
Treatment Options for Advanced Non-Small Cell Lung Cancer:

Effectiveness, Value and Value Based Price Benchmarks

Public Meeting – October 20, 2016

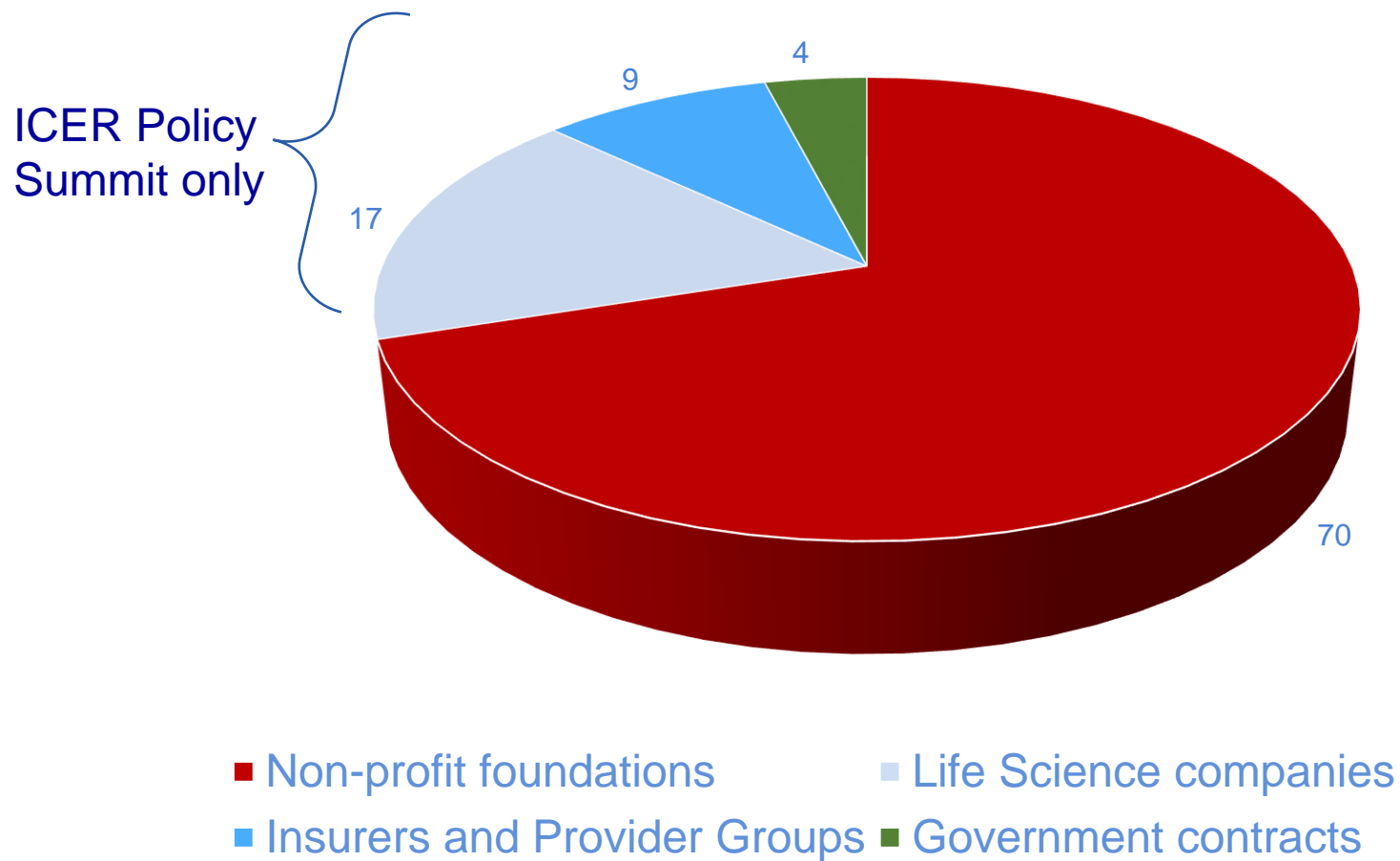


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Welcome and Introduction

- The Institute for Clinical and Economic Review (ICER)
- The Midwest Comparative Effectiveness Public Advisory Council (CEPAC)

Sources of Funding (%)



