For Non-Small Cell Lung Cancer

Do these new drugs meet an important need?

What Is Non-Small Cell Lung Cancer?

Lung cancer is cancer that starts in the tissues of the lung (other types of cancer can spread to the lungs, but lung cancer starts there). Tumor cells can spread to other parts of the lungs and chest and to distant parts of the body. Lung cancer is the number one cause of cancer death in both men and women. There are two main types of lung cancer, small-cell lung cancer and non-small cell lung cancer (NSCLC).

In 2013, there were approximately 416,000 people living with lung cancer in the United States.

NSCLC makes up about 85% of lung cancers.

Treating Non-Small Cell Lung Cancer

Previously, advanced NSCLC was treated with chemotherapy. Although chemotherapy can extend survival, it does not cure patients with advanced disease, and many patients may be unable to tolerate the side effects.

In recent years, newer treatments have been developed:

Tyrosine kinase inhibitors (TKIs) are used to treat people with advanced NSCLC who have EGFR mutations (referred to as EGFR+). These drugs are typically used alone (without chemotherapy) as a first treatment.

Immunotherapy drugs, which trigger the body's immune system to fight the cancer, have also shown promise in treating some patients with advanced NSCLC.

New Drugs Under Review

Tyrosine Kinase Inhibitors (TKIs)

- Afatinib *(Gilotrif®, Boehringer Ingelheim)*
- Erlotinib *(Tarceva®, Genentech)*
- Gefitinib *(Iressa®, AstraZeneca)*

Compared with platinum-based chemotherapy doublets

Treatment with first-line TKI therapy typically costs approximately **$90,000 per year.**

PD-1 Immunotherapies

- Nivolumab *(Opdivo®, Bristol-Myers Squibb)*
- Pembrolizumab *(Keytruda®, Merck)*
- Atezolizumab *(Tecentriq®, Genentech)*

Compared to single-agent chemotherapy with docetaxel

Treatment with PD-1 immunotherapy has been estimated to cost approximately **$150,000 per year.**

How strong is the evidence that tyrosine kinase inhibitors (TKIs) improve patient outcomes?

Overall Survival

Randomized trials comparing first-line TKIs with platinum doublet chemotherapy showed no benefit in overall survival. The lack of benefit is likely due to the high proportion of patients initially treated with chemotherapy who started treatment with a TKI after tumor progression. Observational data suggest that first-line TKI therapy as a class **increases overall survival by approximately nine months, although there is substantial uncertainty in this figure.**

Progression-Free Survival

Progression-free survival (PFS) is calculated from when a patient starts treatment until disease progression or death. Compared with a platinum doublet, TKIs resulted in **improvements in median PFS.** The results were similar across the TKIs studied: 4-month benefit with afatinib, 3-5 months with gefitinib, and 3-9 months with erlotinib.

Harms

All TKIs appear to be **better tolerated** than platinum doublet chemotherapy, which has much higher rates of hematologic toxicity. Rash, diarrhea, and liver function abnormalities are the most common side effects with TKIs.

Quality of Life and Symptom Control

TKIs provided **significant improvements in several symptoms,** including shortness of breath, pain, and a composite symptom score that included shortness of breath, weight loss, clarity of thinking, cough, good appetite, chest tightness, and ease of breathing, compared to platinum doublet chemotherapy.

Sources of Uncertainty

- Due to high levels of crossover in the studies evaluating first-line TKIs, there is substantial uncertainty in the true survival benefit of these agents.
- There are relatively few head-to-head studies of TKIs. As such, it is difficult to judge whether there are important differences between TKIs in the benefits and harms.

How strong is the evidence that PD-1 immunotherapies improve patient outcomes?

Overall Survival

Relative to single-agent chemotherapy with docetaxel, PD-1 immunotherapies (nivolumab, pembrolizumab, and atezolizumab) improved overall survival by an average of about two to three months. **This represents two groups of patients: a larger group who get no benefit, and a smaller group (approximately 20%-40% of patients) who get substantial benefits and prolonged survival.** Subgroup analyses suggest that the levels of PD-L1 protein expressed by the tumor can help predict which patients are most likely to respond to therapy.

Progression-Free Survival

Studies of PD-1 immunotherapies showed **little-to-no differences** in progression-free survival as compared to docetaxel. Patients with tumors that express higher levels of PD-L1 protein are more likely to have improvements in progression-free survival.

Quality of Life and Symptom Control

Evidence was inadequate to assess the effects of PD-1 immunotherapies compared to docetaxel on quality of life and symptoms.

