Treatment Options for Advanced Non-Small Cell Lung Cancer:

Effectiveness, Value and Value Based Price Benchmarks

Public Meeting – October 20, 2016
Welcome and Introduction

• The Institute for Clinical and Economic Review (ICER)

• The Midwest Comparative Effectiveness Public Advisory Council (CEPAC)
Sources of Funding (%)

- Non-profit foundations: 70%
- Life Science companies: 9%
- Insurers and Provider Groups: 4%
- Government contracts: 17%

ICER Policy Summit only
Welcome and Introduction

• Why are we here today?
  • Substantial innovation in treatment and shifts in paradigms of care for patients with NSCLC
  • Innovation often expensive, raising questions about the value and affordability of treatment options, and creating pressure on health systems and patients
  • Clinical practice, medical policies, and pricing considerations can benefit from independent reviews of evidence and public discussion
Welcome and Introduction

• How was the ICER report on NSCLC developed?
  • Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
  • Internal ICER staff evidence analysis
  • University of Washington cost-effectiveness modeling
  • Public comment and revision
  • Clinical expert report consultants
    • James Jett, MD
    • Daniel A. Goldstein, MD

• How is the evidence report structured to support CEPAC voting and policy discussion?
## ICER Value Assessment Framework

### Comparative clinical effectiveness
- Incremental cost for better clinical outcomes (long-term)
- Other benefits or disadvantages
- Contextual considerations

### "Long-Term Value for Money"
- Public discussion and vote
  - HIGH
  - INTERMEDIATE
  - LOW

### Consideration of Potential Health System Budget Impact
- Possible need for extra steps to improve affordability for patients and the health system

### Goal:
- Sustainable access to high-value care for all patients
  - Public and Policy Roundtable to Consider Whether Policy Actions Needed
    - Price reduction
    - Different payment mechanisms
    - Prioritizing patient access
    - Ensuring that patients can afford the service
    - Reallocating health system resources
    - Obtaining outside resources

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**ICER**
Welcome and Introduction

Agenda

- Meeting Convened and Opening Remarks | 10:00 am
- Presentation of the Evidence | 10:15 am
- Public Comments | 11:30 am
- Lunch | 12:15 pm
- Midwest CEPAC Deliberation and Votes | 12:45 pm
- Policy Roundtable Discussion | 2:15 pm
- Meeting Adjourned | 4:00 pm
Evidence Review

David Rind, MD, MSc
Chief Medical Officer
Institute for Clinical and Economic Review
Disclosures:
I have no conflicts of interest relevant to this report.

Key review team members:
Shanshan Liu, MS, MPH
Patricia Synnott, MS, MA
Topic in Context

• Lung cancer is the number one cause of cancer death in the US, expected to cause 158,000 deaths in 2016 (26.5% of all cancer deaths)

• NSCLC typically presents as advanced disease with a poor prognosis

• In recent years, some patients with NSCLC have been treated based on driver mutations

• Most recently, immunotherapy has become an option benefitting at least some patients

• These new therapies are expensive: ~$90,000 to $150,000 per year
Patient groups pointed out that due to the changing demographics of smoking behavior, people at the highest risk of developing lung cancer now have the least ability to deal with the financial toxicities of therapy.
Advanced NSCLC

- **EGFR+ (Nonsquamous/adenocarcinoma)**
  - **Population 1**
    - First-line TKI vs. platinum doublet
  - **Population 4**
    - Second or third-line PD-1 immunotherapy vs. platinum doublet

- **EGFR- (Any histology)**
  - **Population 2**
    - First-line PD-1 immunotherapy vs. platinum doublet
  - **Population 3**
    - Second-line PD-1 immunotherapy vs. single-agent chemotherapy
Issues of Focus for Tyrosine Kinase Inhibitors (TKIs)
Evidence for TKIs

• Eleven key randomized trials
  • 10 compared a TKI with a platinum doublet and were rated fair quality
  • 1 compared afatinib with gefitinib, rated good quality
## Progression Free Survival Benefit

