The Cost-Effectiveness of Treatment Options for Advanced Non-small Cell Lung Cancer: Modeling Analysis Plan

Institute for Clinical and Economic Review

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Background

Lung cancer is the number one cause of cancer death in the United States, expected to cause 158,000 deaths in 2016, and accounting for 26.5% of all cancer deaths.[1] It is the second most common cancer in both men (after prostate cancer) and women (after breast cancer), with 118,000 and 106,000 new cases expected in 2016, respectively.[2] Lung cancer includes different pathological types, broadly divided into small-cell lung cancer and non-small-cell lung cancer (NSCLC).[3] NSCLC makes up about 85% of lung cancers and comprises mainly squamous cell carcinoma, adenocarcinoma, and large-cell lung cancer.[4]

Mutations affecting the kinase region of the epidermal growth factor receptor (EGFR) are found in approximately 10% of patients with adenocarcinoma in the United States. In NSCLC patients with EGFR mutations (referred to as EGFR+ NSCLC), tyrosine kinase inhibitors (TKIs) have become first-line therapy.[5] The main TKIs used as first-line therapy for advanced NSCLC include afatinib (Gilotrif®, Boehringer Ingelheim), erlotinib (Tarceva®, Genentech), and gefitinib (Iressa®, AstraZeneca). Patients with NSCLC without a driver mutation are typically treated with a platinum-based chemotherapy doublet (e.g., cisplatin + paclitaxel, carboplatin + gemcitabine, etc.) as first-line therapy.[5]

Other newer agents are also being used for advanced NSCLC. Immunotherapy aimed at altering checkpoint inhibition through the programmed death 1 (PD-1) receptor or its ligand (PD-L1) shows promise in at least some patients with NSCLC.[6] Agents focused on this pathway include nivolumab (Opdivo®, Bristol-Myers Squibb) and pembrolizumab (Keytruda®, Merck), which are antibodies to PD-1, as well as atezolizumab (Tecentriq®, Genentech), an antibody to PD-L1. PD-1 immunotherapy is recommended as second-line treatment in patients with advanced NSCLC without a driver mutation who progress on a chemotherapy doublet.[5]

A course of treatment with first-line TKI therapy typically costs approximately $90,000 per year.[7] A course of PD-1 immunotherapy has been estimated to cost approximately $150,000 per year.[7]

Approach

The primary aim of this analysis will be to estimate the cost-effectiveness of certain tyrosine kinase inhibitors (TKIs) and programmed death 1 (PD-1) agents in the treatment of advanced non-small-cell lung cancer (NSCLC). The effects of both classes of agents will be evaluated in EGFR+ NSCLC, and PD-1 agents will be evaluated in NSCLC without a driver mutation. The analytic framework for this assessment is depicted in Figure 1 below. The model will be developed in Microsoft Excel.

Key Model Choices and Assumptions

- The model will utilize a network meta-analysis from multiple trials to derive survival estimates for each drug regimen. Indirect treatment comparisons are necessary because head-to-head comparisons are not available for the majority of multiple regimens included in this study. Therefore, the model assumes that the trial populations used in the network are sufficiently homogeneous to allow for statistical pooling of the treatment effect.
- Parametric curve functions will be fit for the baseline comparator in each population/treatment setting and used to extrapolate the data to a lifetime horizon.
- We will use the hazard ratios derived from network meta-analysis applied to the baseline curves to derive survival curves for all comparator interventions. Therefore, we will assume proportional hazards hold for the relative survival curves.

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- The model will assume that the trial-reported survival rates in baseline comparators, as well as the relative differences estimated from the network meta-analyses, will remain constant beyond trial-reported follow-up time in extrapolated survival estimates.
- Survival will be weighted by health state utilities to model quality of life. The model will include separate utilities for progression-free disease undergoing treatment, progression-free disease off treatment, and progressed disease. The model will include disutilities for individual adverse events.
- The model will include grade 3/4 adverse events only, as less severe events are not expected to significantly impact patient health or costs. The models will include all grade 3/4 events that occur in at least 5% of patients in at least one of the included regimens.
- The model will include all treatment costs associated with each individual regimen, including drug acquisition costs (based on average patient characteristics, e.g., body surface area), drug administration costs (for intravenously administered drugs), supportive care costs (e.g., prophylaxis drugs and monitoring), and costs of disease progression.
- Disease progression costs will reflect a distribution of subsequent treatments and best supportive care. The cost per month in disease progression will be consistent across comparators.
- All survival and health care costs will be discounted at 3% per year.

Populations
The populations of focus for the models will be adults with advanced NSCLC who:

P1. Have an EGFR+ tumor and have not previously been treated for advanced disease
P2. Have a tumor without a driver mutation that has progressed after first-line treatment with a platinum-based chemotherapy doublet (e.g., cisplatin + paclitaxel, carboplatin + gemcitabine, etc.).

Interventions
The interventions of interest are listed below. Regimens listed are based on FDA-labeled indications for treatment of NSCLC, as well as expert input regarding common treatment approaches for the populations of interest. The model will utilize a network meta-analysis from multiple trials to derive survival estimates for each drug regimen.

I1. The TKIs erlotinib, gefitinib, and afatinib
I2. PD-1 immunotherapy (after progression on a platinum-based chemotherapy doublet)

Universal Comparators
Parametric curve functions will be fit for the baseline comparator in each population/treatment setting and used to extrapolate the data to a lifetime horizon.

C1. A platinum-based chemotherapy doublet
C2. Single-agent chemotherapy (e.g., docetaxel)

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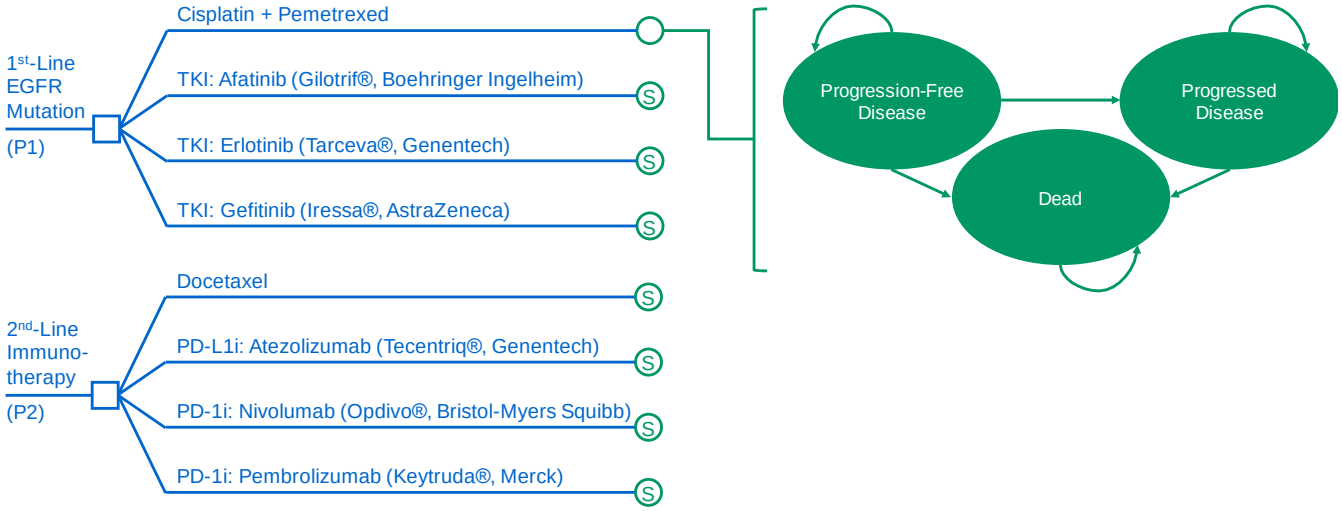
Figure 1. Analytic Framework



For each treatment regimen, a hypothetical patient population will begin the model in the progression-free survival health state, where they remain until they experience either: (a) disease progression or (b) death from cancer or other causes. Patients who transition from the progression-free to the progressed disease state remain there until they either die from progressed cancer or from other causes. Patient survival, quality-adjusted survival, and health care costs will be estimated for each model cycle and then summarized over the entire time horizon for each treatment option. Model cycles will be 7 days each to: (a) accommodate the weekly regimen variability in treatment cycles, and (b) account for the high rates of disease progression in NSCLC.

