourage IVI to also mention that radiation and surgery may be part of a sequence of treatments prescribed. As NCCN guidelines for NSCLC outline these treatment modalities may be recommended depending on the clinical presentation and assessment.[ii] An aspirational goal of the open source value tool would be to focus broadly on all aspects of the healthcare system, not just medications. The availability of granular data needed to include these modalities may not yet be feasible, but improvements in electronic healthcare records may make this one day possible.

B. *Feedback: Provide additional clarity around interpretation of cost outputs*

An important factor to consider when evaluating a value framework is whether it focuses broadly on all aspects of the healthcare system. We are encouraged that the draft value tools provide users with estimates of total costs of entire sequences. That said, for clarity in interpreting cost outputs in the web-based models, we recommend adding contextual information in the interface to inform users that the total cost estimates displayed are inclusive of 1L, 2L and 2L+ costs.

4. *Model Structure*

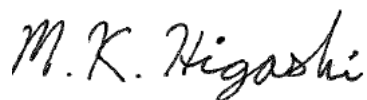### A. *Feedback: Recommend validating extrapolations in related data*

We are encouraged to see IVI has explored various methods for extrapolation of treatment effects. However, the choice of long-term extrapolation beyond the trial period should be based in part on how alternative parametric/statistical fits are validated against related external data sources (i.e. more mature RCTs or real world data, if available) or through expert clinical input. We recommend the selection of the final parametric model be based in part on the plausibility of the extrapolation.

B. *Feedback: Provide clarity around data sources for treatment effects*

We recommend IVI provide further clarity around data sources for treatment effects, particularly around 2L and 2L+, and whether the data supporting these effects come from ITT (supported by level of evidence arguments) or mutation positive subgroups (supported by clinical relevance) of the supporting trials.

Bristol-Myers Squibb appreciates IVI's efforts to engage stakeholders in the development of the IVI-NSCLC model and we look forward to providing continued input to IVI as it refines the model. We welcome the opportunity to meet to further discuss our feedback. If you have any questions, please do not hesitate to contact Mitch Higashi, PhD, Head of U.S. Health Economics & Outcomes Research at (609)302-3798.

Sincerely,

M. K. Higashi

_____
Mitch Higashi, PhD
Head of U.S. Health Economics & Outcomes Research

References:

[i] Healthcare Leadership Council. Principles on Value Assessment Frameworks. Available at: https://www.hlc.org/app/uploads/2017/05/HLC-Final-Principles-on-Value-Frameworks.pdf
[ii] NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 3.2019. January 2019. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

April 1, 2019

Jennifer Bright, MPA
Executive Director
Innovation and Value Initiative

RE: Comments on IVI-NSCLC Model Initial Release

Dear Mrs. Bright,

Boehringer Ingelheim Pharmaceuticals, Inc. ("Boehringer Ingelheim") appreciates the opportunity to review and comment on the Innovation and Value Initiative's (IVI) Open-Source Value Platform (OSVP) model focusing on epidermal growth factor receptor (EGFR) positive, non-squamous non-small cell lung cancer (NSCLC). IVI's efforts, including the OSVP models, provide a valuable opportunity to incorporate stakeholder feedback and most current evidence into value assessments for innovative products.

Boehringer Ingelheim acknowledges the strengths of the IVI-NSCLC model including the use of multi-criteria decision analysis to account for patient preferences and their perspective of value, as well as the inclusion of novel concepts such as the value of hope. Furthermore, we commend IVI for making the model accessible to the public, and for incorporating flexibility into the model structure to accommodate customized treatment scenarios and the use of specific data inputs.

Boehringer Ingelheim offers the following recommendations to aid in improving the model:

1. Use of evidence from a consistent patient population across all clinical studies, (e.g., NSCLC patients with EGFR exon 19 deletion (Del19) or exon 21 substitution (L858R) mutations)

2. Evaluation of each platinum-based doublet chemotherapy (PBDC) regimen individually in the network meta-analysis (NMA) and IVI-NSCLC model, and

3. Inclusion of at least one agent from each of the three generations of EGFR tyrosine kinase inhibitors (TKIs) in the default setting for treatment strategies

4. Consistent use of independently assessed PFS in NMA

5. Reconsideration of including OPTIMAL trial data

6. Use of most current survival assumptions

The context and rationale for these suggestions are provided below.

