Estimands in the presence of treatment switching

Viktoriya Stalbovskaya, Juliane Manitz, Marie-Laure Casadebaig, Emily Martin, Rui (Sammi) Tang, Godwin Yung, Vincent Haddad, Fei Jie, Christelle Lorenzato, Jiangxiu Zhou, Evgeny Degtyarev

DAGStat

Munich, March 19, 2019
Outline

- Introduction to the working group
- Treatment switching subteam
- Overall survival and intercurrent events
- Example study with treatment switch
- Several estimands and analyses approaches in a setting with treatment switching
- Discussion
Estimands in Oncology WG

- initiated and led by Evgeny Degtyarev (Novartis) and Kaspar Rufibach (Roche), first TC Feb 2018
- main purpose: ensure common understanding and consistent definitions for key estimands in Oncology across industry
- 31 members (14 from Europe and 17 from US) representing 19 companies
- established as EFSPI SIG for Estimands in Oncology in Nov 2018
- close collaboration with regulators from EMA, FDA, China, Taiwan and Canada
Estimands in Oncology WG
Communication plan for 2019

- whitepaper(s) and presentations at statistical and clinical conferences
- plans to further engage with Clinical community beyond ASCO
Treatment switching subteam

- Viktoria Stalbovskaya (Merus)
- Juliane Manitz (EMD Serono)
- Marie-Laure Casadebaig (Celgene)
- Emily Martin (EMD Serono)
- Rui (Sammi) Tang (Servier)
- Godwin Yung (Takeda)
- Vincent Haddad (AstraZeneca)
- Fei Jie (Astellas)
- Christelle Lorenzato (Sanofi)
- Jiangxiu Zhou (GSK)
- Evgeny Degtyarev (Novartis)
Overall survival – time from randomization to death from any cause

Experimental
Randomization

Death from any cause

Control
Randomization

Death from any cause
Disease progression often precedes death

Experimental
- Randomization
- Disease progression
- Death from any cause

Control
- Randomization
- Disease progression
- Death from any cause
Disease progression may allow initiation of experimental therapy.
... or a start of new anti-cancer therapy
How about events that are not observed?

Experimental → Randomization → Disease progression → New anti-cancer therapy → Loss to follow-up → Death from any cause
How about events that are not observed?

... or observed after a sequence of therapies?

- Double-blind, multicenter study with patients randomized to receive either everolimus (n = 277) or placebo (n = 139)
- Primary endpoint – Progression-free survival defined as time from randomization until disease progression or death

**STUDY DESIGN**

N=416

- Stratification
  - Prior VEGFR-TK: 1 or 2
  - MSKCC risk group: favorable, intermediate, or poor

**AFINITOR**

+ BSC (n=277)

**Placebo**

+ BSC (n=139)

Crossover to AFINITOR upon disease progression

Motzer et al (2010)
Example: study RECORD-1

- Positive study with clinically meaningful improvement in PFS (HR=0.33, 95% CI: 0.25, 0.43, p-value < 0.001)

Motzer et al (2010)
- Positive study with clinically meaningful improvement in PFS (HR=0.33, 95% CI: 0.25, 0.43, p-value < 0.001)
- Protocol allowed crossover from placebo to everolimus upon progression (106 out of 139 patients, 76%)
- ITT analysis of OS showed trend in OS benefit (HR=0.87, 95% CI: 0.65-1.15, p-value=0.162)

Motzer et al (2010)
- Positive study with clinically meaningful improvement in PFS (HR=0.33, 95% CI: 0.25, 0.43, p-value < 0.001)
- Protocol allowed crossover from placebo to everolimus upon progression (106 out of 139 patients, 76%)
- ITT analysis of OS showed trend in OS benefit (HR=0.87, 95% CI: 0.65-1.15, p-value=0.162)

How can these results be interpreted?
Our focus

- Treatment switching methodology embedded in estimand framework
- Endpoints of interest: overall survival and PFS2
- Intercurrent events of interest: cross-over from control to experimental therapy, start of new anti-cancer therapy
- Scientific questions of interest and description of 4 attributes of corresponding estimands
- Impact on data collection
- Sensitivity and supportive analyses
Several estimands for overall survival (not an exhaustive list)