<table>
<thead>
<tr>
<th>Study name</th>
<th>Model</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LUX LUNG 3</td>
<td></td>
<td>0.58 (0.431,0.781)</td>
<td></td>
</tr>
<tr>
<td>LUX LUNG 6</td>
<td></td>
<td>0.28 (0.201,0.391)</td>
<td></td>
</tr>
<tr>
<td>IPASS</td>
<td></td>
<td>0.48 (0.36,0.64)</td>
<td></td>
</tr>
<tr>
<td>NEJ002</td>
<td></td>
<td>0.36 (0.252,0.514)</td>
<td></td>
</tr>
<tr>
<td>WJTOG3405</td>
<td></td>
<td>0.49 (0.339,0.708)</td>
<td></td>
</tr>
<tr>
<td>FIRST-SIGNAL</td>
<td></td>
<td>0.54 (0.268,1.09)</td>
<td></td>
</tr>
<tr>
<td>EURTAC</td>
<td></td>
<td>0.37 (0.252,0.544)</td>
<td></td>
</tr>
<tr>
<td>ENSURE</td>
<td></td>
<td>0.34 (0.223,0.518)</td>
<td></td>
</tr>
<tr>
<td>OPTIMAL</td>
<td></td>
<td>0.16 (0.099,0.258)</td>
<td></td>
</tr>
<tr>
<td>TORCH</td>
<td></td>
<td>0.6 (0.3,1.2)</td>
<td></td>
</tr>
</tbody>
</table>

Fixed

Random

0.399 (0.354,0.45)

0.389 (0.309,0.49)
No Overall Survival Benefit

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Model</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LL3/LL6 COM MOM</td>
<td></td>
<td>0.81 (0.661,0.992)</td>
</tr>
<tr>
<td>Mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPASS</td>
<td></td>
<td>0.78 (0.503,1.208)</td>
</tr>
<tr>
<td>NE J002</td>
<td></td>
<td>0.887 (0.634,1.241)</td>
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<tr>
<td>WJTOG3405</td>
<td></td>
<td>1.252 (0.883,1.775)</td>
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<tr>
<td>FIRST-SIGNAL</td>
<td></td>
<td>1.043 (0.498,2.183)</td>
</tr>
<tr>
<td>ENRTAC</td>
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<td>1.04 (0.647,1.672)</td>
</tr>
<tr>
<td>ENSURE</td>
<td></td>
<td>0.91 (0.631,1.312)</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td></td>
<td>1.19 (0.829,1.708)</td>
</tr>
<tr>
<td>Fixed</td>
<td></td>
<td>0.932 (0.826,1.053)</td>
</tr>
<tr>
<td>Random</td>
<td></td>
<td>0.937 (0.826,1.063)</td>
</tr>
</tbody>
</table>
Do TKIs improve survival?

• High rates of crossovers (45% to 90%) potentially masking any benefit
• Most likely explanation is that benefit with TKIs is the same whenever they are administered in the sequence of therapy (before or after platinum doublets)
How did we estimate an OS benefit?

• Used data from one trial (IPASS) comparing gefitinib with carboplatin + paclitaxel
  • 261 EGFR+ and 176 EGFR-
  • TKIs do not improve outcomes in EGFR-
  • Median OS in EGFR+: 21.6 vs 21.9 months, HR 1.00
  • OS in the EGFR- chemotherapy arm: 12.7 months
  • Gain of 8.9 months (21.6 months - 12.7 months)

• Caveats
  • Post-hoc observational analysis
  • EGFR+ could be a marker for less aggressive NSCLC or for healthier patients (non-smokers)
Are there any differences between TKIs?