Use of evidence from a consistent patient population across all clinical studies (e.g., NSCLC patients with EGFR Del19 or L858R mutations)

Consistent with the FDA-approved indications, the study populations in the majority of clinical studies in the NMA included only NSCLC patients with EGFR exon 19 deletion or exon 21 L858R substitution mutations (i.e., common EGFR mutations) (Table A19 of the model report). However, Figures A16 and A17 of the model report show the PFS and OS data for first-line afatinib treatment from ITT populations from LUX-Lung 3 and LUX-Lung 6, which included 11% of patients with other uncommon EGFR mutations (Yang 2015). For a more accurate comparison of the EGFR TKIs, it is important to use clinical data for a consistent patient population across all clinical studies (i.e. NSCLC patients with common EGFR mutations). The corresponding data for   patients with common EGFR mutations in LUX-Lung 3 and LUX-Lung 6 are provided below:

LUX –LUNG 3 (common mutations – del19 or L858R)	
PFS HR	0.47 (95% CI: 0.34-0.65) (Sequist 2013)
OS HR	0.78 (95% CI: 0.58-1.06) (Yang 2015)
LUX-LUNG 6 (common mutations – del19 or L858R)	
PFS HR	0.25 (95% CI: 0.18-0.35) (Wu 2014)
OS HR (95% CI)	0.83 (95% CI: 0.62-1.09) (Yang 2015)

Revising the NMA and corresponding model inputs to include only clinical data for the patient population with common EGFR mutations across trials for all comparators will provide consistency   a more accurate representation of the treatment eligible population.

Boehringer Ingelheim therefore requests that IVI update the afatinib PFS and OS inputs with clinical trial data specific to the patient population with common EGFR mutations as provided above.

Evaluate each PBDC regimen individually in the NMA and IVI-NSCLC model

Although efficacy differs among PBDC regimens (Popat 2014; Scagliotti 2008), the IVI-NSCLC model does not distinguish between specific PBDC regimens.

LUX-Lung 3 and LUX-Lung 6 were similarly-designed clinical trials that compared afatinib to different PBDC regimens – pemetrexed-cisplatin in LUX-Lung 3 (*Sequist 2013*) and gemcitabine-cisplatin in LUX-Lung 6 (Wu, 2014). When the Kaplan-Meier curves from both trials were overlaid, the curves for the afatinib arms of both trials matched closely, while the pemetrexed-cisplatin curve was consistently above that for the gemcitabine-cisplatin arm (data on file).

Correspondingly, the PFS hazard ratio in the common EGFR mutation population was almost twice as high in LUX-Lung 3 (HR: 0.47; 95% CI: 0.34-0.65) compared to LUX-Lung 6 (HR: 0.25; 95% CI: 0.18-0.35). These results further demonstrate differences between two PBDC regimens with the same platinum backbone agent. Consolidating PBDC options into a single comparator without allowing or adjusting for clinical differences across combination regimens may lead to potentially inaccurate interpretation of the results.

Boehringer Ingelheim requests that IVI take into account the variation in efficacy and safety across different PBDC regimens by considering each PBDC regimen in the NMA separately, and disaggregating the single PBDC choice in the modeled treatment strategies into specific individual PBDC regimens.

Include at least one agent from each of the three generations of EGFR TKI in the default setting for treatment strategies

There is increasing evidence to indicate heterogeneity among first-, second-, and third-generation EGFR TKIs in efficacy, tolerability, safety, and the propensity of patients to develop acquired T790M resistance (Girard 2018, Hirsh 2018, Kohsaka 2019). Consequently, the decision on which TKI to use in first-line treatment has garnered much discussion in the clinical community (Cai 2019, Hochmair 2018, Takeda 2019). Furthermore, mechanisms of resistance to osimertinib and treatment options following resistance currently are not understood. Given the lack of current treatment options following disease progression on osimertinib, initiating sequential therapy with first- or second-generation TKIs followed by osimertinib in second-line treatment may provide clinical benefits over first-line osimertinib use (Girard 2018, Hirsh 2018).

Currently the default settings for treatment comparators in both versions of the IVI-NSCLC model do not include first-line treatment with osimertinib as a treatment option. The omission of osimertinib from the default setting limits the utility of the model in providing important insights to the current clinical discussion around TKI choice in the first-line treatment setting.

Boehringer Ingelheim requests that the default settings for treatment strategies be revised to include at least one agent from each of the three generations of EGFR TKIs to reflect treatment choices currently made by clinicians.

Consistent use of independently assessed PFS in NMA

While most trials included in the IVI-NSCLC model report the more objective independent assessment of PFS, some trials such as FLAURA report primary outcomes based on investigator assessed PFS. However, both independent and investigator assessments of survival are often available, e.g., estimates of the PFS as determined by an independent assessment are available for FLAURA in the supplementary material of the clinical trial publication.

Boehringer Ingelheim recommends the consistent use of independently assessed PFS throughout the IVI-NSCLC model.

Reconsideration of including OPTIMAL trial data

The OPTIMAL trial was not accepted by the European Medical Agency to support the efficacy and safety assessment of erlotinib for the treatment of EGFR mutation positive tumors (EMA CHMP, 2011).

Boehringer Ingelheim requests that its inclusion in the evidence be reconsidered and if included as part of the erlotinib data, that the model allow for a scenario analysis using estimates that include and exclude the OPTIMAL trial results.

Use of most current survival assumptions

Median OS data from the FLAURA trial are not yet available. The use of interim OS data for osimertinib (25% maturity) in the NMA should be noted as a possible limitation.
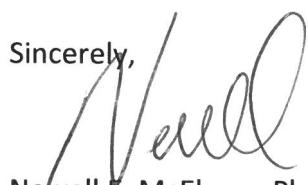
Boehringer Ingelheim recommends, when comparing OS across TKIs, that IVI update the NMA with mature osimertinib OS data when they are available, and to note the current limitation of the use of interim osimertinib OS data in the model report.

