Economic evaluation of EGFR-guided treatment in advanced refractory non small-cell lung cancer

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Why do we need better predictive markers?

Because the average response rate to drug treatment is poor:

- Oncology
- Alzheimer's
- Incontinence
- HCV
- Osteoporosis
- Migraine (prophylaxis)
- Rheumatoid Arthritis
- Migraine (acute)
- Diabetes
- Asthma
- Cardiac arrhythmias
- Schizophrenia
- Depression (SSRI)
- Analgesics (Cox2)
Pharmacogenomics in Oncology

- Increased understanding of the molecular mechanisms of cancer
  - Estimate the risk of cancer development and relapse
  - Target therapy according to tumor tissue's unique molecular characteristics
- Recent studies have indicated that pharmacogenomics may play a significant role in lung cancer treatment.
Epidermal growth factor receptor tyrosine kinase inhibitors

- Epidermal growth factor receptor—
  - Cellular signaling → proto oncogene
  - Over expressed in NSCLC tumors
  - Drug target ~20 years ago
- Erlotinib (Tarceva®) and Gefitinib (Iressa®)
  - Low response rates (~10%)
  - Hypothesized identifiable responder groups
  - EGFR genomic biomarkers associate with tumor response and survival
Survival Curves: Erlotinib genomic biomarkers (BR.21)

Tsao et al. NEJM 2004

Protein Expression

Gene Copy Number
To assess the potential clinical and economic outcomes of implementing an EGFR-guided approach in treating NSCLC with erlotinib in the 2nd line setting.
Description of Analysis

- Cost-utility analysis
- Perspective: Societal
- Time horizon: 2 years
- Study population: Advanced refractory NSCLC patients 60 years old
- Model: Decision tree
- Sensitivity analyses:
  - One-way
  - Probabilistic (2nd order Monte Carlo simulation)
Value of Information

• Expected value of perfect information (EVPI)
  – Cost (including monetized QALYs) of wrong decisions due to uncertainty in model parameters
  – Difference between expected net benefit with perfect information (no wrong decisions) and expected net benefit with current information
  – Effective population = population affected over lifetime of technology
  – Provides the upper bound value of additional information

• Health care system should be willing to pay for additional information if its value is greater than its cost
Stage IV/V refractory NSCLC patients

EGFR gene copy test

- High gene copy number (positive): Erlotinib until progression
  - Disease progression: Die
  - No disease progression: Live
- Low gene copy number (negative): Docetaxel until progression
  - Disease progression: Die
  - No disease progression: Live

EGFR protein expression test

- High protein expression (positive): Erlotinib until progression
  - Disease progression: Die
  - No disease progression: Live
- Low protein expression (negative): Docetaxel until progression
  - Disease progression: Die
  - No disease progression: Live

Erlotinib (No test) until progression

- Disease progression: Die
- No disease progression: Live

Costs

• Unit costs: 2006 reimbursement values
  – Drugs: Wholesale acquisition costs
  – Medical services: CMS reimbursement values
  – Disease progression: Cost per month terminal lung cancer

• Resource utilization:
  – Estimated from the published RCTs.
    ▪ Mean treatment duration
    ▪ Adverse event rates
    ▪ Routine patient evaluations
Outcomes

- Effectiveness = quality-adjusted life-years (QALYs)
- Survival estimates:
  - Published mean values
  - Assumed survival benefit vs. BSC equal for DOC and ERL
- Survival estimates: Testing arms
  - Retrospective analysis of BR.21 (ERL vs. BSC)
  - Mean survival in testing groups weighted by marker prevalence
- Utilities: Community based study in UK
  - EQ-5D & Standard Gamble
  - Relevant NSCLC health states and adverse events
## Results

