Treatment Options for Advanced Non-Small-Cell Lung Cancer: Effectiveness, Value, and Value-Based Price Benchmarks

Draft Background and Scope
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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. 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. The median age at death is 72. Lung cancer rates reflect smoking behavior, and the incidence of lung cancer peaked in men in 1992 with 69.5 cases per 100,000 and in women in 2005 with 53.8 cases per 100,000; those rates declined by 2013 to 52.2 and 47.7 cases per 100,000, respectively, reflecting earlier declines in the prevalence of smoking.

Lung cancer includes different pathological types, broadly divided into small-cell lung cancer and non-small-cell lung cancer (NSCLC). NSCLC makes up about 85% of lung cancers and comprises mainly squamous cell carcinoma, adenocarcinoma, and large-cell lung cancer. Stage at diagnosis is a primary factor in patient survival, and patients with NSCLC commonly present with advanced disease (i.e., distant spread, malignant effusion, or bilateral lung disease); 24% have regional spread at presentation, and 55% have distant spread. Prognosis is generally poor at diagnosis; five-year survival from 2006-2012 was 31.4% in patients with regional spread and 4.9% in patients with distant spread. In recent years, the treatment of some advanced NSCLCs has changed based on the determination of driver mutations in tumors.

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, but in up to 50% of patients from Asia. EGFR mutations are more common in NSCLC among non-smokers and less common in squamous cell carcinoma (approximately 2.7% with EGFR mutations).

In NSCLC patients with EGFR mutations (referred to as EGFR+ NSCLC), tyrosine kinase inhibitors (TKIs) have become first-line therapy. The main TKIs used as first-line therapy for advanced NSCLC include afatinib (Gilotrif®, Boehringer Ingelheim), erlotinib (Tarceva®, Genentech), and gefitinib (Iressa®, AstraZeneca). There is some evidence that the type of EGFR mutation may influence response to TKI therapy. A course of treatment with first-line TKI therapy typically costs approximately $90,000 per year.
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, which have been the comparators for most trials of TKIs. Conclusions about the relative efficacy and toxicity among the TKIs are somewhat limited by the predominance of indirect evidence from trials comparing them each with chemotherapy.

Despite treatment with a TKI, nearly all patients with advanced NSCLC will eventually progress. A common mechanism of TKI resistance is a T790M mutation in EGFR. Commonly, patients who have this mutation are treated second-line with osimertinib (Tagrisso®, AstraZeneca), a TKI that is effective in EGFR+ tumors with a T790M mutation. For patients who progress on osimertinib, guidelines suggest proceeding with chemotherapy doublet treatment as in patients without a driver mutation.

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. 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.

Most patients studied in trials of PD-1 immunotherapy have received prior treatment with a chemotherapy doublet, whether or not they were EGFR+ and/or had received prior TKI therapy. The alternative treatment in this setting would typically be single-agent chemotherapy with an agent that was not used in the original doublet, such as docetaxel.

Recently, clinicians have begun exploring the use of PD-1 agents in patients who have not received a chemotherapy doublet. This includes using PD-1 immunotherapy as first-line treatment in patients with NSCLC without a driver mutation or as third-line therapy (after osimertinib) in patients with EGFR+ NSCLC. As with the TKIs, conclusions about the relative efficacy and toxicity among the PD-1 agents are limited by the predominance of indirect evidence from trials comparing them each with chemotherapy.

A course of PD-1 immunotherapy has been estimated to cost approximately $150,000 per year. In addition to questions of the comparative effectiveness of these agents, both among the agents and compared with alternative therapies, it is uncertain whether tumor expression of PD-L1 is helpful in selecting appropriate patients for PD-1 based therapies.

Report Aims:
This project will evaluate the health outcomes and economic effects 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.
Scope of the Evidence Review Focusing on Comparative Clinical Effectiveness:
The proposed scope for this assessment is described below using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be collected from available randomized controlled trials as well as high-quality systematic reviews; higher-quality comparative cohort studies will also be evaluated as necessary. We will not restrict studies according to study duration or study setting; however, we will limit our review to those that capture the outcomes of interest. We will supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Analytic Framework:
The general analytic framework for assessment of all the interventions is depicted in Figure 1 below.