The NMA indicates (Figure 8 of model report) better survival with erlotinib treatment compared to gefitinib and afatinib. Current literature, however, suggests similar efficacy between erlotinib and gefitinib (Urata 2016, Yang 2017). There is evidence of superior efficacy of second generation TKIs (i.e. afatinib or dacomitinib) compared to first generation TKIs, particularly for progression-free survival (Paz-Ares 2017, Wu 2017, Mok 2018).

Boehringer Ingelheim suggests that IVI review these assumptions to strengthen the compatibility of the IVI-NSCLC model with published evidence.

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Boehringer Ingelheim appreciates the opportunity to provide feedback and welcomes questions and requests for clarification as IVI refines and develops future versions the IVI-NSCLC model.

Sincerely,

Newell E. McElwee, PharmD, MSPH
Vice President, US Health Economics Outcomes Research
Boehringer Ingelheim Pharmaceuticals, Inc.

References:

Cai H, Zhang L, Li N, et al. Cost-effectiveness of Osimertinib as First-line Treatment and Sequential Therapy for EGFR Mutation–Positive Non–Small Cell Lung Cancer in China. Clinical Therapeutics. 2019.

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Wu YL, Cheng Y, Lee KH, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomized, open-label, phase 3 trial. Lancet Oncol. 2017;18(11):1454-66.

Yang JCH, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol. 2015;16:141-151.

Yang JJ, Zhou Q, Yan HH, et al. A phase III randomised controlled trial of erlotinib vs gefitinib in advanced non-small cell lung cancer with EGFR mutations. Br J Cancer. 2017;116:568–574.

The following comments/concerns are from the EGFR Resisters:

1. It is very difficult to put a value, from aggregation of statistics, and apply to an individual patient. For example, it's hard to take overall survival statistics for lung cancer and apply them to one patient.

2. A big concern is that based on using this tool to assess patients, there is concern that a patient would not be offered the best therapy for them. For instance, the current guidelines recommend Tagrisso for first line treatment, but that sequence shows lower overall value than starting with any of the other EGFR TKIs.

3. We don't understand the estimates of some of the costs. For example, the adverse events; diarrhea was so much more expensive than other adverse events. One patient could easily be helped with Immodium, while another may require more intervention.

4. There isn't much data in second-line setting, so estimates could be problematic.

5. Doesn't take into account patients who won't even get as far as second-line treatment.

6. Out of the 19 patients, only 9 were EGFR-positive and we believe only one was from the EGFR Resisters.

7. It doesn't take into account that many patients upon progression have mechanisms of resistance other than T790m, leading to different treatment paths.

8. The model is extremely confusing and difficult to review as patients.

9. Our biggest concern is that the model does not reflect true considerations for the **individual** patient. We are not data or statistics. We are patients that have very specific and unique needs and experiences.

Innovation and Value Initiative
11100 Santa Monica Blvd, Suite 500
Los Angeles, CA 90025

Re: Public Call for Comments on the IVI-NSCLC Model
Submitted electronically to: research@thevalueinitiative.org

Dear IVI Technical Expert Panel,

Genentech appreciates the opportunity to provide feedback on the IVI-NSCLC model. As a leading biotechnology company that discovers, develops and manufactures novel medicines to treat patients with serious and life-threatening conditions, we are deeply committed to comprehensive value assessments that contribute to meaningful improvements to patients, the health care system and society. We share IVI's vision of patient-centered value assessments that are transparent and adaptable to local decision maker needs.

We believe that the IVI-NSCLC model is amongst few publicly available assessments that seek to capture the multidimensional facets of value raised by ISPOR's Special Task Force on Value Assessment Frameworks[1]. Based on our review of the current IVI-NSCLC model, we share feedback that we believe will further enhance the models for broad use.

Treatment strategies in the model should reflect evidence-based treatment guidelines and real-world clinical practice.

There are limited available data that demonstrates immunotherapies have efficacy in populations with driver mutations. As a result, all FDA-approved indications for immunotherapies in NSCLC have been in the EGFR-negative or unknown populations. However, the combination therapy of atezolizumab, bevacizumab, carboplatin and paclitaxel is the only immunotherapy combination to have been listed as a treatment option in NCCN guidelines for EGFR-positive patients who have failed prior TKI treatment and therefore should be considered in the post-TKI setting in the model[2]. The NCCN listing is based on the IMPower150 study, which demonstrated efficacy in EGFR-positive patients who had received prior TKIs[3]. Given the model assumes the use of pembrolizumab after failing TKI treatment and the lack of efficacy data, IVI should consider removing it as a treatment option or attaching a higher degree of uncertainty to the efficacy estimate. In the TKI-failure setting, it is not appropriate to assume that other checkpoint inhibitor immunotherapy combinations have the same efficacy as the combination of atezolizumab, bevacizumab, carboplatin and paclitaxel due to the lack of supportive data.

