Adjusting Global Survival to Make Results More Relevant and Generalizable to Local Markets

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Disclaimer

- The views and opinions expressed in the following PowerPoint slides and accompanying oral presentation are those of the individual presenters and should not be attributed to Pfizer.
More generally, external validity is a key component of assessing effectiveness.

More generally, internal validity is a key component of assessing efficacy.

External Validity & Generalizability

Global multinational trials hope to be generalizable to global market

Global vs. Local Generalizability

Generalizable to local market

Payers reimburse at the local market level
What does “Bias” mean to you?

**Statistician Perspective:** Bias means the expected value of an estimate does not equal the true value

\[ E[\bar{X}] = \mu, \quad \text{biased: } E[\bar{X}] \neq \mu \]

**Payer Perspective:** The **efficacy** estimates do not reflect the **expected effectiveness**

- e.g., “clinical trials are biased and overestimate the true benefit”
Treatment switching and potential bias: An immuno-oncology example

<table>
<thead>
<tr>
<th>Category</th>
<th>Avelumab plus axitinib (N = 442)</th>
<th>Sunitinib (N = 444)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any follow-up anticancer treatments, n (%)³</td>
<td>138 (31.2)</td>
<td>227 (51.1)</td>
</tr>
<tr>
<td>Any VEGF or VEGFR inhibitor</td>
<td>118 (26.7)</td>
<td>123 (27.7)</td>
</tr>
<tr>
<td>Any other drug therapy</td>
<td>46 (10.4)</td>
<td>68 (15.3)</td>
</tr>
<tr>
<td>Any PD-1 or PD-L1 inhibitor</td>
<td>33 (7.5)</td>
<td>159 (35.8)</td>
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Similar example: N. Reinmuth et al. 2019.
Original vs. Adjusted Results

Hazard Ratio = 0.80 vs Adjusted Hazard Ratio = 0.65

Relatively "Unbiased" OS benefit for markets without PD-1/PD-L1 treatment options? 

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<tr>
<td>Primary OS analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with event, $n$ (%)</td>
<td>109 (24.7)</td>
<td>129 (29.1)</td>
</tr>
<tr>
<td>Stratified analysis</td>
<td></td>
<td></td>
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<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.80 (0.616–1.027)</td>
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</tr>
<tr>
<td>Adjusted OS analysis</td>
<td></td>
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<tr>
<td>RPSFT analysis</td>
<td></td>
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<tr>
<td>Hazard ratio (bootstrap 95% CI)</td>
<td>0.65 (0.413–0.933)</td>
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Biased OS Efficacy Results

Relatively “Unbiased” OS benefit, if PD-1/PD-L1 treatment options available?
How to account for Switching?

Common Methods for adjusting overall survival results

1. Censoring patient that switch or crossover
2. Rank Preserving Structural Failure Time models (RPSFT or RPSFTM)
3. Inverse Probability of Censoring Weighting (IPCW)
4. Two-stage estimation (TSE) methods

Censoring

- Option 1: Exclude patients who switched to subsequent therapy
- Option 2: Censor patients’ data starting from the time of switch

Key PROs & CONs:

- Easy for payers to understand
- Payers may view it as a relatively “objective analysis”
- Does not require “pre-planned additional data collection”
- Very susceptible to selection bias, which may draw payer criticism
Rank Preserving Structural Failure time (RPSFT)

On-treatment period for experimental arm

Estimate % increase in time (use as a correction factor)

This correction factor ($\psi_0$) is used to discount the time after switching to “similar” treatment

Note: If $\exp(\psi_0) = 0.5$, a 50% increase in time while on treatment

RPSFT Models Adjustment via Acceleration Factor

Period after crossover or treatment switching

Original survival time for Example patient is 20 months

50% Adjustment is applied to period after treatment switching
Key PROs & CONs for RPSFT

- Complex and difficult to explain to payers
- Viewed as relatively “objective analysis” by payers and regulators
- Typically requires class effect assumption which payers may reject
- Does not require “pre-planned additional data collection”
- Cannot handle more complex switching scenarios

Inverse Probability of Censoring Weighting (IPCW)

Approach assumes no unmeasured confounders.

Approach may be viewed as more subjective than censoring or RPSFT.

Key PROs & CONs for IPCW

- Relatively complex and may be difficult to explain to payers
- Assumes no unmeasured confounders which payers may reject
- May be viewed as a “subjective analysis” by payers
- Require extensive data collection after progression
- Likely requires “pre-planned additional data collection”
- Cannot handle more complex switching scenarios
Two-stage estimation method (TSE)

- First stage
  - Identify a secondary baseline
  - Analyze period after secondary baseline as an “observational study”
  - Use regression analysis (e.g. a failure time model) to estimate the benefit of switching
Two-stage estimation method (TSE)

- Second Stage
  - Similar to RPSFT, use the estimate benefit, i.e. " to adjust the survival times after switch
  - Unlike RPSFT, time from original baseline to progression has no influence on the adjustment

The correction factor used to adjust time after switch is a function of baseline and post-baseline covariates.

Methodological and applied references: Latimer NR et al. 2017, Skaltsa K et al. 2017
Key PROs & CONs for TSE

- Complex and difficult to explain to payers
- Assumes no unmeasured confounders which payers may not accept
- May be viewed as a more “subjective analysis” by payers
- Requires extensive data collection after progression
- Likely requires “pre-planned additional data collection”
- Has the potential to handle more complex switching scenarios
Conclusions

• If the observed switching is likely to occur in a local market, naïve analysis of trial data may be generalizable enough for payers.

• If the observed switching is not likely to occur in a local market, statistical adjustments can make the results more generalizable for payers.

• A range of techniques exist, but selection of the optimal approach is dependent on covariate availability, audience for results, and tolerance for specific assumptions.


N. Reinmuth et al. 2019. Effect of post-study immunotherapy (IO) on overall survival (OS) outcome in patients with metastatic (m) NSCLC treated with first-line durvalumab (D) vs chemotherapy (CT) in the phase III MYSTIC study. Annals of Oncology. Vol 30, Supplement 2, 1177

References