<table>
<thead>
<tr>
<th>Effectiveness Results</th>
<th>Gene Copy</th>
<th>Protein Expression</th>
<th>Erlotinib</th>
<th>Gene Copy – Erlotinib</th>
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</thead>
<tbody>
<tr>
<td>LYs</td>
<td>0.91</td>
<td>0.87</td>
<td>0.79</td>
<td>0.12</td>
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<tr>
<td>QALY PFS</td>
<td>0.27</td>
<td>0.26</td>
<td>0.25</td>
<td>0.03</td>
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<tr>
<td>QALY PD</td>
<td>0.23</td>
<td>0.22</td>
<td>0.20</td>
<td>0.03</td>
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<tr>
<td>Total QALYs</td>
<td>0.50</td>
<td>0.48</td>
<td>0.44</td>
<td>0.06</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cost Results</th>
<th>Total Test Costs</th>
<th>Total Drug Costs</th>
<th>Other Costs</th>
<th>Total Costs</th>
<th>ICER ($/LY)</th>
<th>ICER ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$320</td>
<td>$11,553</td>
<td>$54,573</td>
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Abbreviations: GC=EGFR gene copy number testing; ERL=erlotinib; LY=life-year; QALY=quality-adjusted life-year; PFS=progression-free survival; PD=progressive disease; ICER=incremental cost-effectiveness ratio
One-way sensitivity: GC vs. ERL

Effectiveness Drivers

- Effectiveness driven by survival and utility weights
- Costs driven by survival, drug costs and cost per month in DP

Cost Drivers
Probabilistic sensitivity analysis: Cost-effectiveness acceptability frontier

Abbreviations: ERL=erlotinib, IHC=protein expression testing, GC=gene copy number testing, EVPI=expected value of perfect information

University of Washington
Pharmaceutical Outcomes Research and Policy Program
# Expected value of perfect information in U.S. over 5 years

Effective U.S. population | % | Count | Source
--- | --- | --- | ---
Advanced/Distant stage | 87,486 | SEER, 1998-2003
NSCLC | 69,989 | Ramsey et al., 2006
Likely to be treated with chemotherapy | 55,151 | Ramsey et al., 2006
Likely to receive 2nd line treatment | 17,496 | Kutikova et al., 2005

<table>
<thead>
<tr>
<th>Ceiling ratio</th>
<th>EVPI per person</th>
<th>EVPI in US over 5 years (discounted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$50,000/QALY</td>
<td>$1,117</td>
<td>$92,201,000</td>
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<tr>
<td>$100,000/QALY</td>
<td>$381</td>
<td>$31,430,000</td>
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<tr>
<td>$150,000/QALY</td>
<td>$1,219</td>
<td>$100,635,000</td>
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Abbreviations: EVPI=expected value of perfect information, NSCLC=non-small cell lung cancer
Limitations

• Indirect comparison
  – We do not have information as to the relative clinical efficacy, safety, and resource utilization for the interventions in the same population.

• Retrospective subset analysis
  – Gene copy number: 17% of total study population
  – Protein expression: 33% of total study population
  – Loss of randomization integrity
    • Potential for confounding
Summary & Implications

- **EGFR gene copy number test:**
  - 3 additional QALW (1.4 month survival) vs. erlotinib
  - Increase of $9,200
  - ICER: ~$160,000/QALY (~$80,000/LY)

- Relative to generalized cost-effectiveness thresholds (i.e. $50 - $100,000/QALY)
  - Not cost-effective

- Relative to currently used treatments in NSCLC
  - Cost per month of care:
    - Erlotinib: $6,025
    - EGFR gene copy number testing: $6,090
    - Docetaxel: $6,330
Conclusion

• EGFR gene copy number testing has the potential to improve quality-adjusted life expectancy in refractory NSCLC patients by a clinically meaningful margin.

• Value commensurate with the approved therapies available in this setting.

• Uncertainty remains as to the relative effectiveness of these treatments, particularly in the genomic subgroups.

• Results of ongoing and future comparative clinical trials will provide valuable insight into the optimal treatment in 2nd line NSCLC and the potential of pharmacogenomic testing therein.
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Thank You

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