The model will better align with real-world treatment patterns by including "no treatment" and end of life care.

The number of treatment lines may vary considerably from patient to patient due to disease severity and individual choice. The option of "no treatment" or end of life care, such as hospice, enables the model to account for the proportion of advanced NSCLC patients who choose to discontinue systemic therapy or are too sick to continue. For example, in a real-world analysis of advanced NSCLC patients who received systemic treatment (n=8,542), 47% of advanced NSCLC patients (n=4,033) continued on to receive second-line treatment[4]. We believe having these options in the model will closer resemble the variability in treatment course observed in real-world settings.

Expanding cost inputs and sensitivity analyses, and clarifying novel value concepts will enhance the user's ability to customize the model.

We are encouraged by the user-friendly interface of the basic and expert versions of the model and the addition of important value elements. We provide specific suggestions to further enhance model flexibility and customization by users.

- Incorporating the Average Sales Price and Average Wholesale Price (as applicable) of drug treatments will expand the choice of price inputs relevant to various health care decision makers.
- The inclusion of a one-time discounted cost for hospice and end of life care will more accurately reflect treatment patterns observed in the real-world.
- The value of hope and the value of perfect information should be further clarified. A brief tutorial of the concept, its impact to the incremental cost-effectiveness ration (i.e. impact to cost, QALYs or both), and how the information can be used to inform decisions would be helpful.
- In the advanced model, cost of progression in second-line treatment is lower than the cost of progression in first-line. We recognize there is limited literature to support this model input and the current reference used to inform this assumption suggests that progression costs between first and second-line therapy settings are not significantly different [5]. Some additional clarity on how the results of this study were incorporated into the model would be useful in the technical documentation.
- The MCDA is an important component of the IVI-NSCLC. We suggest that out-of-pocket costs be included as a parameter in addition to the total cost of care, as the concept of cost can take on different meanings based on the stakeholder's perspective.
- Deterministic sensitivity analyses should be included as an option to provide insight into key drivers and supplement the existing probabilistic sensitivity analyses.

To enhance the technical documentation of model, particularly for experienced users, we offer the following suggestions for IVI's consideration:

- Report sections should clarify whether outcomes are simulated from the individual-level continuous-time state transition model or estimated from source data. For example, the model structure is described to simulate AEs based on their probabilities of occurrence (page 19-20).

However, AE costs are calculated from a weighted average based on the probability of each AE occurring. It is unclear why costs were calculated in this manner, as opposed to estimating AE costs based on the simulation.

- The specification of the random effects in the model is a bit unclear. For example, a random effect is only explicitly mentioned for one of the parameters in the model described by equation (2) (page 25). However, random-effects models should theoretically describe random components for all study-specific effects.
- We suggest further detailing the rationale for the choice of prior distributions in the model (page 28). Some specific examples to enhance the documentation include details on what informed the specific variance values used in equation (7) and rationale on why the variance for some treatment effect parameters a 2 while others are 1.

Genentech appreciates IVI's efforts in engaging a broad set of stakeholders in developing the IVI-NSCLC model. We offer our support in further refining the model. Please do not hesitate to contact us should you have any questions or wish to further discuss.

Sincerely,

Elaine Yu, PharmD, MS
Team Leader, Evidence for Access
Genentech, U.S. Medical Affairs

References

1. Lakdawalla, Doshi J, Garrison L, et al. Defining Elements of Value in Health Care—A Health Economics Approach: An ISPOR Special Task Force Report [3]. Value in Health. 2018;21(2), 131-139
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March 26, 2019

To: IVI

RE: IVI's Open-Source Model for Assessing Value Of EGFR+ Non-Small Cell Lung Cancer Treatment Sequences

Dear Sir/Madam:

Merck thanks IVI for the opportunity to comment on the draft Open-Source Model for Assessing Value of EGFR+ Non-Small Cell Lung Cancer (NSCLC) Treatment Sequences. We appreciate IVI's willingness to solicit input openly from stakeholders. Attached please find Merck's comments on the model. These comments and our suggestions are tabulated in the order of the model's sections (A Description of the IVI-NSCLC Model v1.0).

Please feel free to reach out to us if IVI has any questions about our comments. We look forward to further discussion with IVI regarding the proposed model.

Sincerely,

Boris Rachev

Director, Outcomes Research
Center for Observational and Real-World Evidence (CORE)
Merck & Company, Inc.