- We have only one head-to-head trial, LUX-Lung 7 (comparing afatinib and gefitinib)
  - Median PFS slightly better with afatinib (11.0 vs. 10.9 months; HR 0.73, 95% CI 0.57-0.95)

Afatinib versus Gefitinib

- Our NMA found a similar PFS benefit for afatinib (0.71) that was not statistically significant
- PFS is mainly a surrogate outcome
- The randomized trial found no statistically significant OS benefit for afatinib (27.9 vs. 25.0 months; HR 0.87, 95% CI 0.66-1.15)
- The authors state that with a median follow-up of 27.3 months, these OS results are not mature
- OS results presented at ESMO (42.6 months median follow-up) are essentially identical
TKI Results (QoL, Symptoms, AEs)

• QoL: Evaluated in 6 RCTs. All showed greater improvements with TKIs on at least one QoL outcome

• Symptom changes found in at least one trial:
  • Improvements or delayed deterioration: Dyspnea, pain, cough, composite score

• Adverse Events:
  • All TKIs better tolerated than platinum doublets
  • Rash, diarrhea, liver function abnormalities most common TKI side effects
**TKIs: Controversies and Uncertainties**

- Few head-to-head studies
  - Single RCT (LUX-Lung 7) suggests a small PFS benefit of afatinib over gefitinib; unclear if this translates to OS benefit
  - Estimation method for OS really precludes comparisons of TKIs based on OS

- Current standard of care has moved forward
  - Our analysis looks at benefit of adding TKIs to prior standard (platinum doublet)
  - Currently about half of patients who progress on TKI would get 2\textsuperscript{nd} line TKI (osimertinib)
  - Use in patients too sick for chemotherapy
TKI Summary

• High certainty that TKIs provide at least a small net health benefit relative to platinum chemotherapy
  • Less side effects, at least equivalent OS

• Moderate certainty that TKIs provide a clinically meaningful OS benefit

• Inadequate evidence to distinguish between TKIs on patient-important outcomes (OS and QoL)
Issues of Focus for PD-1 Immunotherapy
Evidence for PD-1 Immunotherapy

- Second-line (P3): 4 key randomized trials
  - All 4 compared a PD-1 immunotherapy with docetaxel
  - All 4 were of good quality for this population
  - One additional trial presented in October at ESMO

- First-line (P2):
  - One good quality published RCT (Supplement)
  - One presentation at ESMO (Supplement)

- EGFR+ second/third-line (P4):
  - No published RCTs were identified
What do the curves tell us?

PD-L1 Assays and Comparing Agents

- Response improves with higher levels of PD-L1
- Even at high levels, a minority of patients respond
- Even at low levels, some patients respond
- Thus, cannot accurately identify responders with current tests
- Assays and cut points are not comparable across trials
PD-1 (second-line) Results

- Different assays and cut points made populations not comparable across agents
- Median OS improved 2-3 months compared with docetaxel
  - Survival curves have different shapes
  - Two populations with PD-1 immunotherapies
    - Majority do not respond
    - Minority have substantial response
    - Exact magnitude of benefit is uncertain (limited follow-up), but typically duration of response ≥1 year longer
    - PD-L1 levels help predict responders
- PFS benefits are small and inconsistent
PD-1 (second line) QoL, Symptoms, AEs

- Evidence was inadequate to assess the effects of PD-1 immunotherapy on quality of life and symptom control
- PD-1 immunotherapy was generally better tolerated than docetaxel
  - Common AEs include fatigue, nausea, decrease appetite
  - Immune-related AEs are less common but also not generally seen with other therapies. These include dermatologic, gastrointestinal, pulmonary, and neurologic immune AEs
PD-1 (second line) Controversies and Uncertainties

• No head-to-head trials. We could not assess differences in any outcomes across agents
• Few data assessing the percentage of patients with sustained responses and whether there is a very long tail of responders beyond two years
• Uncertain whether PD-L1 levels affect response equally for all three agents
PD-1 (second line) Summary

• High certainty that a substantial minority of patients achieve important gains in overall survival

• Inadequate evidence to distinguish among PD-1 immunotherapies on any outcome
PD-1 First Line

And yet….