Model Structure

Outcomes will be modeled using a partition survival approach and three health states: progression-free, progression, and death.[8] The advantage of partition survival models is that they are less data intensive than more advanced modeling approaches. Statistical fitting methods allow the extrapolation of the survival results beyond the observed time frame, but rely on assumptions that may differ substantially between different parametric models. We will ensure that our assumptions do not lead to invalid models and nonsensical survival rates, such as the tail of the extrapolated progression-free survival curve crossing the tail of the overall survival curve.

We will fit parametric survival curves to progression-free survival (PFS) and overall survival (OS) Kaplan-Meier data for the universal comparator utilizing the approach described by Hoyle and Henley.[9] First we will extract data points from digitized copies of published survival curves, then use the extracted values, the number of surviving patients at each time interval, and maximum likelihood functions to estimate the underlying individual patient data. The model curves will include the distributional forms Weibull, exponential, log-normal, log-logistic, gamma, and Gompertz. The base case parametric function will be selected based on best model fit using AIC values and visual comparison.

We will then use hazard ratios acquired from the network meta-analysis, applied to the comparator curves, to derive survival curves for the other interventions. This approach will allow us to model the relative efficacy of the interventions, model survival beyond available follow-up time, and facilitate probabilistic sensitivity analyses of survival.

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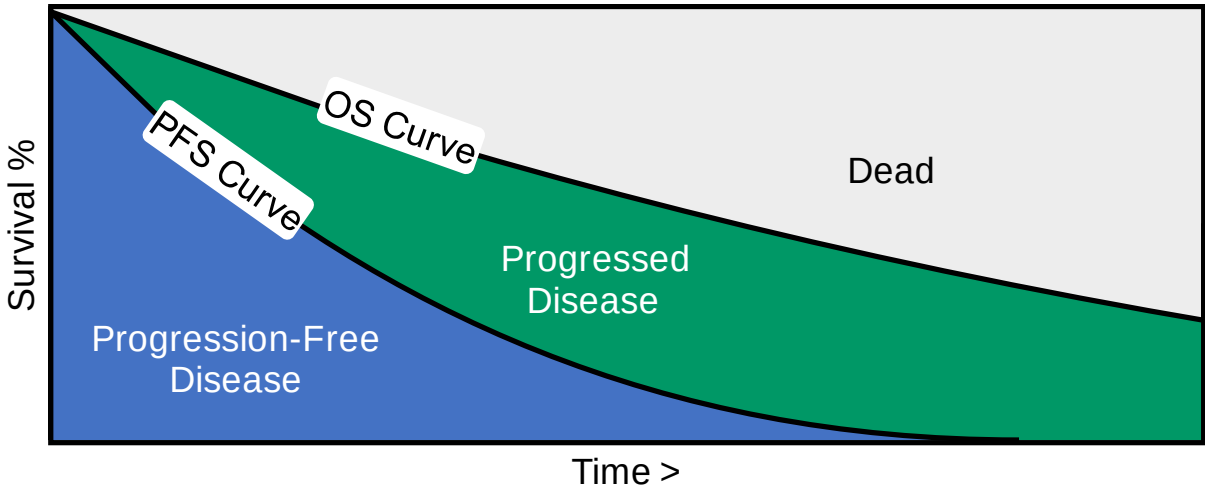
Figure 2. Partition survival model approach



Clinical Inputs

Base case survival will be derived from parametric fits to each baseline comparator's PFS and OS Kaplan-Meier data as described above. We will then apply PFS and OS hazard ratios acquired from the network meta-analyses to derive survival curves for the comparator interventions.