Attachment: *Merck Comments on IVI's Open-Source Model for Assessing Value Of EGFR+ Non-Small Cell Lung Cancer Treatment Sequences (8 pages)*

Merck Comments on Open-Source Model for Assessing Value Of EGFR+ Non-Small Cell Lung Cancer Treatment Sequences

Section	Page #	Content of Concern	Merck Comments
2. Topic Definition, 2nd paragraph	12	"…(NSCLC) accounts for an estimated 85% of lung cancer…"	There is a newer statistic (see, for example, https://www.swedish.org/services/cancer-institute/cancer-types/lung-cancer/about-lung-cancer) that the estimated rate for NSCLC now is 87% of all lung cancer.
2. Topic Definition, 2nd paragraph	12	"The five-year survival of Stage IV NSCLC is less than 2% (Cetin et al., 2011)"	With the availability of new immunotherapies, this statement is no longer accurate. One could either modify to refer to a historical period prior to the availability of a number of current therapies, analyze more recent data (e.g., from SEER) and report as, 'based on the most recent data available' or refer to published cost-effectiveness models of newer therapies reporting modeled survival to 5 years. For instance, as an example of the second suggestion, using SEER*Stat software, survival for non-squamous metastatic NSCLC patients, using a recent 6 years of data (2009-2014), is around 4%, and would be higher if reflecting use of more recently available therapies.
3.1. Value Assessment, paragraph 3	13	"…CEA based on cost per quality adjusted life year (QALY) expressed as net-monetary benefit (NMB) and MCDA."	Will the model also accommodate (components of) Augmented CEA and Extended CEA from the 2nd U.S. Panel on Cost-effectiveness in Health and Medicine?
3.1. Value Assessment, paragraph 4		"Garrison et al. (2017) suggest five concepts…"	See, for example, Lakdawalla et al., "Defining Elements of Value in Health Care - A Health Economics Approach: An ISPOR Special Task Force Report", 2018 for more concepts suggested for CEA value elements inclusion.

Section	Page #	Content of Concern	Merck Comments
7. Treatment Strategies	16	Presumably the various 2L and 2L+ treatments are modeled to have an identical efficacy and cost regardless of the 1L treatment which is modeled to precede it?	This is a strong assumption, as 1L treatments with higher efficacy may leave a smaller, harder to treat 2L population, with a lower efficacy obtainable for 2L and 2L+ therapies, than a 1L treatment with lower efficacy. Understandably data are lacking to fully inform efficacies with all individual sequences. However, this assumption could be discussed in the report, along with any available data or analyses to support differential efficacy of 2L/2L+ therapies dependent on choice of 1L treatment. If no data are available to inform, the theoretical direction of impact on ICERs of 1L and 2L therapies could be noted based on exploring modified efficacies for 2L/2L+ treatments dependent on choice of 1L therapy.
Figure 1.	16	Renaming in figure	Suggest renaming 2L+ to 3L+ as it appears to not include 2L, which is a separate treatment line.
8.1 Disease Model – 1st paragraph	17	Reasons for discontinued treatment	Would be helpful to understand whether patients in trials/clinical practice have also discontinued treatment for reasons beyond progression, such as due to AEs or other factors, and take into account in the modeling.

Section	Page #	Content of Concern	Merck Comments
8.1 Disease Model – 3rd paragraph	17	Factors for discontinued treatment	The description seems to imply that patients who progress on 1L treatment (P1) all move to S2 and receive 2L treatment (with a similar process following P2). However, a substantial proportion of patients who discontinue 1L therapy due to progression never receive a 2L therapy due to factors such as being too frail to continue treatment, not wishing to undergo further treatment due to therapeutic toxicities, giving up hope for cure, cost or other factors, which can have an important impact on costs and outcomes within a given treatment sequence chosen. If these data are not already available in the clinical trial or real-world evidence literature, it likely exists within clinical trial databases and an effort should be made to obtain from trial sponsors.
8.2. Adverse Events	19	Criteria for selecting adverse events	Please identify the criteria used to select adverse events. The list in Table 1 appears to be a subset of those reported in clinical trials.
8.4. Productivity – 2rd paragraph	20	Modeled retirement age	Many individuals work past age 65, which is the modeled retirement age. Consider incorporating a probability of employment by age and sex in future modeling.
9.2. Value Assessment	22	MCDA criteria	Another criterion to include in MCDA can be Adverse Event burden of each treatment.
10.1.1. Network meta-analysis model - 1st paragraph	25	Confirmation	In a 3-state economic model, use of a proportional hazards approach would not seem to require that transition probabilities from stable to death and progression to death be equal as described. Suggest confirming if correct.

Section	Page #	Content of Concern	Merck Comments
10.1.1	26	Transition rates between stable disease and death are … assumed to be independent of time and the same for all treatments.	This is a strong assumption. Was it validated with any data?
10.1.1.4	27-30	Confirmation	Regarding the NMA with time-varying hazard ratio approach, 1. is it an underlining assumption that the survival curves of ALL comparators have to follow the same parametric distribution? If yes, can you comment on the limitation? 2. What criteria did you use to choose the "optimal" parametric distribution?
Figure 7.	32	Confirmation	Transition from stable to dead appears to be zero. Are there any data to inform this as being true?
Figure 8.	32	Adding a table	In addition to the information displayed in the figure, it would be useful for future work to also report in a table or figure the mortality risk (% dying by end of interval among those alive at start of interval) by month or year for each therapy. This would more readily enable comparison of absolute as well as relative mortality changes over time, comparison with external data sources (e.g., SEER) and assessment of clinical plausibility.
10.1.3	34	Confirmation	The objective of the model is to evaluate different treatment sequence. Did you consider the impact of 1L treatment on the treatment effects of later lines?