Objective Response Rate

Patients treated with nivolumab and pembrolizumab had **significantly higher rates of response** relative to chemotherapy with docetaxel (18-20% vs. 9-12%). Patients were still showing response to treatment at the time trial results were analyzed.

While atezolizumab and docetaxel produced similar objective response rates, the median duration of response was about seven months longer with atezolizumab.

As with overall survival, objective response rates among those treated with PD-1 immunotherapy were higher in patients whose tumors expressed greater levels of PD-L1 protein.

How strong is the evidence that PD-1 immunotherapies improve patient outcomes? *(continued)*

Harms

PD-1 immunotherapy is generally **much better tolerated than chemotherapy**, with the most common side effects being fatigue, nausea, and decreased appetite. Serious immune-related adverse events can occur with PD-1 immunotherapy, including pneumonitis (inflammation of lung tissue) and encephalitis (inflammation of the brain), but these are relatively uncommon.

Sources of Uncertainty

- Estimates of overall survival with second-line PD-1 immunotherapy are uncertain. The randomized trials typically ran for only two years, yet a substantial proportion of the patients who responded to PD-1 immunotherapy appeared to have ongoing responses at two years.
- There are no head-to-head studies of PD-1 immunotherapies, and the trials used different approaches for measuring PD-L1, so it is unclear if the populations studied are similar. As such, any assessment of the comparative effects of these agents is severely limited. Additionally, it is difficult to be certain whether the effect of PD-L1 expression is the same for the three therapies.
- ICER only had access to direct evidence from a single published randomized trial comparing pembrolizumab to a platinum doublet for first-line treatment of advanced NSCLC. Trial results have been presented at a conference for the use of nivolumab in this setting.
- ICER did not identify any direct evidence comparing PD-1 immunotherapy with a platinum doublet as subsequent-line treatment (after TKIs) for EGFR+ advanced NSCLC.

ICER's Evidence Ratings

Tyrosine kinase inhibitors (TKIs) and PD-1 immunotherapies

- For patients with EFGR+ advanced NSCLC, we have moderate certainty that first-line TKI therapy provides **a small-to-substantial overall net health benefit** relative to a platinum doublet chemotherapy regimen.
- Even with uncertainties about the duration of benefit with second-line PD-1 immunotherapies, the current evidence base gives us high certainty that a substantial minority of patients with EGFR- advanced NSCLC respond and achieve **important gains in overall survival.**
- We also have moderate certainty that first-line therapy with pembrolizumab provides a small-to-substantial net health benefit relative to a platinum chemotherapy doublet.
- Although the evidence base is insufficient, indirect evidence raises concerns that in patients with EGFR+ advanced NSCLC who have progressed after TKI therapy, treatment with PD-1 immunotherapy may be inferior to a platinum doublet.

What is a fair price for tyrosine kinase inhibitors (TKIs) based on their value to patients and the health care system?

Long-Term Cost-Effectiveness at List Price

$110,840 to $147,244/QALY

- Computer modeling of long-term clinical benefits and costs estimated **gains in both quality of life and survival.**
- Despite cost offsets associated with oral administration and lower rates of side effects, TKIs were associated with **higher costs than platinum chemotherapy due primarily to higher drug costs.**

The incremental cost-effectiveness ratio was measured by calculating the cost per additional quality-adjusted life year (QALY). Cost-effectiveness estimates were similar across the TKIs, ranging from $110,840 to $147,244 per QALY gained.

The cost per QALY range that is generally accepted as "reasonable" value in the US is $100,000-$150,000, so the TKIs at list prices would **represent reasonable value in the long-term.**

ICER's Value-Based Price Benchmark

Because we did not find adequate evidence to distinguish among the TKIs, we did not calculate a separate value-based price benchmark for each of the drugs.

To achieve a cost-effectiveness threshold of $100,000/QALY, TKIs would need to be **discounted approximately 21%.**

To meet a cost-effectiveness threshold of $150,000/QALY, each drug's list price could be increased. The average of these increases would represent an approximately **15% rise in price.**

What is a fair price for **PD-1 immunotherapies** based on their value to patients and the health care system?

Long-Term Cost-Effectiveness at List Price

Atezolizumab:* **$219,179/QALY**

Nivolumab: **$415,950/QALY**

Pembrolizumab:† **$236,492/QALY**

Note: These cost-effectiveness ratios are not directly comparable since the populations of patients (based on PD-L1 level and the tests used to measure PD-L1) are different.