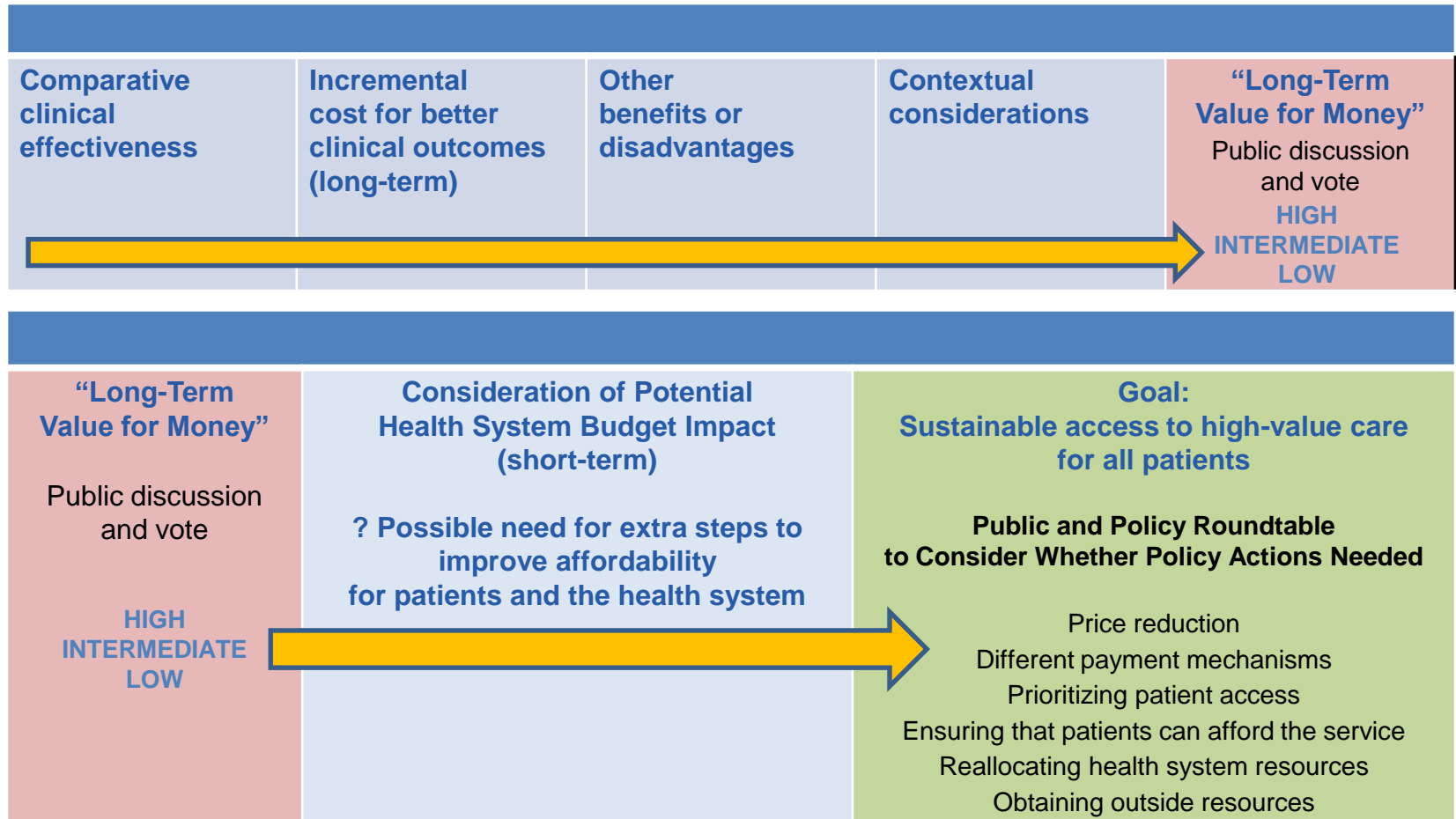
Welcome and Introduction

- 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



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



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Disclosures:

I have no conflicts of interest relevant to this report.

Key review team members:

Shanshan Liu, MS, MPH

Patricia Synnott, MS, MA

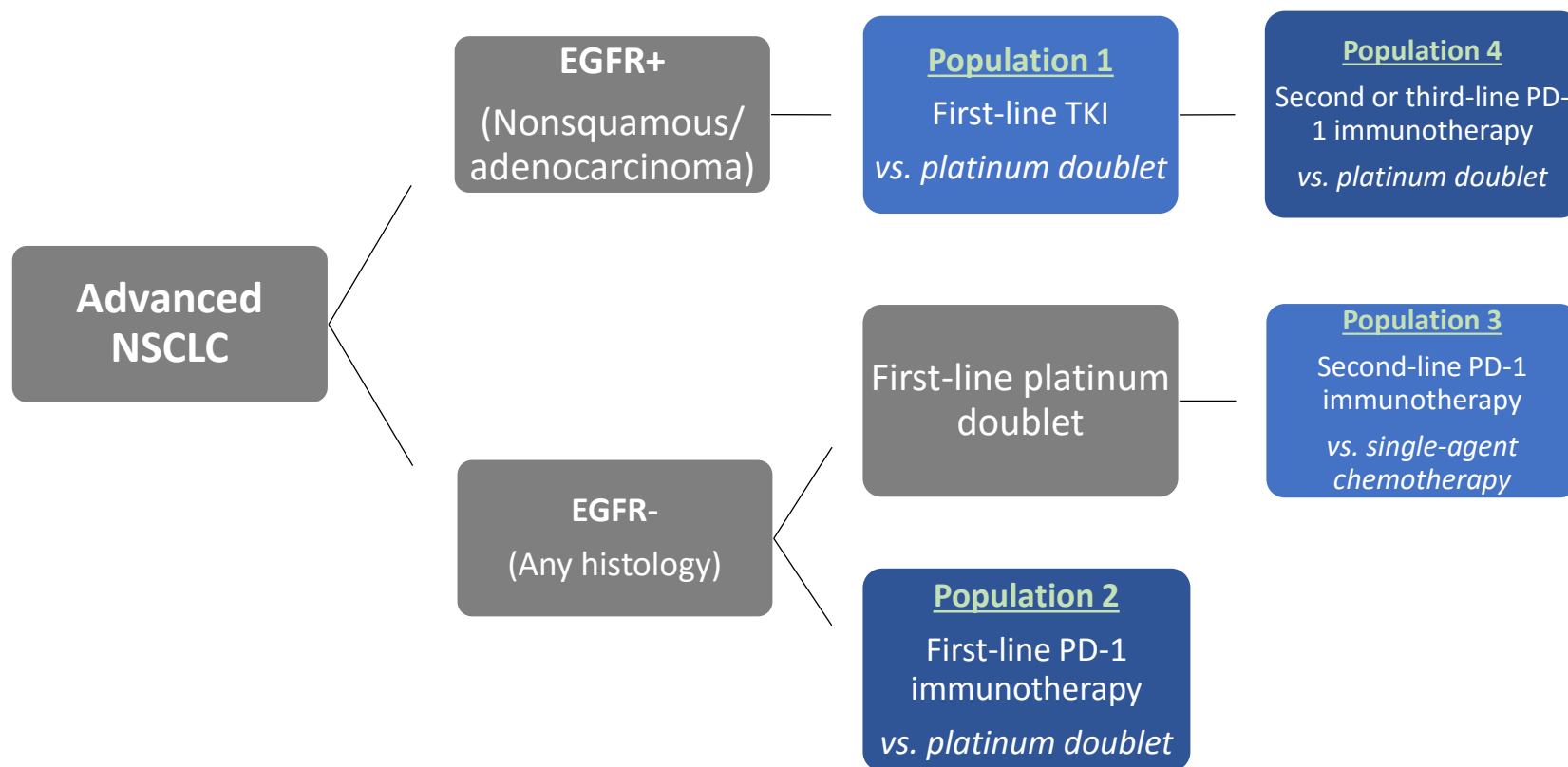
Topic in Context

- 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

Topic in Context (continued)

- 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

Review Scope (PIC)