Section	Page #	Content of Concern	Merck Comments
Figure 9.	35	Clinical explanation	Is there a clinical explanation as to why the hazard for Progression to Death would fall over time for platinum-based doublet chemotherapy and rise over time for Osimertinib? If not, and there is considerable uncertainty around the true relationship, it may be fairer to both treatments to assume a constant HR over time. Later, in Section 10.1.5. it is mentioned that no treatment effect for the transition from progression to death is assumed, but it is not clear if hazard curves reflecting that assumption for Osimertinib and platinum-based doublet chemotherapy were presented.
10.1.5. Model selection	37	Clarification	Suggest clarifying for which treatments and endpoints a Weibull model vs. a fractional polynomial model (and which of the family of FP models) was used within the last sentence of the section.
10.2. Adverse Events	37	Methodology	It may not be appropriate to shrink AEs towards a drug class mean. This would likely be considered objectionable if doing so for efficacy data and validity is unclear for safety as well.

Section	Page #	Content of Concern	Merck Comments
10.3. Utilities	39	Adjust utility values	Health utilities exhibit important variation by country as seen in Nafees et al. (2017) and other publications. An estimate of health utilities based on values derived from 6 non-U.S. countries would seem to not represent health utilities for a U.S. population (e.g., one would not pool costs across countries in a model). Specifically, for the S1 health state, the highest value reported among the 6 countries in Nafees et al. (2017) was for the UK, yet studies have consistently found that US-based utilities for health states are higher than in the UK (e.g., Luo et al., Med Decis Mkg, 2007). It is suggested to either further look within the literature for U.S. based utility values which correspond to the NSCLC health states, or to find literature which compares U.S. values for a set of TTO health states to those elicited from individuals in one of the countries featured in Nafees et al. (e.g., UK) and adjust the Nafees values up or down to better reflect U.S. health state preferences.
10.4. Health care sector costs	40	Consider including more value elements	Look at the table on p.134 in Lakdawalla et al., in "Defining Elements of Value in Health Care - A Health Economics Approach: An ISPOR Special Task Force Report", 2018 for other value elements that can be included in the calculation of health care sector costs, not just value of hope.
10.4.1. Treatment Costs	40	Measurement correction	The dosage for Pemetrexed should be 500 mg/m2 rather than 500 mg.
10.4.1. Treatment Costs	40	"…so patients use 1 100mg vial and 1 50 mg vial of cisplatin…"	Suggest spelling the number of vials in words, i.e., "one" instead of "1" – it may be confusing to the reader otherwise.

Section	Page #	Content of Concern	Merck Comments
10.4.1. Treatment Costs	41	Verify costs in Table 5	The WAC costs per 100 mg. vial for pembrolizumab and nivolumab seem low and may be for other therapies as well. Suggest to re-check the costs in Table 5.
10.4.2. Inpatient Costs/ 10.4.3. Outpatient Costs	42	Time-varying costs	The costs of progression-free and progressed disease states have been found to vary by time (e.g., long-term survivors are more likely to be in remission or cured and have much lower monthly healthcare costs than newly diagnosed individuals with active disease management). A lack of incorporation tends to bias cost-effectiveness against treatments which extend life expectancy, due to the relatively higher costs of additional years of life. See Insinga et al. (J Med Econ 2018) for an example for NSCLC. It is suggested to incorporate time varying costs within the model based on available literature.
10.4.2. Inpatient Costs, first paragraph	42	"Inpatient costs… who separate costs due to adverse events from costs due to adverse events.	Suggest taking another look at the ending of the first sentence.
10.4.4. Adverse Event Costs	43	Analysis assumptions	The analysis seems to assume that all adverse events lead to hospitalization based on the costing approach applied. If so, this will over-estimate costs for adverse events as most such patients are not hospitalized (e.g., see Insinga et al., J Med Econ 2018).
Model Validation			How was the model validated? It would be helpful to have a section to describe model validation in detail.

Section	Page #	Content of Concern	Merck Comments
Limitations Section before Appendices	46	Adding a limitations section	Prior to the Appendices, it would be helpful to add a section specifically describing the limitations of the modeling. This would both aid understanding of the work as well as suggest and promote future avenues of research to better inform certain model parameters.

At Novartis, we are united by a single purpose: reimagining medicine to improve and extend people's lives. We have committed to bringing more of our medicines to more people, no matter where they are. For all our new medicines we are systematically integrating access in how we research, develop and deliver globally.

We thank The Innovation and Value Initiative (IVI) for the opportunity to provide comments on the open source value platform for EGFR+ non-small cell lung cancer (NSCLC). We hope IVI's initiative will bring clarity to all stakeholders involved - patients, providers of care, payers and investors.

We have not evaluated the technical aspect of model implementation. Broadly, our comments are confined to three major areas - methods and modeling approach, perspectives on value and user experience.