The cost per QALY range that is generally accepted as "reasonable" value in the US is $100,000-$150,000. While the cost-effectiveness of PD-1 immunotherapies exceeds these thresholds, there is greater uncertainty in these findings given variability in estimates of overall and progression-free survival.

ICER's Value-Based Price Benchmark

Atezolizumab: **$4,026-$5,954 per 100mg vial**	A 31%-53% discount from the wholesale acquisition cost list price
Nivolumab: **$799-$1,064 per 100mg vial**	A 57%-68% discount from the wholesale acquisition cost list price
Pembrolizumab: **$1,719-$2,694 per 100mg vial**	A 39%-61% discount from the wholesale acquisition cost list price

ICER's value-based price benchmark is comprised of two components: a range associated with the prices needed to achieve long-term cost-effectiveness between $100,000–$150,000 per QALY; and the price at which the potential short-term budget impact could be so substantial that policymakers should consider whether special coverage, pricing, or payment mechanisms are needed to assure sustainable access to high-value care for all patients.

* After the publication of this report, the FDA approved atezolizumab with a broader indication than was assumed in our analyses. The conclusions here apply only to the narrower subpopulation of patients who are PD-L1 positive.

†After the meeting of the Midwest CEPAC, the FDA expanded the indication of pembrolizumab to a broader second-line population. The conclusions here apply only to the narrower subpopulation of patients analyzed.

Public Deliberation and Evidence Votes

Midwest Comparative Effectiveness Public Advisory Council Panel Votes

The Midwest Comparative Effectiveness Public Advisory Council deliberated on key questions raised by ICER's report at a public meeting on October 20, 2016. The results of the vote are presented below.

Voting Summary

1. In patients with EGFR+ advanced NSCLC, is the evidence adequate to distinguish the net health benefit among the TKIs erlotinib, gefitinib, and afatinib?

Yes: 1 votes	No: 9 votes

2. In patients with EGFR+ advanced NSCLC, is the evidence adequate to demonstrate that the net health benefit of first-line treatment with a TKI is greater than that of treatment with a platinum doublet?

Yes: 10 votes	No: 0 votes

3. Given the available evidence on net health benefit with TKI therapy, the additional cost of TKI therapy, and taking into account other benefits, disadvantages, and contextual considerations, what is the long-term value for money of TKI therapy?

Low: 0 votes	Intermediate: 9 votes	High: 1 votes

4. In patients with EGFR- advanced NSCLC who have progressed after treatment with a platinum doublet, is the evidence adequate to distinguish the net health benefit among the PD-1 immunotherapies nivolumab, pembrolizumab, and atezolizumab?

Yes: 0 votes	No: 10 votes

Public Deliberation and Evidence Votes *(continued)*

Midwest Comparative Effectiveness Public Advisory Council Panel Votes

5. In patients with EGFR- advanced NSCLC who have progressed after treatment with a platinum doublet, is the evidence adequate to demonstrate that the net health benefit of treatment with each of the following PD-1 immunotherapies used for their actual or expected labeled indications is greater than that of treatment with docetaxel?

   a. Nivolumab *(indicated for treatment irrespective of PD-L1 level)*

Yes: 8 votes	**No: 2 votes**

   b. Pembrolizumab *(indicated for treatment for PD-L1 level ≥50%)**

Yes: 10 votes	**No: 0 votes**

   c. Atezolizumab *(anticipated indication for treatment for PD-L1 test of TC 2/3 or IC 2/3)**

Yes: 8 votes	**No: 2 votes**

6. Given the available evidence on net health benefit with PD-1 immunotherapy, the additional cost of PD-1 immunotherapy, and taking into account other benefits, disadvantages, and contextual considerations, in patients with EGFR- advanced NSCLC who have progressed after treatment with a platinum doublet, what is the long-term value for money of each of the following PD-1 immunotherapies used for its actual or anticipated labeled indications?

   a. Nivolumab *(indicated for treatment irrespective of PD-L1 level)*

Low: 6 votes	**Intermediate: 4 votes**	**High: 0 votes**

   b. Pembrolizumab *(indicated for treatment for PD-L1 level ≥50%)**

Low: 3 votes	**Intermediate: 7 votes**	**High: 0 votes**

   c. Atezolizumab *(anticipated indication for treatment for PD-L1 test of TC 2/3 or IC 2/3)**

Low: 4 votes	**Intermediate: 6 votes**	**High: 0 votes**

Public Deliberation and Evidence Votes *(continued)*

Midwest Comparative Effectiveness Public Advisory Council Panel Votes

7. In patients with advanced NSCLC without a driver mutation who have not previously been treated for advanced disease, is the evidence adequate to demonstrate that the net health benefit of treatment with pembrolizumab in patients with a positive test for PD-L1 using the pembrolizumab assays is greater than that of treatment with a platinum doublet?

