Value of immunotherapy and combination therapies

Health Economics Perspective

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Estimating Economic Value of Immunotherapies: The Same Rules Apply

- Health economic evaluation considers *incremental value*:
  - What is the additional health gain for additional cost compared to alternative therapies?

- Due to the very high cost of immunotherapy, other considerations may come into play:
  - Burdens to payers
  - Burden to patients (financial toxicity)
But…

• What if immunotherapy can produce durable responses (i.e., “cures”)?
  • Does the standard economic approach apply?
• **Grouping** cured and uncured patients together and reporting one mean value for OS **does not account for heterogeneity** in population
  
  • Incomplete assessment of therapy that cures proportion of patients
  
  • Biased assessments of OS
Estimating mean overall survival with survival plateau

Survival curves plateau - cannot estimate mean OS from empirical curve

Standard approach and previous work: **Parametric models**

Mixture cure models: Basic approach

General idea: Explicitly model the mixture of “cured” and uncured patients.

Use regression models to

1. Estimate probability that a patient is cured, and
2. Predict survival of patients who are not cured

Population survival = \( p_{\text{cured}} \times \text{survival}_{\text{cured}} + (1 - p_{\text{cured}}) \times \text{survival}_{\text{uncured}} \)

Ipilimumab case study: Incorporating heterogeneity
Standard Weibull model and Mixture Cure Model

Estimates projected out to 10 years past randomization
- **Standard Weibull model** does not fit tail well, assumes all patients will have died within 10 years
- **Mixture Cure model** fits data well, projected survival shows slow decline in expected mortality

### Ipilimumab case study: Parameters

<table>
<thead>
<tr>
<th></th>
<th>gp100</th>
<th>Ipi</th>
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</thead>
<tbody>
<tr>
<td><strong>Weibull analysis (without cure modeling)</strong></td>
<td></td>
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<tr>
<td>Mean OS (yrs)</td>
<td>0.90</td>
<td>1.60</td>
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<tr>
<td><strong>Mixture cure model analysis</strong></td>
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<tr>
<td>Mean OS of cured patients (yrs)</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Mean OS of uncured patients (yrs)</td>
<td>0.75</td>
<td>0.83</td>
</tr>
<tr>
<td>Cure proportion (%)</td>
<td>6</td>
<td>21</td>
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- Mean OS cured patients >> Mean OS uncured patients
- 15% more patients cured by Ipi compared to gp100
Estimating Mean Costs and QALYs

For **mixture cure model analysis**, and for both Ipi and gp100 arms, **Costs:**

- **Cured patients:**
  - Initial phase
  - Interim phase (KMSA)
  - 2012 national average

- **Uncured patients:**
  - Initial phase
  - Interim phase (KMSA)
  - Terminal phase
  - (Lin et al, 1997; Seidler et al, 2010)

**QALYs:**

- **Cured patients:**
  - 0.583
  - 0.796

- **Uncured patients:**
  - 0.583

(Tromme et al, 2014)

For **standard Weibull analysis**, assumed response rate = cured fraction
Ipilimumab case study: ICERs

- Standard Weibull model that does not incorporate potential cure factions
  - ICER = $324,000/QALY (95% CI: $254,000, $600,000)

- Using the mixture cure model
  - ICER = $113,000/QALY (95% CI: $101,000, $154,000)
Conclusions

• Incremental evaluations of cost and outcome still apply when evaluating the value of immunotherapies

• Consider mixture cure modeling over standard survival modeling when treatments “cure” a proportion of patients
  • Durable remissions, long-term survivors

• Other issues beyond cost-effectiveness are important
  • Burden on health insurers
  • Burden on patients