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

Study name

Model

LUX LUNG 3

LUX LUNG 6

IPASS

NEJ002

WJTOG3405

FIRST-SIGNAL

EURTAC

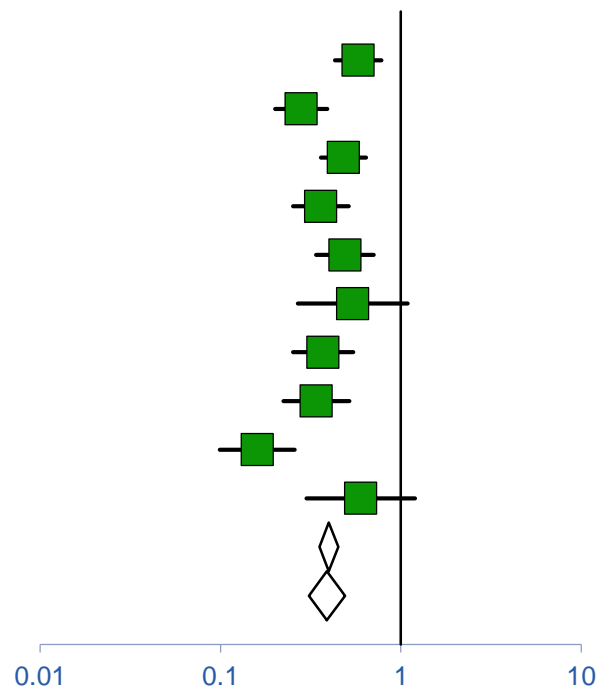
ENSURE

OPTIMAL

TORCH

Fixed

Random



No Overall Survival Benefit

Study Name

Model

LL3/LL6 COM MOM
Mutation

IPASS

NE J002

WJTOG3405

FIRST-SIGNAL

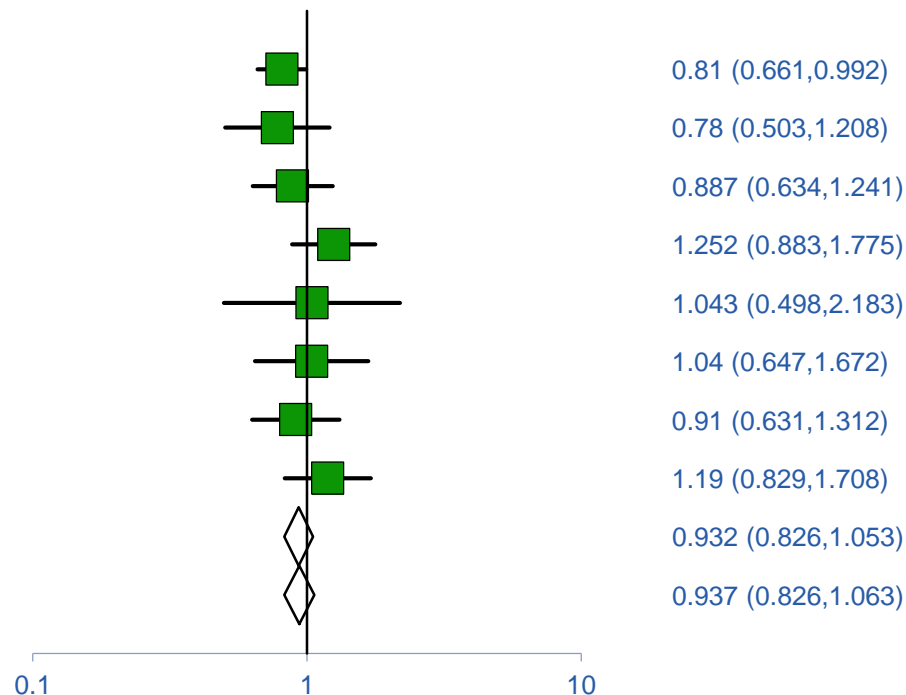
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ENSURE

OPTIMAL

Fixed

Random



Do TKIs improve survival?

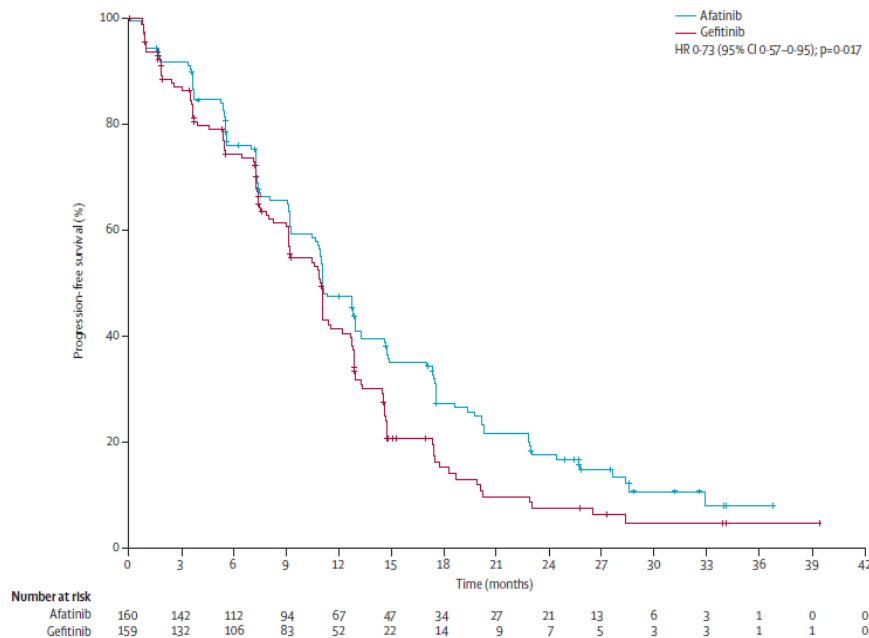
- High rates of crossovers (45% to 90%) potentially masking any benefit
- Most likely explanation is that benefit with TKIs is the same whenever they are administered in the sequence of therapy (before or after platinum doublets)

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)



Source: Park K, et al. Lancet Oncol 2016.

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 2nd 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?

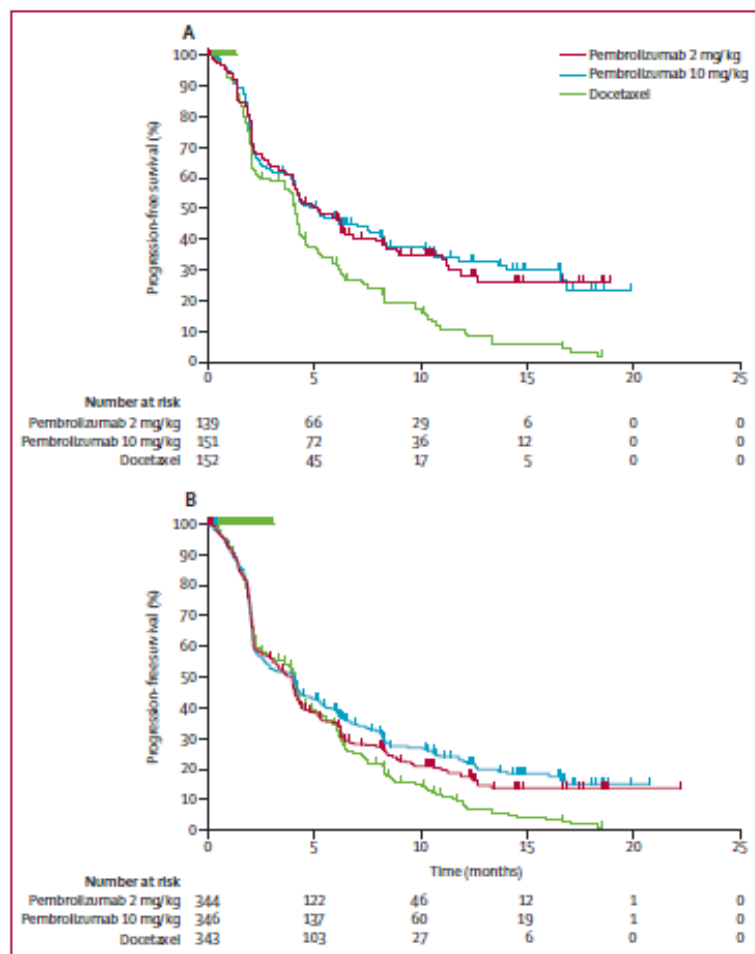


Figure 4: Kaplan-Meier analysis of progression-free survival
(A) For patients with a PD-L1 tumour proportion score of 50% or greater. (B) For all patients.

Source: Herbst RS, et al. N Engl J Med 2016.

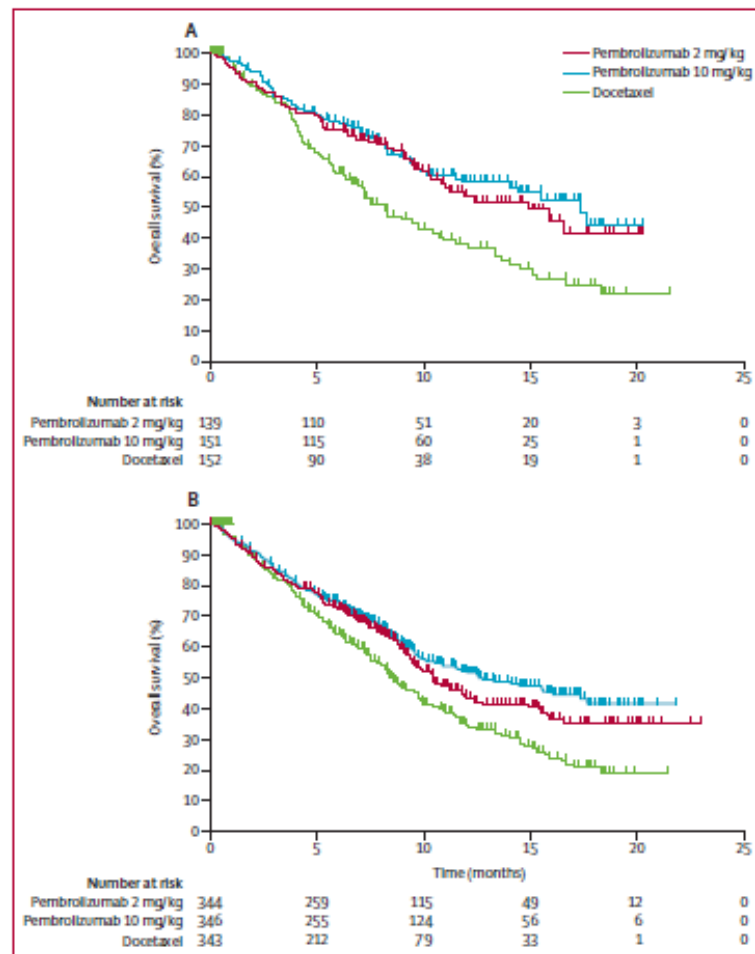


Figure 2: Kaplan-Meier analysis of overall survival
(A) For patients with a PD-L1 tumour proportion score of 50% or greater. (B) For all patients.

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

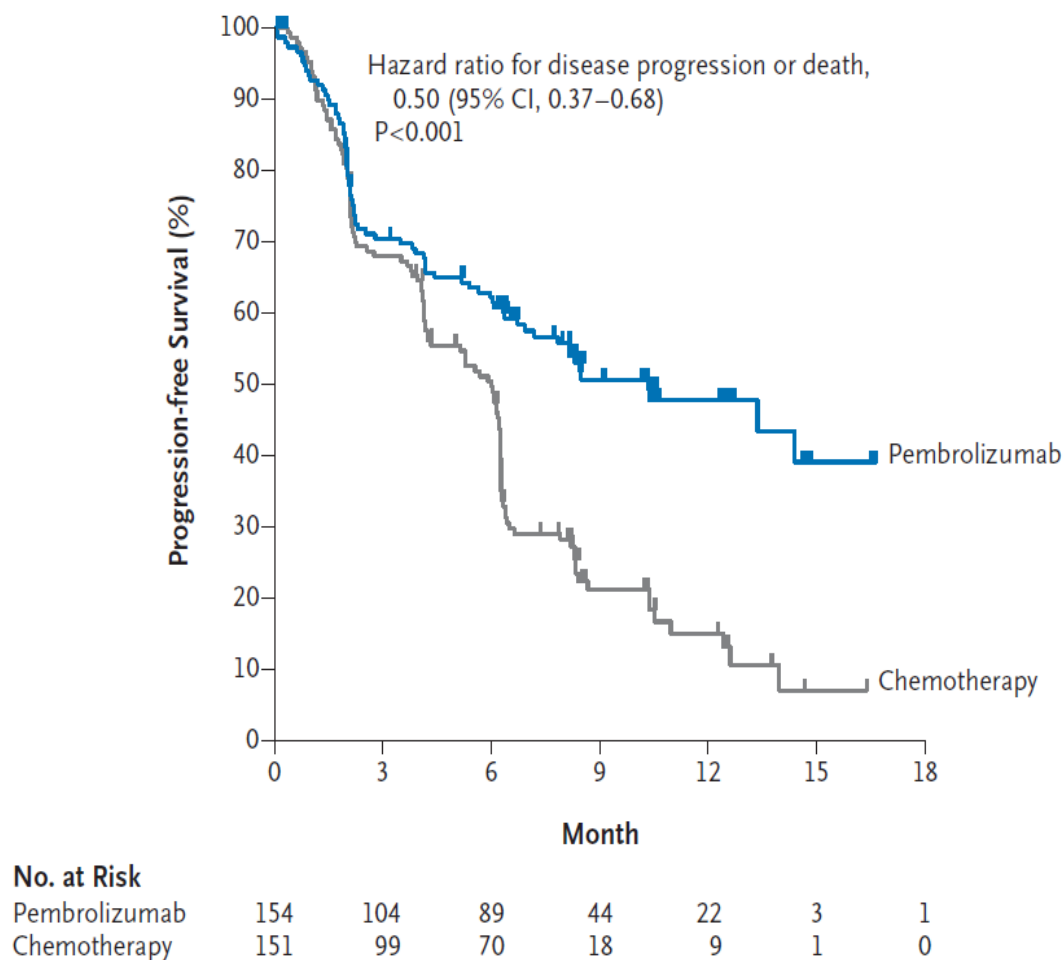
PD-1 (second line) Controversies and Uncertainties

- 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



Source: Reck M, et al. N Engl J Med 2016.

And yet....

- Presentation on CheckMate 026
- Nivolumab in patients with PD-L1 $\geq 1\%$
- Primary population $\geq 5\%$
 - 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

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Objectives

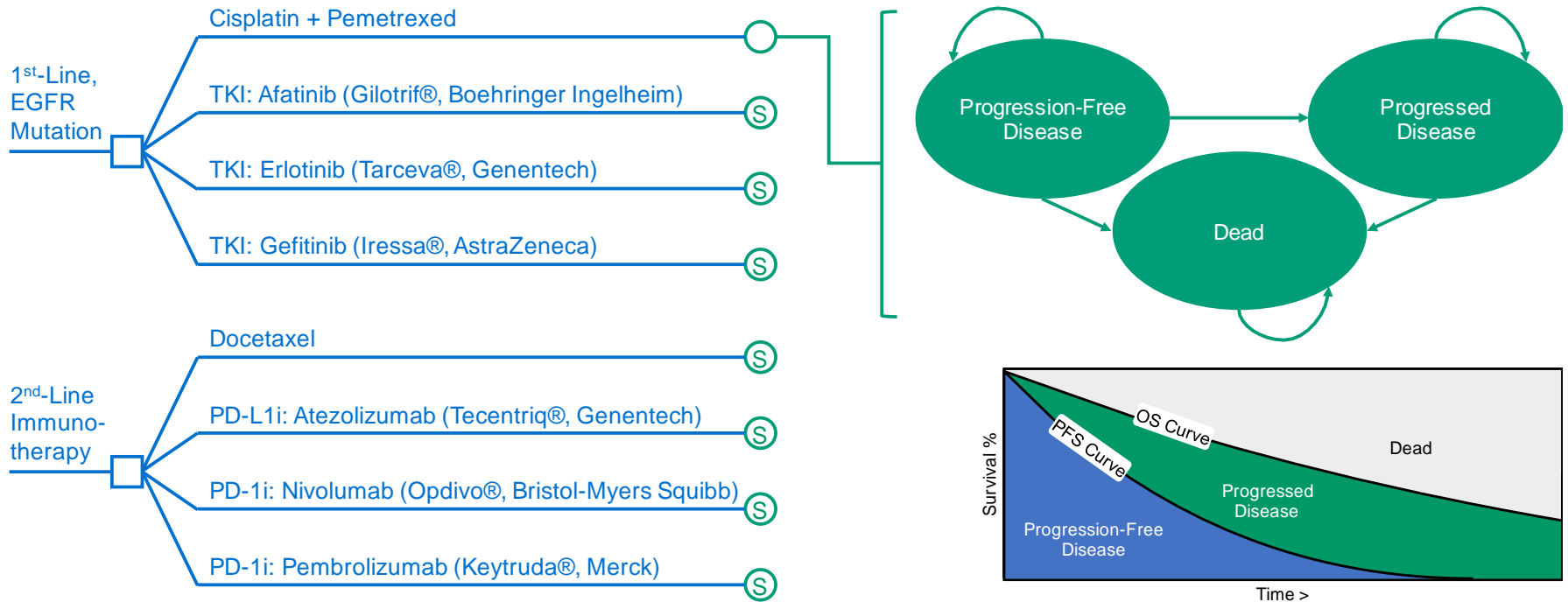
- Aim 1: Compare first-line treatment with TKIs versus chemotherapy doublet (cisplatin+pemetrexed, CIS-PEM) for EGFR+ patients
 - Afatinib (Gilotrif®, Boehringer Ingelheim, AFAT)
 - Erlotinib (Tarceva®, Genentech, ERLO)
 - Gefitinib (Iressa®, AstraZeneca, GEFI)
- Aim 2: Compare second-line treatment 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