Figure 1. Analytic Framework: Management of Advanced Non-Small-Cell Lung Cancer

Populations
The four populations of focus for the review 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 and have not previously been treated for advanced disease
P3) 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.)
P4) Have an EGFR+ tumor that has progressed after first-line or first- and second-line TKI therapy (patients who do not develop a T790M mutation will only receive first-line TKI therapy)

**Interventions**

P1) The interventions will be the TKIs erlotinib, gefitinib, and afatinib
P2) The intervention will be a treatment sequence of PD-1 immunotherapy (i.e., nivolumab, pembrolizumab, or atezolizumab), followed by a platinum-based chemotherapy doublet at the time of progression
P3) The intervention will be PD-1 immunotherapy (after progression on a platinum-based chemotherapy doublet)
P4) The intervention will be PD-1 immunotherapy (after progression on first-line or first- and second-line TKI therapy)

**Comparators**

P1) The comparator will be a platinum-based chemotherapy doublet
P2) The comparator will be a treatment sequence of a platinum-based chemotherapy doublet, followed by PD-1 immunotherapy at the time of progression
P3) The comparator will be single-agent chemotherapy (e.g., docetaxel)
P4) The comparator will be a platinum-based chemotherapy doublet

**Outcomes**

This review will examine key clinical outcomes that occur in all four populations of patients being treated for advanced NSCLC, including surrogate outcomes common to cancer trials. We will also engage with patient groups and clinical experts to ascertain which outcomes are of greatest importance to patients and determine whether patient-reported outcomes or other evidence sources can be found to enrich the available data. Initial discussions with patient groups indicate that patients with NSCLC have particularly high levels of distress, even when compared with other cancer patients, that NSCLC and its treatments cause substantial disruption of work and family life over time, and that burdens of therapy to the patient and family can accumulate over time as patients live longer and remain on therapy longer; these outcomes may not have been captured well in clinical trials.

Outcomes of interest will include:

- Overall survival
- Disease progression-related measures (progression-free survival, time to progression)
- Objective response rate
- Symptom control
- Health-related quality of life
- Treatment-related adverse events
  - Rates of key adverse events by type (e.g., systemic, gastrointestinal, dermatologic, etc.)
  - Rates of Grade 3 or 4 adverse events
  - Discontinuation due to adverse events
- Treatment-related deaths

Evidence tables will be developed for each outcome and meta-analysis will be used to quantitatively summarize outcomes for therapies. To assess comparisons within classes of TKIs and PD-1 immunotherapies, network meta-analysis will be used to combine direct and indirect evidence.

Timing
Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings
All relevant settings will be considered, including inpatient, clinic, and outpatient settings.

Simulation Models Focusing on Comparative Value:
As a complement to the evidence review, we will develop a simulation model to assess the lifetime cost-effectiveness of the regimens of interest relative to standard treatments. Model structure will be based in part on a previously-developed model of NSCLC from a health-system perspective over a lifetime horizon. The model will focus attention on regimens most likely to be used for first- and second-line treatment; key model estimates will differ to reflect differences in disease severity and quality of life for patients receiving first- vs. second-line treatment.

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 and have not previously been treated for advanced disease

P3) 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.).

We are not planning to model population P4 above. We will explore whether there is sufficient evidence to adequately model population P2.

Effectiveness will be estimated based on network meta-analyses of progression-free and/or overall survival.

Based on input from clinical experts as well as listed FDA indications, proposed regimens include:

P1) Erlotinib, gefitinib, and afatinib, compared to platinum-based chemotherapy doublet

P2) Treatment sequence of PD-1 immunotherapy (i.e., nivolumab, pembrolizumab, or atezolizumab) followed by platinum-based chemotherapy doublet at time of progression, compared to a treatment sequence of platinum-based chemotherapy doublet followed by PD-1 immunotherapy at the time of progression
P3) PD-1 immunotherapy (after progression on a platinum-based chemotherapy doublet) compared to single-agent chemotherapy (e.g., docetaxel).

For populations P2 and P3, we may model whether a strategy that does or does not include testing for PD-L1 levels affects the results.

Key model outputs will include rates of progressive disease as well as time spent in these health states, treatment-related adverse events, disease-related survival, and the impact of these measures on health-related quality-of life. Costs will include those of current and subsequent treatment, management of adverse events, and ongoing cancer-related care. Results will be expressed primarily in terms of the incremental cost per quality-adjusted life year (QALY) gained.

We will also assess the potential budgetary impact of each regimen over a 5-year time horizon, utilizing information on treatment costs and cost offsets from extended response and/or time off treatment. Potential budgetary impact analyses will assume a product “uptake” rate over the 5-year period based on ICER criteria. Finally, we will develop a “value-based price benchmark” for each regimen reflecting prices aligned with long-term cost-effectiveness thresholds and below a threshold for potential budgetary impact that would exceed growth targets for national health care costs.

More information on ICER’s methods for estimating product uptake and calculating value-based price benchmarks can be found on ICER’s website.
References: