Estimands for PFS2

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

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Outline

- Introduction of the oncology estimands working group
- PFS2
  - Definitions of PFS2
  - PFS2 mapped to the estimands framework
  - PFS2 data collection

Oncology Estimands Working Group

- 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

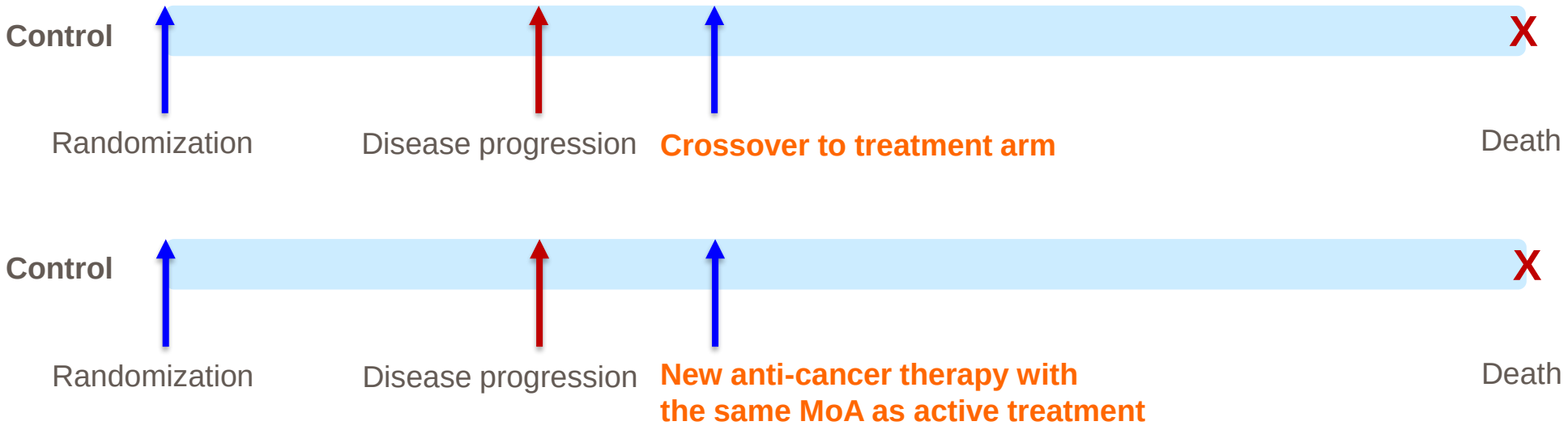
- Causal subteam (Causality and principal stratification strategy)
- Censoring subteam (Censoring mechanisms and their impact on interpretation of estimands)
- Solid tumor case studies subteam (Position on estimands targeting PFS/DFS)
- Hematology case studies subteam (Position on estimands targeting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

Treatment Switching Subteam

- Viktoriya Stalbovskaya Merus closing in on cancer
- Juliane Manitz Merck KGaA Darmstadt, Germany
- Marie-Laure Casadebaig Celgene
- Emily Martin Merck KGaA Darmstadt, Germany
- Rui (Sammi)Tang SERVIER
- Godwin Yung Takeda
- Vincent Haddad AstraZeneca
- Fei Jie astellas
- Christelle Lorenzato SANOFI
- Jiangxiu Zhou gsk
- Evgeny Degtyarev NOVARTIS
- Hannes Buchner stabu ro Statistical Consulting