Yes: 10 votes	No: 4 votes

8. In patients with EGFR+ advanced NSCLC who have progressed after treatment with a platinum doublet, is the evidence adequate to demonstrate that the net health benefit of treatment with PD-1 immunotherapy is greater than that of treatment with docetaxel?

Yes: 2 votes	No: 8 votes

For further detail on the voting results, please see the full report.

* Atezolizumab was approved with a broader indication (no PD-L1 testing required) just prior to the meeting. As such, this question did not apply to the actual indication for atezolizumab and is not directly relevant to policy issues around atezolizumab. Additionally, after the meeting, the FDA expanded the indication of pembrolizumab to a broader second-line population.

Key Policy Implications and Recommendations

Patients, Clinicians, and Researchers

- Take various steps to increase the number of patients enrolling in clinical trials and to enhance the role that patients play in identifying key outcome measures for future research.

Patients and Patient Advocacy Groups

- Seek action by manufacturers, insurers, and policymakers to address the affordability of treatments for lung cancer.

Purchasers and Insurers

- In conjunction with a movement toward a more value-based pricing system, purchasers and insurers should design insurance plans that protect patients from significant financial toxicity.
- Similar mechanisms of action and the lack of evidence to distinguish whether TKI drugs differ in their risks and benefits suggests that these drugs might be considered for step therapy in insurance coverage, but justification of step therapy for these and other cancer drugs faces a high burden given that even minor differences among treatments may have important clinical consequences for individual patients.
- Incentives for clinicians that encourage the use of high-value care options are reasonable if applied to clinically equivalent options. Efforts should be taken to share the benefits of more cost-effective care options with patients by reducing their financial burden.
- Genetic testing of lung cancer tumors is standard practice, and CMS should revisit its current payment criteria for tumor testing so as to avoid delaying the receipt of actionable information.

Insurers and Manufacturers

- PD-1 immunotherapy may be an appropriate area for considering innovative outcomes-based payment mechanisms, particularly in the treatment of patients who are not tested for PD-L1 levels.

Insurers and Clinicians

- First-line PD-L1 testing may be needed to guide appropriate care for all patients.

Manufacturers and Researchers

- Develop studies to allow populations and subpopulations to be compared across different PD-1 immunotherapies.

Clinicians

- Caution should be exercised in using PD-1 immunotherapy in patients with EGFR+ advanced NSCLC.

For more information on the policy implications, please see the full report.

Conclusion

Comparative Clinical Effectiveness

Newer agents for first- and second-line use in NSCLC substantially improve survival while having fewer harms and burdens than prior treatments.

Comparative Value

At current wholesale acquisition costs, the estimated cost-effectiveness of each of the TKIs appears to fall within commonly-accepted thresholds. While the cost-effectiveness of PD-1 immunotherapies exceeds these thresholds, there is greater uncertainty in these findings given variability in estimates of overall and progression-free survival.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit ICER's website (www.icer-review.org).

Key Terms

EGFR+/-	EGFR stands for epidermal growth factor receptor. Some patients with NSCLC have mutations in their tumor that affects the EGFR. EGFR+ indicates that this mutation is present, while EGFR- indicates that it is not present. Whether a patient is EGFR+ or EGFR- can affect which treatments will work best for them.
PD-1 Immunotherapy	Tumor cells can produce substances that alter how the immune system responds to a tumor, such as by affecting a regulatory "checkpoint" or brake on the T cell response to the tumor, which allows the tumor to evade the immune system. Immunotherapy aimed at inhibiting such a checkpoint through the programmed death 1 (PD-1) receptor or its ligand, PD-L1, have demonstrated benefit in at least some patients with NSCLC. Several drugs that focus on this pathway are available; some are antibodies to PD-1 while others are antibodies to its ligand, PD-L1. We use the term "PD-1 immunotherapy" to refer to both groups of antibodies.
TKI	Tyrosine kinase inhibitors (TKIs) are once-daily oral medications typically used as a first-line treatment option for patients with EGFR+ NSCLC.