- Presentation on CheckMate 026
- Nivolumab in patients with PD-L1 ≥1%
- Primary population ≥5%
  - No benefit on PFS (HR 1.15)
  - No benefit on OS (HR 1.02)

- Explanation for differences?
  - Differences in the populations/PD-L1 levels
  - Differences in the agents

- We have moderate certainty that first-line pembrolizumab provides a small or substantial net health benefit ("B+)") relative to platinum chemotherapy
PD-1 second/third line for EGFR+ patients

- Analysis of post-doublet RCTs (versus docetaxel)
- OS by EGFR status
  - EGFR-: HR 0.66, 95% CI 0.58-0.74
  - EGFR+: HR 1.12, 95% CI 0.69-1.81
  - Interaction: p=0.036
- PFS by EGFR status
  - EGFR-: HR 0.80, 95% CI 0.72-0.90
  - EGFR+: HR 1.57, 95% CI 1.07-2.31
  - Interaction: p=0.0002
- Evidence is inadequate, but concern that PD-1 immunotherapy may be inferior to a platinum doublet in this setting
Public Comments Received

• Analysis of PD-1 immunotherapies is premature
• Questions about how patient input is used
• Combining analysis of pemetrexed regimens with other platinum doublets for TKIs
• Afatinib OS benefit in Del19 patients
• Effects of histology for PD-1s
Comparative Value

Greg Guzauskas, MSPH, PhD
Anirban Basu, MS, PhD

University of Washington
Department of Pharmacy
Pharmaceutical Outcomes Research and Policy Program
Objectives

• Aim 1: Compare first-line treatment with TKIs versus chemotherapy doublet (cisplatin+pemetrexed, CIS-PEM) for EGFR+ patients
  • Afatinib (Gilotrif®, Boehringer Ingelheim, AFAT)
  • Erlotinib (Tarceva®, Genentech, ERLO)
  • Gefitinib (Iressa®, AstraZeneca, GEFI)

• Aim 2: Compare second-line treatment with PD-1 immunotherapy versus docetaxel (DOCX) among patients who have progressed on a first-line chemotherapy doublet
  • Atezolizumab (Tecentriq®, Genentech, ATEZ)
  • Nivolumab (Opdivo®, Bristol-Myers Squibb, NIVO)
  • Pembrolizumab (Keytruda®, Merck, PEMB)
Methods in Brief
Key Model Assumptions: Overall Approach

• We fit mathematical curves to available survival data (trials’ PFS and OS curves), which allowed us to approximate survival beyond trial-reported follow-up times.

• TKIs improve PFS compared with a platinum-based doublet, but have little observed effect on OS due to treatment crossover in clinical trials. Therefore, the model utilized an assumed 8.9-month increase in median OS for TKIs versus CIS-PEM.

• The model included grade 3/4 adverse events occurring in at least 5% of patients in at least one of the included regimens.

• Disease progression costs reflect assumed subsequent treatments and supportive care. Post-progression treatment costs were derived by calculating the average weekly cost of regimens for cisplatin+pemetrexed (post-TKI), docetaxel (post-PD-1) and gemcitabine (post-docetaxel).
Model Structure

1st-Line, EGFR Mutation
- Cisplatin + Pemetrexed
  - TKI: Afatinib (Gilotrif®, Boehringer Ingelheim) (S)
  - TKI: Erlotinib (Tarceva®, Genentech) (S)
  - TKI: Gefitinib (Iressa®, AstraZeneca) (S)

2nd-Line Immuno-therapy
- Docetaxel (S)
  - PD-L1i: Atezolizumab (Tecentriq®, Genentech) (S)
  - PD-1i: Nivolumab (Opdivo®, Bristol-Myers Squibb) (S)
  - PD-1i: Pembrolizumab (Keytruda®, Merck) (S)

Progression-Free Disease
Progressed Disease
Dead
Survival %
Time >

OS Curve
PFS Curve
Progression-Free Disease
### Health State Utilities

<table>
<thead>
<tr>
<th></th>
<th>Utility Weight</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1L Progression-free disease</td>
<td>0.78</td>
<td>LUX-Lung</td>
</tr>
<tr>
<td>1L Progressed disease</td>
<td>0.67</td>
<td>Chouaid et al.</td>
</tr>
<tr>
<td>2L Progression-free disease</td>
<td>0.65</td>
<td>Nafees et al.</td>
</tr>
<tr>
<td>2L Progressed disease</td>
<td>0.47</td>
<td>Nafees et al.</td>
</tr>
</tbody>
</table>

- **Note on 2\(^{nd}\)-line utilities:** the Nafees et al. utilities used in the 2\(^{nd}\)-line setting are the most widely-used in NSCLC economic models, and the findings are specific to 2\(^{nd}\)-line patients.