<table>
<thead>
<tr>
<th>Scientific question: does experimental therapy prolongs survival ...</th>
<th>... regardless of crossover or new therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>All randomized patients</td>
</tr>
<tr>
<td>Variable</td>
<td>OS</td>
</tr>
<tr>
<td>Intercur. event: cross-over to experimental therapy</td>
<td>Treatment Policy</td>
</tr>
<tr>
<td>Intercur. event: switch to new anticancer therapy excl. cross-over</td>
<td>Treatment Policy</td>
</tr>
<tr>
<td>Population-level summary</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>Analysis</td>
<td>Estimate HR using Cox model and reported survival times</td>
</tr>
<tr>
<td>Additional data collection</td>
<td>--</td>
</tr>
</tbody>
</table>
# Several estimands for overall survival (not an exhaustive list)

<table>
<thead>
<tr>
<th></th>
<th>Estimand 1</th>
<th>Estimand 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scientific question:</strong></td>
<td>does experimental therapy prolongs survival ...</td>
<td>... regardless of crossover or new therapies</td>
</tr>
<tr>
<td></td>
<td>... regardless of crossover or new therapies</td>
<td>... in patients who did not cross-over</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>All randomized patients</td>
<td>All randomized patients excluding patients who cross-over</td>
</tr>
<tr>
<td><strong>Variable</strong></td>
<td>OS</td>
<td>OS</td>
</tr>
<tr>
<td><strong>Intercur. event:</strong></td>
<td>cross-over to experimental therapy</td>
<td>Treatment Policy</td>
</tr>
<tr>
<td></td>
<td>to experimental therapy</td>
<td>Treatment Policy</td>
</tr>
<tr>
<td></td>
<td>switch to new anticancer therapy excl. cross-over</td>
<td>Treatment Policy</td>
</tr>
<tr>
<td><strong>Population-level summary</strong></td>
<td>Hazard ratio</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td><strong>Analysis</strong></td>
<td>Estimate HR using Cox model and reported survival times</td>
<td>Estimate HR using Cox model excluding patients who switched</td>
</tr>
<tr>
<td></td>
<td>--</td>
<td>Indicator for treatment switch</td>
</tr>
<tr>
<td></td>
<td>Indicator for treatment switch</td>
<td>Indicator for treatment switch</td>
</tr>
</tbody>
</table>
Several estimands for overall survival (not an exhaustive list)

<table>
<thead>
<tr>
<th></th>
<th>Estimand 1</th>
<th>Estimand 2</th>
<th>Estimand 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific question:</td>
<td>... regardless of crossover or new therapies</td>
<td>... in patients who did not cross-over</td>
<td>... in patients while they remained on randomized treatment or no treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>All randomized patients</td>
<td>All randomized patients excluding patients who cross-over</td>
<td>All randomized patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercur. event: cross-over to experimental therapy</td>
<td>Treatment Policy</td>
<td>Exclude switchers</td>
<td>While on treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercur. event: switch to new anticancer therapy excl. cross-over</td>
<td>Treatment Policy</td>
<td>Treatment policy</td>
<td>Treatment policy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population-level summary</td>
<td>Hazard ratio</td>
<td>Hazard ratio</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis</td>
<td>Estimate HR using Cox model and reported survival times</td>
<td>Estimate HR using Cox model excluding patients who switched</td>
<td>Estimate HR using Cox model censoring survival time at the time of switch</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional data collection</td>
<td>--</td>
<td>Indicator for treatment switch</td>
<td>Indicator for treatment switch, verification that no additional treatment had started</td>
</tr>
</tbody>
</table>
Several estimands for overall survival (not an exhaustive list)