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

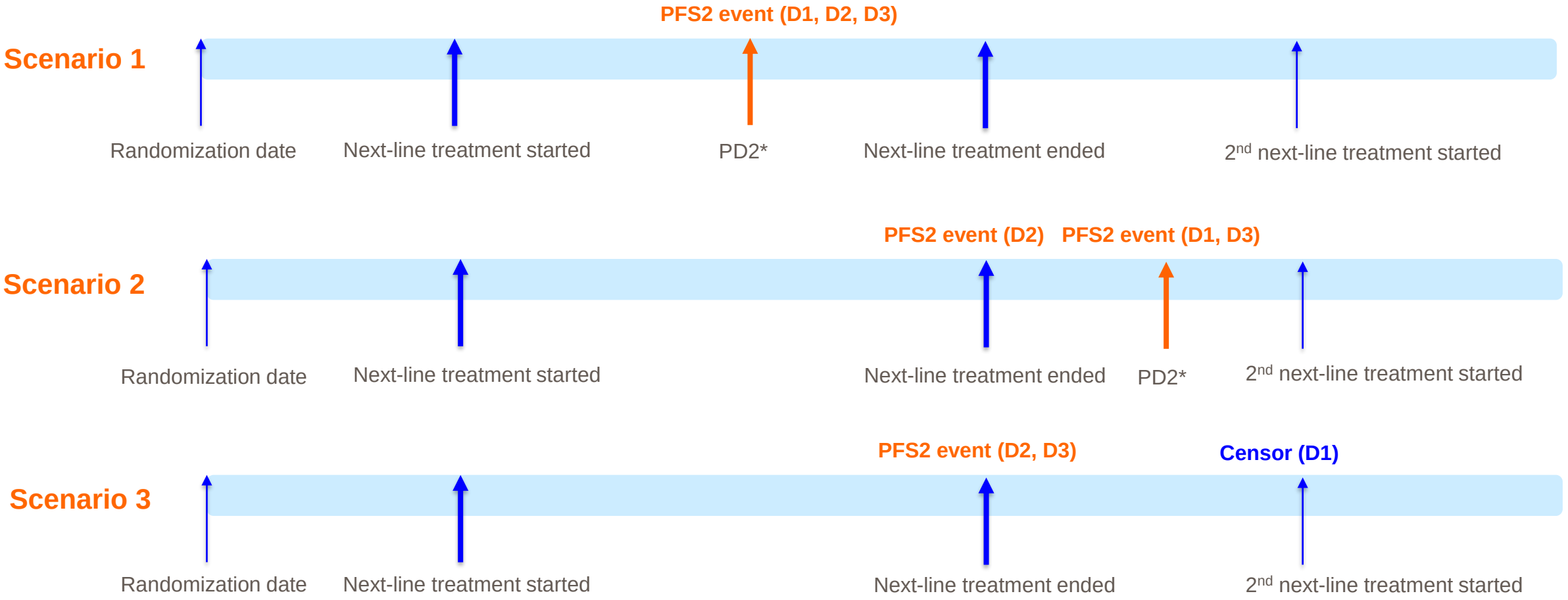
PFS2

- 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

Illustration of three definitions



*PD2: progression on next-line treatment

PFS2 mapped to the estimands framework

	Estimand 1 (EMA)	Estimand 2 (EMA)	Estimand 3
Scientific question	Relative effect of prolonging time to **progression** on next-line treatment or **death** if patients do not start a 2nd next line therapy	Relative effect of prolonging time to **discontinuation** of next-line treatment, **progression** on it or **death**	Relative effect of prolonging time to **progression** (or **discontinuation** if progression is not observed) on next-line treatment or **death**
Population	Target population per key Incl./Excl. criteria		
Endpoint	PFS2 (Event: PD2/death)	PFS2 (Event: next-line treatment discontinuation/PD2/death)	PFS2 (Event: PD2/death OR next-line treatment discontinuation/death)
Intercurrent event: **discontinuation** of next-line[1] treatment when progression on next-line treatment **is observed**	Treatment policy (no censoring/no event)	Composite (Event)	Treatment policy (no censoring/no event)
Intercurrent event: **discontinuation** of next-line[1] treatment when progression on next-line treatment **is not observed**	Treatment policy (no censoring/no event)	Composite (Event)	Composite (Event)
Intercurrent event: start of 2nd next-line treatment	Hypothetical (Censor)	Composite[2] (Event)	Composite[2,3] (Event)
Summary measure	HR		

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, 2nd 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

Data Collection	Estimand 1 (progression/death)	Estimand 2 (discontinuation/progression/death)	Estimand 3 (progression/death OR discontinuation/death)
Start date of next-line treatment	Y	Y	Y
Stop date of next-line treatment		Y	Y
Reason for stopping next-line treatment*		Y	Y
Date of PD on next-line treatment	Y	Y	Y
Date of death	Y	Y	Y
Start date of 2nd next-line treatment	Y	Y	Y

*If the next-line treatment is not treated until progression and only treated for a fixed number of doses, e.g., CAR-T therapy

Summary

- PFS2 is increasingly included as an endpoint to evaluate sustained PFS benefit beyond subsequent therapy when OS cannot be measured
- Currently no concensus 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