1. Methods and Modeling Approach

a. *Treatment Sequence:*

- Estimating the clinical and cost effectiveness begins with a clear statement of decision problem laying out the technologies being compared and the relevant patient groups. IVI's OSVP model frames the decision problem as estimation of value of alternative treatment sequence for patients with EGFR+ NSCLC.
- We think that model would benefit from inclusion of a standard of care treatment sequence derived from real world data and/or expert opinion/treatment guidelines. Comparator treatment sequences could remain customizable.
- Given the expanding treatment options there is interest in understanding appropriate sequencing that is relevant from value perspective. However, selection of comparator treatment sequence should be based on the evidence that allows a robust assessment of relative clinical and cost effectiveness. Given the lack of evidence in later lines of treatment (2L+), we are unsure whether a comparison of treatment sequences provides desirable precision for a decision-makers.
- The use of tyrosine kinase inhibitors for NSCLC treatment invariably leads to acquired drug resistance which is often mediated by T790M resistance mutation. However, there are multiple genetic mutations associated with this drug resistance - alterations in MET (amplification), BRAF (mutation), PIK3CA (mutation) or PTEN (loss). These genetic mutations could also lead to gefitinib and erlotinib resistance. By construct OSVP model does not account for these complexities.
- We think instead of comparing treatment sequences it is more relevant to compare the technology of interest, in its expected place in the pathway of care for the relevant patient group(s). The expected place in pathway of care for NSCLC could be informed by the approved indication, clinical opinion, and patient perspective. A review of selected recent health technology assessments for immune checkpoint inhibitors for NSCLC (NICE TA 428 and TA 520) would reinforce this consideration.
- NSCLC is a heterogeneous disease marked with a high rate of somatic mutations. Additional benefits of aforementioned approach would be to facilitate explicit consideration of additional genetic alterations.
- Use of immune checkpoint inhibitors in treatment sequence without factoring in tumor mutation burden and PD-1 expression is problematic. Multiple studies have also shown that immunotherapy has limited impact on progression free survival (PFS) or overall survival (OS) in EGFR+ NSCLC. In fact NCCN guidelines do not recommend immunotherapy for patients carrying EGFR mutation.

- b. *Evidence Synthesis*
  - We note the use of multi-state Network Meta-Analysis does not require proportional hazard assumption and explicitly takes into account the structural relationship between stable disease, progression and death. However, we were unable to comment on efficiency gains from this method as opposed to traditional approach. Ideally the transition rates derived from the two methods should be summarized and their impact on economic evaluation should be explored in the sensitivity analyses.

- c. *Adverse Events, Treatment Switch and Discontinuations & Stopping Rules*
  - Although impact of adverse events on cost and utilities is explicitly accounted for in the model, we are unsure whether adverse event related treatment discontinuations/switches were considered.
  - The evidence for immunotherapies on treatment stopping rules is immature and there are no clear data on the effect of stopping treatment. NICE's appraisal committee suggests that often clinicians stop treatment with immunotherapy anywhere between 6 months and 2 years (TA 520). It would be preferable for the model output to include the distribution of time spent on each of the treatments in the sequence. This would facilitate the user's assessment of the face validity of the model.

2. Perspective on Value

- We note the inclusion of novel metrics for value assessment such as Multi-Criteria Decision Making and attempts to augment ICER analyses with value of hope. An ISPOR special task force had identified a series of value elements that warrant consideration in value assessment of medical technologies (https://doi.org.10.1016/j.jval.2017.12.007). These novel elements of value broaden the view of what constitutes value in health care over and above QALYs and costs.
- Employers are the principal source of health insurance in the United States, providing health benefits for about 152 million non-elderly people in America. We think inclusion of productivity gains in the model will aide informed decision-making on the value of medical technologies for EGFR+ NSCLC employers. It is also important to note that US Panel on Cost Effectiveness in Health and Medicine had recommended that all Cost Effectiveness Analysis (CEA) include two reference cases one based on health care sector perspective and the other based on societal perspective. Recently ICER has noted that it will conduct a scenario analysis that includes work productivity in their assessments.
- Recent advances in value assessment have demonstrated the importance of Real Option Value for treatments that extend survival for patients. These advances have estimated that incorporating the option value adds about 10% to conventional net monetary benefits of technologies treating chronic myeloid leukemia, and about 25% in case of breast cancer. Accordingly, model would benefit from the inclusion of Real Option Value as more evidence emerges on survival benefit of these treatments.
- Much of health technology evaluation involves trade-off decisions, where funding a particular research initiative or technology may come at the expense of another. In making such choices, individual patient interests may conflict with the desire to distribute resources "fairly." As stated above recent advances now allow us to include patient perspective in CEA assessments. It is time for decision-makers to proactively include patient centric approaches in assessment of value of medical technologies.
- We also understand that each of these methods have their own challenges and may add incremental layers of complexity in decision-makers' challenge of making values based choices among the ever growing list of innovative treatments in budget constrained environment.
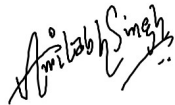
3. User Experience

- Overall the model is well implemented, transparent and is easy to execute. Menus are well-laid out and inputs and outputs of the model are neatly separated in the panels making the navigation easy. Probabilistic sensitivity analyses is efficiently implemented. As stated above the model would benefit from clear characterization of time spent on each treatment in the sequence. Perhaps an additional graphic could be inserted in the outcomes panel.