Survival hazard ratios in treatment-naïve EGFR patients, from NMA

EGFR+ TKI Therapy	Default	<Range>		SE	Distribution	Reference
PFS HRs						
AFAT	0.40	0.19	0.82	0.37	LogNormal	NMA
ERLO	0.42	0.18	1.05	0.45	LogNormal	NMA
GEFI	0.53	0.25	1.10	0.38	LogNormal	NMA
OS HRs						
AFAT	0.48	0.38	0.58	0.10	LogNormal	Assumption
ERLO	0.48	0.38	0.58	0.10	LogNormal	Assumption
GEFI	0.48	0.38	0.58	0.10	LogNormal	Assumption

Progression-free survival hazard ratios in second-line immunotherapy patients

Second-Line Immunotherapy	Default	< Range >		Distribution
PFS Hazard Ratios vs. DOCX				
ATEZ: TC1/2/3 or IC1/2/3	0.85	0.63	1.16	LogNormal
NIVO: All Comers	0.77	0.52	1.13	LogNormal
PEMB: PD-L1 >1%	0.88	0.74	1.05	LogNormal

OS Hazard Ratios vs. DOCX				
ATEZ: TC1/2/3 or IC1/2/3	0.59	0.40	0.85	LogNormal
NIVO: All Comers	0.67	0.55	0.83	LogNormal
PEMB: PD-L1 >1%	0.71	0.58	0.88	LogNormal

Adverse Events

The model will include grade 3/4 adverse events derived from key clinical trials and/or the drug's prescribing information. The model will include any grade 3/4 adverse events that occur in ≥5% of patients in any of the treatment comparators, as listed in the table below.

Grade 3/4 Adverse Events	CIS-PEM[35]	DOCX[79]	AFAT[80]	ERLO[45]	GEFI[81]	ATEZ[21]	NIVO[82]	PEMB[83]
Anemia	6.3%	9.0%	*	1.0%	*	*	*	5.0%
Diarrhea	0.0%	3.0%	15.0%	5.0%	3.0%	1.0%	*	0.0%
Dyspnea	*	*	*	*	*	7.0%	*	2.0%
Fatigue	12.6%	*	*	6.0%	*	*	*	7.0%
Hyponatremia	*	*	*	*	*	*	5.0%	9.0%
Infection	*	10.0%	*	*	*	*	*	*
Leukopenia	8.1%	49.0%	*	*	*	*	*	*
Nausea	3.6%	5.0%	*	*	*	1.0%	*	0.0%
Neuromotor	*	5.0%	*	*	*	*	*	*
Neutropenia	18.0%	65.0%	*	*	*	*	*	*
Paronychia/Nail disorders	0.0%	1.0%	11.0%	*	0.1%	*	*	*
Pneumonitis/Pneumonia	*	*	*	1.0%	*	6.0%	0.4%	0.2%
Pulmonary/respiratory tract infection	*	21.0%	*	*	*	*	*	1.0%
Rash	0.0%	*	*	13.0%	*	*	0.4%	0.0%
Skin reactions	*	1.0%	16.0%	*	2.0%	*	*	*
Stomatitis	0.9%	2.0%	9.0%	*	0.3%	*	*	*

*Not reported

Drug utilization

The following inputs are necessary to model drug utilization and associated costs:

- Number of treatment cycles for each regimen
- Number of doses/cycle for each drug in each regimen
- The protocol dosage for the indication
    - The dose may be fixed, by weight, or by body surface area (BSA)
- If a regimen is based on treat-to-progression, the treatment utilization and cost will be applied to all patients who remain in the PFS health state over time. If a finite number of cycles is used, patients may remain in the PFS state without active treatment.
- Dose intensity adjustment factor

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Table 3. Treatment Regimen Recommended Dosage

	Dosage	Schedule	Route	Duration
Cisplatin	75 mg/m^2	1x/cycle	IV	6 21-day cycles
Pemetrexed	500 mg/m^2	1x/cycle	IV	6 21-day cycles
Docetaxel	75 mg/m^2	every 3 weeks	IV	until progression
Afatinib	40 mg	1x daily	oral	until progression
Erlotinib	150 mg	1x daily	oral	until progression
Gefitinib	250 mg	1x daily	oral	until progression
Atezolizumab	1200 mg	every 3 weeks	IV	until progression
Nivolumab	3 mg/kg	every 2 weeks	IV	until progression
Pembrolizumab	2 mg/kg	every 3 weeks	IV	until progression

