Impact of Cross-over in the Evaluation of Overall Survival in cancer RCTs

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Hypothetical vs. treatment policy estimand?

Concern with estimand or (assumptions for) estimation methods(s)?

PFS vs. OS?

Treatment policy:
1) Subsequent therapy SOC or not?
2) Define "policy"!

We (statisticians!) are not precise enough!

Clear formulation of causal question.

Wrong use of sensitivity vs. supplementary.

Wrong use of *non-informative* vs. *non-independent* censoring.

FDA interaction Glofitamab

Relapsed / refractory mantle cell lymphoma.

Phase 3 randomized: Single-agent Glofitamab vs. investigator's choice.

Endpoints:

- Primary: **PFS**.
- Secondary: **OS** (type I error protected within hierarchy).

OS: Intercurrent event **crossover from control to experimental**.

Trial not feasible in US without crossover (availability of CAR-T therapy at 2L+).

FDA interaction Glofitamab

Pre-phase III meeting:

- FDA requested **not to allow crossover**. **Why? Ethical at all? Patients go on to other therapies anyway (CAR-T!).**
- In response to sponsor's comments FDA suggested to limit crossover.

Sponsor proposed:

- Hypothetical strategy for ICE of crossover.
- Estimation via rank-preserving structural failure time (RPSFM) model.

FDA did not agree:

- RPFSM recognized method. **"Common treatment assumption":** relative effect independent of (1) when crossover happens, (2) characteristic of patient (3) type of subsequent therapy.
- *We still recommend the log-rank test as the primary analysis.* Note: just taking OS data as it is.
- *We suggest using RPSFM as your sensitivity analysis.*
- Recommends to put a **cap** on number of patients who crossover.

Questions:

What is primary interest? Putting cap on number of X-overs insinuates interest in hypothetical strategy.

RPSFM makes strong assumptions for estimation. Independent of estimand - do we need other estimation methods?

RPSFM: supplementary for treatment policy, NOT sensitivity.

Glofitamab not approved in 2L+ in MCL.

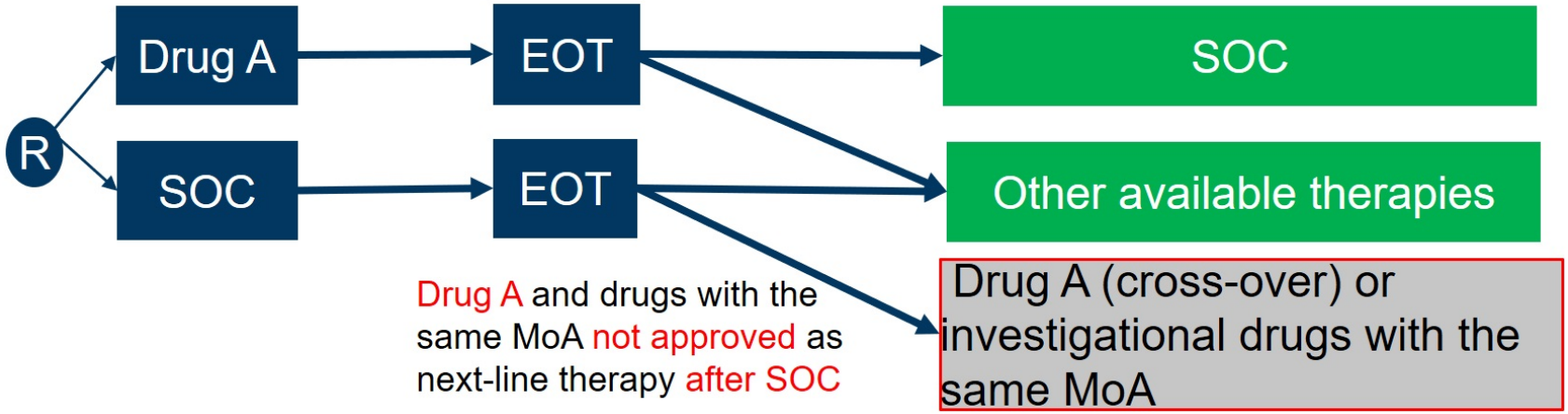
Actual (causal) comparison:

Arm 1: Glofitamab $\rightarrow$ NALT vs.
Arm 2: SOC $\rightarrow$ Glofitamab $\rightarrow$ NALT.

PFS vs. OS in FDA interaction for Glofit

	PFS	**OS**
Intercurrent event	non-protocol anti-cancer therapy prior to PD	crossover from control to experimental
FDA preferred strategy	**hypothetical**	**treatment policy**
FDA preferred estimation method	simple censoring	OS as observed, with cap on crossover.
Assumptions for estimation to give unbiased estimates for **targeted** estimand	independent censoring	Cap: - Purpose? - Limit bias for estimation of treatment policy estimand? - Patients go on to other therapies anyway?

Subsequent therapy
does not reflect SOC.



Subsequent therapy after EOT **does not** reflect clinical practice:

- Immuno-oncology.
- Open-label trials: Patients **may leave trial** immediately after being randomized to SOC.
- Treatment policy: Clear what it is? Estimand relevant?
- Benefit on OS in a world without cross-over more informative? **Hypothetical estimand**?

Randomized but not treated

- **Blinding** often infeasible.
- Checkmate-37:
  - **20% vs 1.5%**.
  - Weber *et al.* (2015).
- Quantum-R:
  - **23% vs 1.6%**.
  - Cortes *et al.* (2019).

Overall survival in all randomized patients **interpretable**?

Treatment policy:

Available therapies need to reflect clinical practice.

Need to define *policy of interest*, **not just** *take what we get*.

Feasibility?

If you want a causal answer you should start with a causal question.

Vanessa Didelez.

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Oncology estimand WG:
www.oncoestimand.org

Manitz et al. (2022)

Thank you for your attention.

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Slides can be downloaded on

www.kasparrufibach.ch

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Doing now what patients need next

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