We hope that our comments are useful and are addressed in the next iteration of the model. We look forward to further future collaboration. We will be delighted to clarify any questions you may have.

A focus on value drives research agendas and investment in the areas of highest value for patients. Rewarding interventions that deliver the best possible value for patients, health systems and society set the right incentives to develop and deliver effective and efficient care. As discussed, Novartis is committed to value-based healthcare. However, value needs to be measured in a holistic manner by taking into account additional value elements such as those included in the ISPOR task force (cited above). In addition, there needs to exist a willingness of collaboration across stakeholders to close the uncertainty gaps.

Sincerely,

Amitabh Singh
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To the IVI-NSCLC modeling team:

Thank you very much for sharing your model and providing the opportunity to provide feedback. I was successfully able to run your CE model and found the tutorial very helpful and easy to follow. I also found the WebEx presentation very insightful.

I did not have as much time as I would have liked for working with the model, so have only a few comments - but I hope you find them useful as you move to the next version of the model.

My comments are:

- A few very minor comments on the text and inputs
  - o p15: estimate from Ma et al. (82 of 15 [52%]) - I read this paper and think there might be a small calculation error - I think the sum of the numerators from Table 3 should be 85 (54%). Apologies if I made a mistake or misinterpreted their data.
  - o p16: The % women used in the model is based on an EGFR unselected population but in the introduction and elsewhere in the literature, it is stated that women are more likely to have EGFR+ than men. Perhaps % women should be estimated from a source population of EGFR+ patients.
  - o At some point in the description, it might be useful to make clear that these TKIs are typically used until progression (and hence costs are applied until progression). This is to distinguish them from other types of 1L treatments for NSCLC (e.g. chemotherapies) where regimens are continued only for a certain number of cycles at which point patients stop and optionally move on to maintenance therapy.
- For the NMA inputs, it would be a nice feature if there were more user-end functions to explore and visualize the raw and modeled data more transparently, to further evaluate modeling choices. I have not yet prepared any specific suggestions for this, but would be happy to do so, if you are interested.
  - o I think this could be useful especially given the innovative approach you have used to model the transition hazards directly; users may be less familiar with the approach and this could allow them to become more familiar with the inputs and potentially more confident in the outputs.
  - o In the Webinar, Dr. Jansen mentioned using a weighted average of the ERL and GEF arms to address the fact that the FLAURA trial allowed for the use of either agent in the control arm. I did not notice this in the report text, though it is evident in all of the JAGS code (the comments provided in the OS / PFS code make this more transparent than in the AE code). As this is a main feature in the network of evidence, it may be useful to highlight in the report: this approach successfully avoids a number of other possible implementations that force assumptions that may be untrue. Ideally, the JAGS code could be set up more flexibly in the future

to allow the study number, arms, and weights as inputs rather than being hard-coded.
- For AEs, a brief statement on how/why the 10 AEs were selected for inclusion in the model, over others identified in the SLR would be useful to ensure full transparency. Apologies if I missed this.

Again, thank you very much for the opportunity to comment and for all of the work that went into developing this impressive open-source model in R.

Sincerely,

Sarah Goring

Received via e-mail on 4/1/19.

Thanks Mark. Due to time constraints, I've had to do a pretty cursory review and am not responding on Tufts letterhead or anything like that, apologies. In any event, my feedback is from the perspective of an end user and focuses on documentation and rationale issues, please see below:

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- The model structure, default parameters, and major assumptions all appear to be reasonable and well-documented. However, improvements could be made. Please see suggestions below.
- It was probably done for space reasons, but the uninitiated MCDA participant may feel that adverse events are not given equal weight, since treatment attributes appear as a default and the user must click on adverse events to see that list. I would suggest two click boxes, one for treatment attributes and one for adverse events, with the categories expanded once the user clicks on either.
- What is the genesis of the 10-point scale for MCDA? There is no mention of why a 10-point scale is used, versus a 5-point scale or something else derived based on a prior empiric exercise in NSCLC. Some discussion of this is warranted.
- There is no clear explanation to the user that the setting used for each MCDA weight involves tradeoffs with the others—in other words, if users think everything should be given a weight of 10, that diminishes the importance of all weights. There should be some description of ranking the importance of each attribute, with the resulting importance % changes as a result.
- It appears that the alternative survival scenarios do not have their own explanatory text associated with them. Once can see how the curves change, but some explanation of what is being changed in the underlying survival functions would be helpful.
- I see results from the simulations that include "value of hope", but no mention of how this is derived anywhere, nor any definition of it in the glossary. This should be described clearly up front so that users are able to interpret its contribution to results.

All the best,

Dan

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