Table 4. Drug Wholesale Acquisition and Administration Parameters[10]

Drug Cost Parameters	Default	< Range >		Distribution	Reference
Cisplatin per mg	$0.36	$0.29	$0.43	Normal	Redbook
Cisplatin administration	$91.72	$73.38	$110.06	Normal	CPT 96417 & 96415
Cisplatin dose intensity	100.0%	80.0%	100.0%	Beta	Assumption
Pemetrexed 500 mg vial	$3,162.00	$2,529.60	$3,794.40	Normal	Redbook
Pemetrexed 100 mg vial	$632.40	$505.92	$758.88	Normal	Redbook
Pemetrexed administration	$136.15	$108.92	$163.38	Normal	CPT 96413
Pemetrexed dose intensity	100.0%	80.0%	100.0%	Beta	Assumption
Docetaxel per mg	$9.55	$7.64	$11.46	Normal	Redbook
Docetaxel administration	$136.15	$108.92	$163.38	Normal	CPT 96413
Docetaxel dose intensity	100.0%	80.0%	100.0%	Beta	Assumption
Afatanib 40 mg tablet	$233.05	$186.44	$279.66	Normal	Redbook
Afatanib dose intensity	100.0%	80.0%	100.0%	Beta	Assumption
Erlotinib 150 mg tablet	$241.52	$193.22	$289.83	Normal	Redbook
Erlotinib dose intensity	100.0%	80.0%	100.0%	Beta	Assumption
Gefitinib 250 mg tablet	$241.20	$192.96	$289.44	Normal	Redbook
Gefitinib dose intensity	100.0%	80.0%	100.0%	Beta	Assumption
Atezolizumab 1200 mg vial	$8,620.00	$6,896.00	$10,344.00	Normal	Redbook
Atezolizumab administration	$136.15	$108.92	$163.38	Normal	CPT 96413
Atezolizumab dose intensity	100.0%	80.0%	100.0%	Beta	Assumption
Nivolumab 100 mg vial	$2,470.48	$1,976.38	$2,964.58	Normal	Redbook
Nivolumab 40 mg vial	$988.19	$790.55	$1,185.83	Normal	Redbook
Nivolumab administration	$136.15	$108.92	$163.38	Normal	CPT 96413
Nivolumab dose intensity	100.0%	80.0%	100.0%	Beta	Assumption
Pembrolizumab 100 mg vial	$4,380.74	$3,504.59	$5,256.89	Normal	Redbook
Pembrolizumab administration	$136.15	$108.92	$163.38	Normal	CPT 96413
Pembrolizumab dose intensity	100.0%	80.0%	100.0%	Beta	Assumption

We will use the wholesale acquisition cost (WAC) for each drug, and note each available formulation. Based on the regimen dosage specified above, the model will utilize the lowest cost combination of tablets/vials for each regimen.

Adverse event costs will be derived from reasonable treatment assumptions used in previous analyses[11,12] and the Centers for Medicare and Medicaid Services (CMS) list of Medicare severity diagnosis-related groups (MS-DRGs) relative weighting factors for the fiscal year 2016.

To incorporate costs in the progression health state, we will use a treatment landscape analysis to estimate the proportion of patients who receive different available treatments upon progression. The specific treatment distribution is pending further analysis. We will then calculate a mean cost per month weighted by the proportion of patients receiving each treatment.

Table 5. Health State Utilities

1st Line	Base Case	Lower Range	Upper Range	Std. Error	Distribution	Source
Progression-free disease	0.78	0.77	0.80	Beta	Beta	LUX-Lung
Progressed disease	0.67	0.59	0.75	Beta	Beta	Chouaid et al.

2nd Line	Base Case	Lower Range	Upper Range	Std. Error	Distribution	Source
Progression-free disease	0.65	0.61	0.70	0.02	Beta	Nafees et al.
Progressed disease	0.47	0.43	0.52	0.02	Beta	Nafees et al.