<table>
<thead>
<tr>
<th></th>
<th>Estimand 1</th>
<th>Estimand 2</th>
<th>Estimand 3</th>
<th>Estimand 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific question:</td>
<td>does experimental therapy prolongs survival ...</td>
<td>... regardless of crossover or new therapies</td>
<td>... in patients while they remained on randomized treatment or no</td>
<td>... had cross-over not occurred and regardless of new therapies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>treatment</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>All randomized patients</td>
<td>All randomized patients excluding patients who cross-over</td>
<td>All randomized patients</td>
<td>All randomized patients</td>
</tr>
<tr>
<td>Variable</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
</tr>
<tr>
<td>Intercur. event:</td>
<td>cross-over to experimental therapy</td>
<td>Exclude switchers</td>
<td>While on treatment</td>
<td>Hypothetical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercur. event:</td>
<td>switch to new anticancer therapy excl. cross-over</td>
<td>Treatment policy</td>
<td>Treatment policy</td>
<td>Treatment Policy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population-level</td>
<td>Hazard ratio</td>
<td>Hazard ratio</td>
<td>Hazard ratio</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>summary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis</td>
<td>Estimate HR using Cox model and reported survival times</td>
<td>Estimate HR using Cox model excluding patients who switched</td>
<td>Estimate HR using Cox model censoring survival time at the time of switch</td>
<td>Estimate HR using RPSFT and re-calculate survival times based on time spent on experimental treatment</td>
</tr>
<tr>
<td>Additional data</td>
<td>--</td>
<td>Indicator for treatment switch</td>
<td>Indicator for treatment switch, verification that no additional treatment had started</td>
<td>Start and stop dates on experimental therapy for patients who switched</td>
</tr>
<tr>
<td>collection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A. Population
   *All randomized patients: patients defined through inclusion/exclusion criteria to reflect the target patient population for drug approval*

B. Endpoint
   *Overall survival: time from randomization until death from any cause*

C. Handling of intercurrent events
   *Crossover to experimental therapy in control arm patients: survival time will be re-calculated based on time spent on experimental therapy and*
   *New antineoplastic therapy with the same class of drugs as experimental arm: follow treatment policy approach and not account for it*

D. Summary measure for the variable
   *Estimate hazard ratio using reconstructed data through Cox model.*

Estimand: hazard ratio of overall survival between experimental and control therapy in the targeted patient population had the crossover not occurred
• Model-based method that reconstructs survival times of patients who switched as if they had not received experimental treatment.
• Treatment effect is expressed on the time scale as acceleration factor. It can also be estimated on HR scale (Cox model with counterfactual survival times for crossover patients)
• Assumption: the treatment effect is multiplicative and only the time spent on experimental treatment affects the difference in survival expectation.
Summary for RPSFT

Pros
- Provides a randomization-based treatment effect estimator
- May use HR and KM curves
- Crossover may happen any time independent of disease-related events
- Doesn’t require information on covariates unlike IPCW
- Can handle larger proportion of patient switching

Cons
- Requires ”common treatment effect” assumption (assumes that treatment effect is the same regardless of when the experimental treatment is initiated)
- The structural failure time assumption (treatment is acting by multiplying survival time by a given factor once patient starts receiving active treatment) is not testable
- HR CIs requires extra computation
Selected sensitivity and supplementary analyses

Addressing robustness towards model assumptions

- Technical implementation:
  - Use different step size for the G-estimation
  - Use of different test statistic for G-estimation

- Model assumptions:
  - Common treatment effect – the treatment effect in the control arm after switchover is \( w \) times the treatment effect in the experimental arm (apply weight on multiplication factor after switchover).

Addressing alternative estimands

- Calculation of counterfactual survival time after discontinuation of experimental treatment based on “treatment group” approach – once experimental therapy started the treatment effect applies to the entire follow up time (e.g. surgery, curative treatment)
- Preparation of the position paper with the estimands, strategies for handling intercurrent events, recommendations to data collection
- Active engagement within the industry, with regulators and payers
- Influence and feedback to the agency guideline to fit for oncology estimand framework
- Raise awareness of the estimands framework with the wider audience
ICH E9 working group. ICH E9 (R1): Addendum on estimands and sensitivity analyses in clinical trials to the guideline on statistical principles for clinical trials. 2017.