Health State Utilities

	Utility Weight	Reference
1L Progression-free disease	0.78	LUX-Lung
1L Progressed disease	0.67	Chouaid et al.
2L Progression-free disease	0.65	Nafees et al.
2L Progressed disease	0.47	Nafees et al.

- Note on 2nd-line utilities: the Nafees et al. utilities used in the 2nd-line setting are the most widely-used in NSCLC economic models, and the findings are specific to 2nd-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.

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: 1st-Line TKI Therapy, EGFR+

BASELINE Cisplatin + Pemetrexed	Cost	QALYs	Life Years
	\$111,443	0.88	1.22
	(\$60,594 - \$431,119)	(0.81 - 0.95)	(1.16 - 1.29)

Afatinib	Cost	QALYs	Life Years	ICER
	\$195,398	1.50	2.06	\$135,095
	(\$127,692 - \$508,724)	(1.24 - 1.86)	(1.70 - 2.55)	(\$85,626 - \$222,278)

Erlotinib	Cost	QALYs	Life Years	ICER
	\$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	Cost	QALYs	Life Years	ICER
	\$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

BASELINE Docetaxel	Cost	QALYs	Life Years
	\$94,405	0.57	1.04
	(\$43,096 - \$416,547)	(0.39 - 1.91)	(0.67 - 3.74)

Atezolizumab TC2/3 or IC2/3	Cost	QALYs	Life Years	ICER
	\$206,190	1.08	2.02	\$219,179
	(\$112,756 - \$773,155)	(0.59 - 4.24)	(1.05 - 8.43)	(\$68,144 - \$518,560)

Nivolumab all comers	Cost	QALYs	Life Years	ICER
	\$201,877	0.83	1.47	\$415,950
	(\$108,405 - \$766,918)	(0.54 - 3.14)	(0.93 - 5.77)	(\$138,508 - \$604,256)

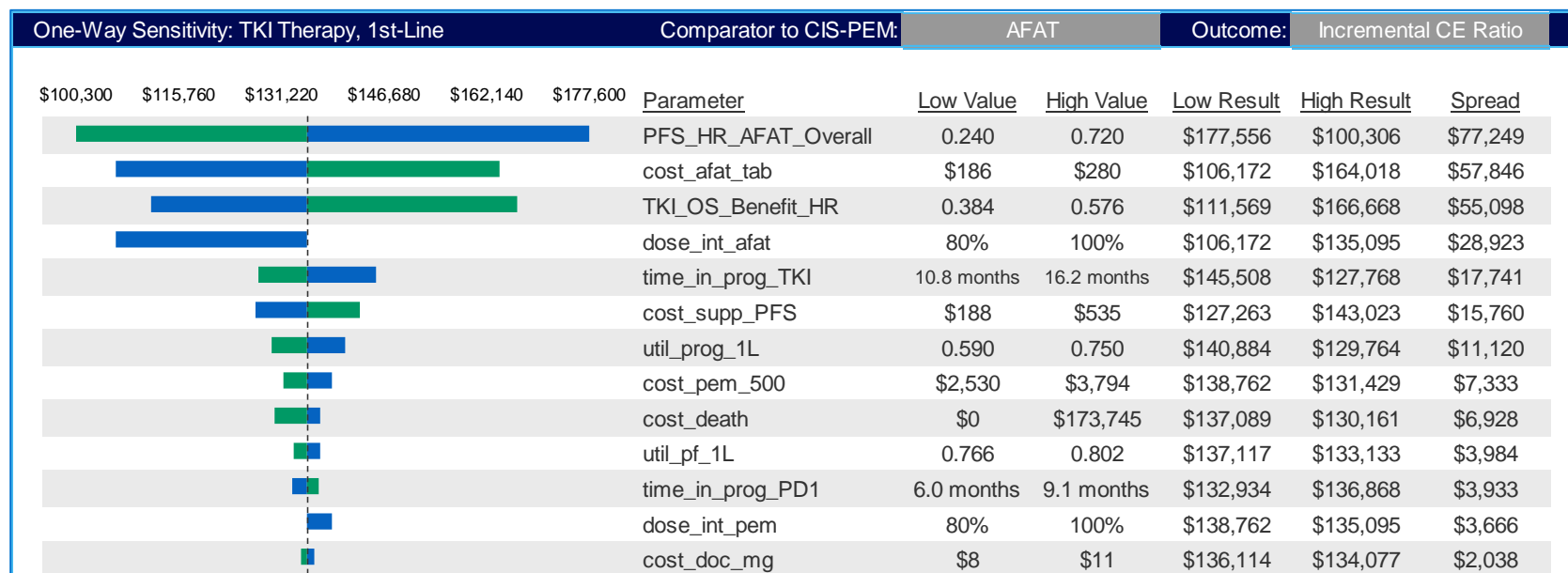
Pembrolizumab PD-L1 >50%	Cost	QALYs	Life Years	ICER
	\$295,512	1.41	2.53	\$240,049
	(\$172,986 - \$1,076,289)	(0.80 - 4.76)	(1.35 - 8.92)	(\$89,158 - \$392,239)