- **We received a request from a PD-1 manufacturer to utilize utilities from a recent clinical trial (2L PF = 0.77, 2L Prog = 0.68).**\(^1\) We did not use these estimates for the base case for 2nd-line, as they were similar to 1st-line estimates reported in other settings.

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Sensitivity Analyses

• We ran one-way sensitivity analyses to identify the key input drivers of model outcomes.
• Probabilistic sensitivity analysis was performed by jointly varying all model parameters over 4,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results.
Model Results
# Results: 1\textsuperscript{st}-Line TKI Therapy, EGFR+

<table>
<thead>
<tr>
<th>Baseline Therapy</th>
<th>Cost</th>
<th>QALYs</th>
<th>Life Years</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin + Pemetrexed</td>
<td>$111,443</td>
<td>0.88</td>
<td>1.22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>($60,594 - $431,119)</td>
<td>(0.81 - 0.95)</td>
<td>(1.16 - 1.29)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TKI</th>
<th>Cost</th>
<th>QALYs</th>
<th>Life Years</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib</td>
<td>$195,398</td>
<td>1.50</td>
<td>2.06</td>
<td>$135,095</td>
</tr>
<tr>
<td></td>
<td>($127,692 - $508,724)</td>
<td>(1.24 - 1.86)</td>
<td>(1.70 - 2.55)</td>
<td>($85,626 - $222,278)</td>
</tr>
</tbody>
</table>

| Erlotinib                         | $204,789 | 1.51  | 2.06       | $147,244      |
|                                   | ($133,696 - $533,804) | (1.26 - 1.89) | (1.70 - 2.58) | ($90,315 - $249,030) |

| Gefitinib                         | $177,281 | 1.47  | 2.06       | $110,840      |
|                                   | ($113,933 - $493,528) | (1.21 - 1.84) | (1.68 - 2.58) | ($68,633 - $185,897) |
## Results: 2nd-Line PD-1 Immunotherapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost</th>
<th>QALYs</th>
<th>Life Years</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASELINE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>$94,405</td>
<td>0.57</td>
<td>1.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>($43,096 - $416,547)</td>
<td>(0.39 - 1.91)</td>
<td>(0.67 - 3.74)</td>
<td></td>
</tr>
<tr>
<td><strong>ATEZOLIZUMAB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC2/3 or IC2/3</td>
<td>$206,190</td>
<td>1.08</td>
<td>2.02</td>
<td>$219,179</td>
</tr>
<tr>
<td></td>
<td>($112,756 - $773,155)</td>
<td>(0.59 - 4.24)</td>
<td>(1.05 - 8.43)</td>
<td>($68,144 - $518,560)</td>
</tr>
<tr>
<td><strong>NIVOLUMAB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all comers</td>
<td>$201,877</td>
<td>0.83</td>
<td>1.47</td>
<td>$415,950</td>
</tr>
<tr>
<td></td>
<td>($108,405 - $766,918)</td>
<td>(0.54 - 3.14)</td>
<td>(0.93 - 5.77)</td>
<td>($138,508 - $604,256)</td>
</tr>
<tr>
<td><strong>PEMBROLIZUMAB</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>PD-L1 &gt;50%</td>
<td>$295,512</td>
<td>1.41</td>
<td>2.53</td>
<td>$240,049</td>
</tr>
<tr>
<td></td>
<td>($172,986 - $1,076,289)</td>
<td>(0.80 - 4.76)</td>
<td>(1.35 - 8.92)</td>
<td>($89,158 - $392,239)</td>
</tr>
</tbody>
</table>
# PD-1 Results with Alternative Utilities