Health state utilities will be derived from publicly available literature and applied to the disease states of progression-free and progressed disease. We will assume that health state utility values do not vary across the treatments evaluated in the model. For the progression-free health state, different utilities will be applied depending on whether the patient receives first- or second-line treatment, to represent decreased quality of life due to progression following first-line treatment. We will apply a regimen-weighted disutility for experiencing any Grade 3/4 adverse event; the total percentage of patients who experience any Grade 3/4 adverse event for each regimen will be multiplied by the adverse event disutility and then subtracted from the first month of PFS for each regimen. We will assume that the total time with a Grade 3/4 adverse event for patients experiencing any Grade 3/4 adverse event is one month.

Table 6. Disutilities for Grade 3/4 Adverse Events

Disutility	Base Case	Lower Range	Upper Range	Distribution	Source
Anemia	0.090	0.059	0.120	Beta	Nafees et al.
Diarrhea	0.047	0.016	0.077	Beta	Nafees et al.
Dyspnea	0.050	0.026	0.074	Beta	Doyle et al.
Fatigue	0.073	0.037	0.110	Beta	Nafees et al.

Hyponatremia	0.090	0.059	0.120	Beta	Nafees et al.
Infection	0.047	0.016	0.077	Beta	Nafees et al.
Leukopenia	0.090	0.059	0.120	Beta	Nafees et al.
Nausea	0.048	0.016	0.080	Beta	Nafees et al.
Neuromotor	0.069	0.045	0.093	Beta	Doyle et al.
Neutropenia	0.090	0.059	0.120	Beta	Nafees et al.
Paronychia/Nail disorders	0.032	0.010	0.055	Beta	Nafees et al.
Pneumonitis/Pneumonia	0.073	0.037	0.110	Beta	Nafees et al.
Pulmonary/Respiratory infection.	0.046	0.024	0.068	Beta	Doyle et al.
Rash	0.032	0.010	0.055	Beta	Nafees et al.
Skin reactions	0.032	0.010	0.055	Beta	Nafees et al.
Stomatitis	0.032	0.010	0.055	Beta	Nafees et al.

Other Inputs and Assumptions

The assumption of proportional hazards for the entire time horizon of the model may not agree with observed data, especially for PD-1 inhibitors. To address this concern, we will program the capability to "flatten" survival curves to reflect the potential of patients to be cured if they survive to a given point in time. The specific approach for implementing this effect is pending further analysis.

An average patient height and weight will be acquired from trial evidence. This will be necessary for accurately calculating drug dosage in each regimen. Patient height and weight will be fixed among regimens to enable direct comparisons.

We will utilize a health system perspective (i.e., focus on direct medical care costs only) and a lifetime horizon, modeling patients from treatment initiation until death. We will use a 3% discount rate and employ a half-cycle correction.

For population P2, it appears likely that tumor expression of PD-L1 is helpful in selecting appropriate patients for PD-1 based therapies; however there are concerns about the comparability of various methods used to assess levels of expression. Thus there is the question of whether to treat all comers versus treating based on PD-L1 levels. We expect to model whether a strategy that does or does not include testing for PD-L1 levels affects the results.

Model Outcomes

The model will estimate the amount of time, on average, patients spend progression-free and in progression. Unadjusted and utility-adjusted time spent in each health state will be summed to provide estimates of life expectancy and quality-adjusted life expectancy.

Model outcomes of interest will include:

- By intervention:
    - Quality adjusted life expectancy (undiscounted and discounted)
    - Life expectancy (undiscounted and discounted)
    - Mean time in the progression-free and post-progression health states (undiscounted and discounted)
- Pairwise comparisons:

- Incremental cost-effectiveness ratios for each intervention versus the standard comparators

Sensitivity Analyses

We will run one-way sensitivity analyses to identify the key drivers of model outcomes. Probabilistic sensitivity analysis will also be performed by jointly varying all model parameters over 10,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We will also perform threshold analyses comparing changes in drug prices across a range of incremental cost-effectiveness ratios (from $50,000 to $150,000 per QALY).

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