PD-1 Results with Alternative Utilities

Utilities (progression-free, progressed)	ATEZ TC2/3 or IC2/3 ICER	NIVO All Comers ICER	PEMB PD-L1 >50% ICER
<i>BC: Nafees (0.65, 0.47)</i>	\$219,179	\$415,950	\$240,049
KEYNOTE (0.77, 0.68)	\$161,348	\$333,114	\$185,866
CheckMate (0.75, 0.59)	\$179,296	\$352,950	\$200,700

One-Way Sensitivity: TKIs

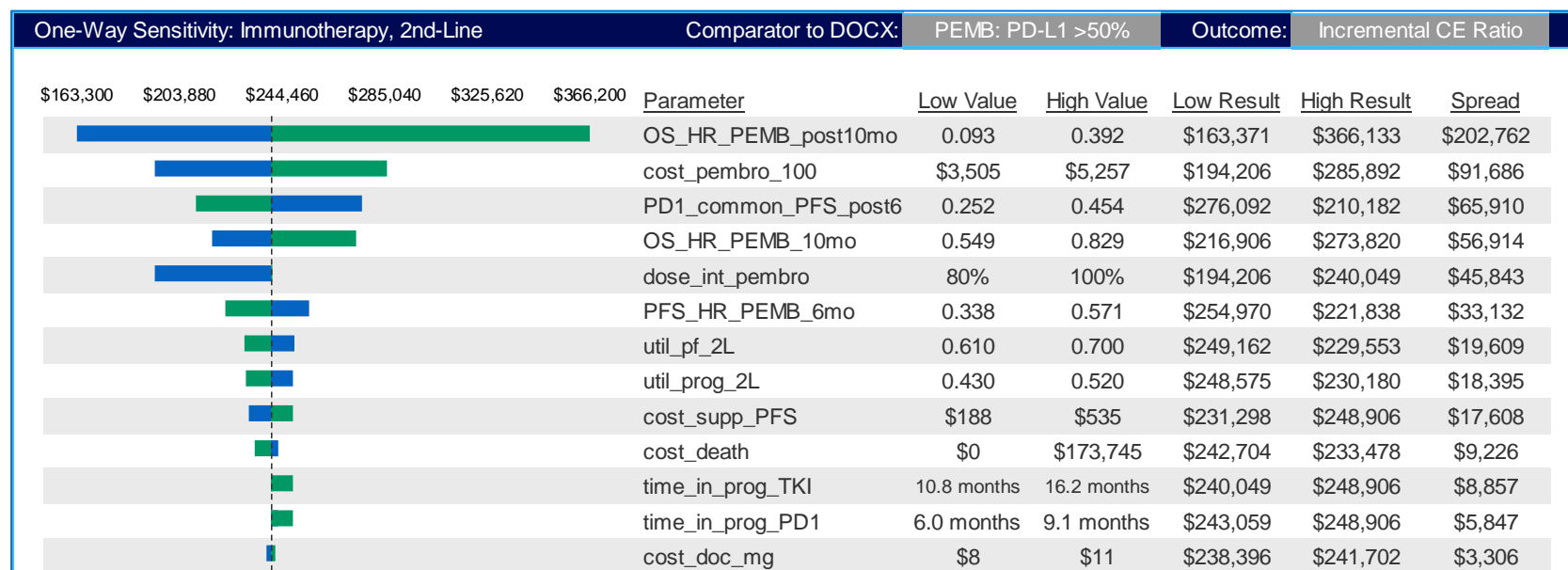
In each one-way analysis, results were most sensitive to PFS and OS HRs, drug costs, and the assumption of an 8.9-month OS benefit for TKIs.



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.



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



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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 \approx 415,700 patients
 - 85% NSCLC, 70% with advanced disease
 - 40% receive second-line treatment
 - 60% with PD-L1 expression \approx 59,400
 - 40% with no PD-L1 expression \approx 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 \approx 14,850 each
 - NIVO \approx 59,400

Estimated Potential Budget Impact of PD-1 Immunotherapy at 5 Years

	Number Treated	Weighted BI per Patient	Average BI per Year (millions)
ATEZ	14,850	\$77,800	\$230.8
PEMB	14,850	\$140,700	\$417.7
NIVO*	59,400	\$83,200	\$987.8

*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 with 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 with 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 with 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 $\geq 50\%$?

- 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



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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/>