Estimands for PFS2

Jiangxiu Zhou

On behalf of Estimands in Oncology Working Group, Treatment Switching Subteam

Sep 24th, 2019
Outline

- Introduction of the oncology estimands working group
- PFS2
  - Definitions of PFS2
  - PFS2 mapped to the estimands framework
  - PFS2 data collection
Initiated and led by Evgeny Degtyarev (Novartis) and Kaspar Rufibach (Roche) in Feb 2018
35 members (16 from Europe and 19 from US) representing 19 companies
To ensure common understanding and consistent definitions in close collaboration with regulators
Established as EPSPI SIG (Nov 2018) and ASA Biopharmaceutical Section SWG (Apr 2019)
Collaboration with regulators from the EMA, FDA, Japan, China, Taiwan and Canada
Ongoing discussions with academia to define the scope for collaboration
Oncology Estimands Working Group Subteams

- Causal subteam (Causality and principal stratification strategy)
- Censoring subteam (Censoring mechanisms and their impact on interpretation of estimands)
- Solid tumor case studies subteam (Position on estimands targeting PFS/DFS)
- Hematology case studies subteam (Position on estimands targeting PFS/DFS)
- Treatment switching subteam (Position on estimands targeting OS and PFS2)
Treatment Switching Subteam

- Viktoriya Stalbovskaya
- Juliane Manitz
- Marie-Laure Casadebaig
- Emily Martin
- Rui (Sammi) Tang
- Godwin Yung
- Vincent Haddad
- Fei Jie
- Christelle Lorenzato
- Jiangxiu Zhou
- Evgeny Degtyarev
- Hannes Buchner
Focus of the treatment switching subteam

- Estimands for overall survival in presence of treatment switching
  - Treatment switching may affect interpretation of OS

- Estimands for PFS2
  - Intermediate endpoint recommend by the EMA when OS is very long
PFS2 is

- recommended by the EMA as a surrogate endpoint for OS when OS cannot be measured (EMA, 2012)
  - Included in EMA labels, e.g., Olaparib
- valued by the HTA for reimbursement evaluations
- increasingly included as an endpoint in oncology studies to assess benefits of maintenance or sequential treatments
- frequently presented at clinical conferences, e.g., ASCO
- currently not considered as an endpoint by the FDA
Variety of definitions for PFS2

- **EMA definition 1 (D1):**
  - Time from randomization to progression on next-line treatment, or death from any cause, whichever is earlier; otherwise censored at the last time known to be alive and without second objective disease progression

- **EMA definition 2 (D2):**
  - Time from randomization to end of next-line treatment, second progression, or death from any cause, whichever is earlier; otherwise censored at the last time known to be alive and without second objective disease progression

- **Alternative definition (D3):**
  - Time from randomization to progression on next-line treatment, or death from any cause, whichever is earlier
  - Time from randomization to end of next-line treatment, or death from any cause, whichever is earlier if progression on next-line treatment is not available
  - Otherwise censored at the last time known to be alive and without second objective disease progression
**Scenario 1**
- Randomization date
- Next-line treatment started
- PD2*
- Next-line treatment ended
- 2nd next-line treatment started

**Scenario 2**
- Randomization date
- Next-line treatment started
- Next-line treatment ended
- PD2*
- 2nd next-line treatment started

**Scenario 3**
- Randomization date
- Next-line treatment started
- Next-line treatment ended
- 2nd next-line treatment started

*PD2: progression on next-line treatment*
## PFS2 mapped to the estimands framework

<table>
<thead>
<tr>
<th>Scientific question</th>
<th>Estimand 1 (EMA)</th>
<th>Estimand 2 (EMA)</th>
<th>Estimand 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative effect of prolonging time to <strong>progression</strong> on next-line treatment or <strong>death</strong> if patients do not start a 2\textsuperscript{nd} next line therapy</td>
<td>PFS2 (Event: PD2/death)</td>
<td>PFS2 (Event: next-line treatment discontinuation/PD2/death)</td>
<td>PFS2 (Event: PD2/death OR next-line treatment discontinuation/death)</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Target population per key Incl./Excl. criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>Treatment policy (no censoring/no event)</td>
<td>Composite (Event)</td>
<td>Treatment policy (no censoring/no event)</td>
</tr>
<tr>
<td><strong>Intercurrent event:</strong> <strong>discontinuation</strong> of next-line\textsuperscript{1} treatment when progression on next-line treatment <strong>is observed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intercurrent event:</strong> <strong>discontinuation</strong> of next-line\textsuperscript{1} treatment when progression on next-line treatment <strong>is not observed</strong></td>
<td>Treatment policy (no censoring/no event)</td>
<td>Composite (Event)</td>
<td>Composite (Event)</td>
</tr>
<tr>
<td><strong>Intercurrent event:</strong> start of 2\textsuperscript{nd} next-line treatment</td>
<td>Hypothetical (Censor)</td>
<td>Composite\textsuperscript{2} (Event)</td>
<td>Composite\textsuperscript{2,3} (Event)</td>
</tr>
<tr>
<td><strong>Summary measure</strong></td>
<td></td>
<td></td>
<td>HR</td>
</tr>
</tbody>
</table>

---

1. If the next-line treatment is not treated until progression and only treated for a fixed dose or a fixed duration of period, e.g., CAR-T therapy, 2\textsuperscript{nd} next-line treatment minus 1 day should be used instead.
2. If discontinuation date of next-line treatment is not available.
3. When progression on next-line treatment is not observed.
## Requirements for data collection

<table>
<thead>
<tr>
<th>Data Collection</th>
<th>Estimand 1 (progression/death)</th>
<th>Estimand 2 (discontinuation/progression/death)</th>
<th>Estimand 3 (progression/death OR discontinuation/death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start date of next-line treatment</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Stop date of next-line treatment</td>
<td></td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Reason for stopping next-line treatment*</td>
<td></td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Date of PD on next-line treatment</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Date of death</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Start date of 2nd next-line treatment</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

*If the next-line treatment is not treated until progression and only treated for a fixed number of doses, e.g., CAR-T therapy*
PFS2 is increasingly included as an endpoint to evaluate sustained PFS benefit beyond subsequent therapy when OS cannot be measured.

Currently no consensus on definition of PFS2

- Different definitions correspond to different scientific questions
- Estimand 1 is most commonly adopted due to simplicity and EMA recommendation, e.g., Olaparib
  - However PD on next-line treatment may not be easily collected
- Estimand 2 and 3 require extra data collection however it helps prevent heavy censoring which may lead to biased estimate

- More guidance on PFS2 needed from the health authority and HTA