<table>
<thead>
<tr>
<th>Utilities (progression-free, progressed)</th>
<th>ATEZ TC2/3 or IC2/3 ICER</th>
<th>NIVO All Comers ICER</th>
<th>PEMB PD-L1 &gt;50% ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC: Nafees (0.65, 0.47)</td>
<td>$219,179</td>
<td>$415,950</td>
<td>$240,049</td>
</tr>
<tr>
<td>KEYNOTE (0.77, 0.68)</td>
<td>$161,348</td>
<td>$333,114</td>
<td>$185,866</td>
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<tr>
<td>CheckMate (0.75, 0.59)</td>
<td>$179,296</td>
<td>$352,950</td>
<td>$200,700</td>
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</tbody>
</table>
## One-Way Sensitivity: TKIs

In each one-way analysis, results were most sensitive to PFS and OS HRs, drug costs, and the assumption of an 8.9-month OS benefit for TKIs.

### Parameter Low Value High Value Low Result High Result Spread

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low Value</th>
<th>High Value</th>
<th>Low Result</th>
<th>High Result</th>
<th>Spread</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS_HR_AFAT_Overall</td>
<td>0.240</td>
<td>0.720</td>
<td>$177,556</td>
<td>$100,306</td>
<td>$77,249</td>
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<td>$186</td>
<td>$280</td>
<td>$106,172</td>
<td>$164,018</td>
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<td>TKI_OS_Benefit_HR</td>
<td>0.384</td>
<td>0.576</td>
<td>$111,569</td>
<td>$166,668</td>
<td>$55,098</td>
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<tr>
<td>dose_int_afat</td>
<td>80%</td>
<td>100%</td>
<td>$106,172</td>
<td>$135,095</td>
<td>$28,923</td>
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<tr>
<td>time_in_prog_TKI</td>
<td>10.8 months</td>
<td>16.2 months</td>
<td>$145,508</td>
<td>$127,768</td>
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<td>cost_supp_PFS</td>
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<td>$535</td>
<td>$127,263</td>
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<td>util_prog_1L</td>
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<td>0.750</td>
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<td>cost_pem_500</td>
<td>$2,530</td>
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<td>cost_death</td>
<td>$0</td>
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<td>$137,089</td>
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<td>util_pf_1L</td>
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<td>0.802</td>
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<td>$133,133</td>
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</tr>
<tr>
<td>time_in_prog_PD1</td>
<td>6.0 months</td>
<td>9.1 months</td>
<td>$132,934</td>
<td>$136,888</td>
<td>$3,933</td>
</tr>
<tr>
<td>dose_int_pem</td>
<td>80%</td>
<td>100%</td>
<td>$138,762</td>
<td>$135,095</td>
<td>$3,666</td>
</tr>
<tr>
<td>cost_doc_mg</td>
<td>$8</td>
<td>$11</td>
<td>$136,114</td>
<td>$134,077</td>
<td>$2,038</td>
</tr>
</tbody>
</table>

### Incremental CE Ratio

<table>
<thead>
<tr>
<th>AFAT</th>
<th>$100,300</th>
<th>$115,760</th>
<th>$131,220</th>
<th>$146,680</th>
<th>$162,140</th>
<th>$177,600</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome:</td>
<td>$100,300</td>
<td>$115,760</td>
<td>$131,220</td>
<td>$146,680</td>
<td>$162,140</td>
<td>$177,600</td>
</tr>
<tr>
<td>Incremental CE Ratio</td>
<td>$100,300</td>
<td>$115,760</td>
<td>$131,220</td>
<td>$146,680</td>
<td>$162,140</td>
<td>$177,600</td>
</tr>
</tbody>
</table>

### Afatanib vs. CIS-PEM
One-Way Sensitivity: PD-1 Immunotherapies

In each one-way analysis, results were most sensitive to PFS HRs, OS HRs, and drug costs.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low Value</th>
<th>High Value</th>
<th>Low Result</th>
<th>High Result</th>
<th>Spread</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS_HR_PEMB_post10mo</td>
<td>0.093</td>
<td>0.392</td>
<td>$163,371</td>
<td>$366,133</td>
<td>$202,762</td>
</tr>
<tr>
<td>cost_pembro_100</td>
<td>$3,505</td>
<td>$5,257</td>
<td>$194,206</td>
<td>$285,892</td>
<td>$91,686</td>
</tr>
<tr>
<td>PD1_common_PFS_post6</td>
<td>0.252</td>
<td>0.454</td>
<td>$276,092</td>
<td>$210,182</td>
<td>$65,910</td>
</tr>
<tr>
<td>OS_HR_PEMB_10mo</td>
<td>0.549</td>
<td>0.829</td>
<td>$216,906</td>
<td>$273,820</td>
<td>$56,914</td>
</tr>
<tr>
<td>dose_int_pembro</td>
<td>80%</td>
<td>100%</td>
<td>$194,206</td>
<td>$240,049</td>
<td>$45,843</td>
</tr>
<tr>
<td>PFS_HR_PEMB_6mo</td>
<td>0.338</td>
<td>0.571</td>
<td>$254,970</td>
<td>$221,838</td>
<td>$33,132</td>
</tr>
<tr>
<td>util_pf_2L</td>
<td>0.610</td>
<td>0.700</td>
<td>$249,162</td>
<td>$229,553</td>
<td>$19,609</td>
</tr>
<tr>
<td>util_prog_2L</td>
<td>0.430</td>
<td>0.520</td>
<td>$248,575</td>
<td>$230,180</td>
<td>$18,395</td>
</tr>
<tr>
<td>cost_supp_PFS</td>
<td>$188</td>
<td>$535</td>
<td>$231,298</td>
<td>$248,906</td>
<td>$17,608</td>
</tr>
<tr>
<td>cost_death</td>
<td>$0</td>
<td>$173,745</td>
<td>$242,704</td>
<td>$233,478</td>
<td>$9,226</td>
</tr>
<tr>
<td>time_in_prog_TKI</td>
<td>10.8 months</td>
<td>16.2 months</td>
<td>$240,049</td>
<td>$248,906</td>
<td>$8,857</td>
</tr>
<tr>
<td>time_in_prog_PD1</td>
<td>6.0 months</td>
<td>9.1 months</td>
<td>$243,059</td>
<td>$248,906</td>
<td>$5,847</td>
</tr>
<tr>
<td>cost_doc_mg</td>
<td>$8</td>
<td>$11</td>
<td>$238,396</td>
<td>$241,702</td>
<td>$3,306</td>
</tr>
</tbody>
</table>

Pembrolizumab PD-L1 >50% vs. DOCX
Summary

1st-Line TKIs targeted at an EGFR mutation:

- We estimate similar incremental cost-effectiveness ratios that are within commonly-cited cost-effectiveness thresholds (i.e., $50,000-$150,000/QALY gained), although both deterministic and probabilistic sensitivity analyses suggest some uncertainty in these findings. These results were highly contingent on our OS assumption.

2nd-Line PD-1 Immunotherapies

- Results were more uncertain. In base case analyses, cost-effectiveness ratios ranged from approximately $220,000/QALY to $420,000/QALY. However, findings in all analyses varied widely in both deterministic and probabilistic sensitivity analyses.
Public Comments Received

- Requests to consider the societal impacts of low-grade adverse events and financial toxicity
- Concern regarding the 8.9-month survival difference assumption
- Questions about health state utilities
- Requests for greater model transparency, particularly regarding modeled survival curves
Potential Budget Impact Analysis

Rick Chapman, PhD, MS
Director of Health Economics
Institute for Clinical and Economic Review
Disclosures

I have no conflicts of interest.

*Key review team members:*
Varun Kumar, MSc, MPH
Dan Ollendorf, PhD
Potential Budget Impact: Methods

• Total incremental cost of using PD-1 immunotherapy rather than docetaxel for treated NSCLC population
  • Calculated as incremental health care costs (including drug costs) minus any offsets in costs from averted health care events
• Note: this analysis is performed from an *ex ante* perspective
  • Treats all drugs being evaluated as though new to market, whether or not already launched
• Estimated net costs of using each drug rather than docetaxel, assuming no current use of the drug, over 5 year time horizon, using modeled results for treatment costs and cost offsets per patient
Potential Budget Impact: Population

- Estimated entire candidate population for treatment
  - Adults with advanced NSCLC who have a tumor that has progressed after first-line treatment with a platinum-based chemotherapy doublet
- Lung cancer prevalence ≈ 415,700 patients
  - 85% NSCLC, 70% with advanced disease
  - 40% receive second-line treatment
  - 60% with PD-L1 expression ≈ 59,400
  - 40% with no PD-L1 expression ≈ 39,600
Potential Budget Impact: Population

• Assumed uptake over 5 years:
  • ATEZ: 25% of PD-L1+
  • PEMB: 25% of PD-L1+
  • NIVO: 50% of PD-L1+, 75% of PD-L1-

• Year 5 treated estimates:
  • ATEZ, PEMB ≈ 14,850 each
  • NIVO ≈ 59,400
## Estimated Potential Budget Impact of PD-1 Immunotherapy at 5 Years

<table>
<thead>
<tr>
<th></th>
<th>Number Treated</th>
<th>Weighted BI per Patient</th>
<th>Average BI per Year (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATEZ</td>
<td>14,850</td>
<td>$77,800</td>
<td>$230.8</td>
</tr>
<tr>
<td>PEMB</td>
<td>14,850</td>
<td>$140,700</td>
<td>$417.7</td>
</tr>
<tr>
<td>NIVO*</td>
<td>59,400</td>
<td>$83,200</td>
<td>$987.8</td>
</tr>
</tbody>
</table>

*Includes PD-L1 positive and negative patients
Public Comments Received

- Request for scenario where patients are treated with an indicated PD1 inhibitor regardless of PD-L1 status ("all comers") versus scenario where only PD-L1 positive patients are treated with a PD1 inhibitor ("biomarker enriched")

- Cost offsets should be defined broadly to include changes in cost due to patient productivity and caregiver burden

- Remove budget impact threshold analysis
Lunch

Meeting will resume at 12:45 pm CT
Voting Questions
Q1. In patients with EGFR+ advanced NSCLC, is the evidence adequate to distinguish the net health benefit among the TKIs: erlotinib, gefitinib, and afatinib?

Yes  No
Q2. 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  No
Q3. 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?

a. Low
b. Intermediate
c. High
Q4. 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  No
Q5. 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 which nivolumab, used for its indication for treatment irrespective of PD-L1 level, is greater than that of treatment with docetaxel?

Yes    No
Q6. 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 which pembrolizumab, used for its indication for treatment for PD-L1 level $\geq 50\%$, is greater than that of treatment with docetaxel?

Yes  No
Q7. 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 which atezolizumab, used for its anticipated indication for treatment for PD-L1 test of TC 2/3 or IC 2/3, is greater than that of treatment with docetaxel?

Yes  No
Q8. 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 nivolumab, used for its indication for treatment irrespective of PD-L1 level?

a. Low
b. Intermediate
c. High
Q9. 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 pembrolizumab, used for its indication for treatment for PD-L1 level ≥ 50%?

a. Low
b. Intermediate
c. High
Q10. 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 atezolizumab, used for its anticipated indication for treatment for PD-L1 test of TC 2/3 or IC 2/3?

a. Low
b. Intermediate
c. High
Q11. 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 is greater than that of treatment with a platinum doublet?

Yes  No
Q12. 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  No
Policy Roundtable Participants

• James Jett, MD,
  • Professor of Medicine, Division of Oncology, Cancer Center, National Jewish Health

• Karen Loss
  • Lung Cancer Survivor

• Jay Moore
  • Senior Clinical Officer, Anthem Blue Cross Blue Shield

• Jyoti Patel, MD
  • Professor of Medicine, Director of Thoracic Oncology, University of Chicago

• Don Stranathan
  • Lung Cancer Survivor
Meeting Adjourned
Next Steps

• Final Report and accompanying materials expected on or before November 3, 2016

• Meeting materials and outputs: https://icer-review.org/meeting/nsclc/

For more information please visit: https://icer-review.org/programs/midwest-cepac/