Estimands in the Presence of Treatment Switching

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Conference: ISCB, Leuven, July 2019

Outline

- Introduction to the working group
- Treatment switching subteam
- Estimand Framework
- Example study with treatment switch
- Several estimands and analyses approaches in a setting with treatment switching
- Discussion

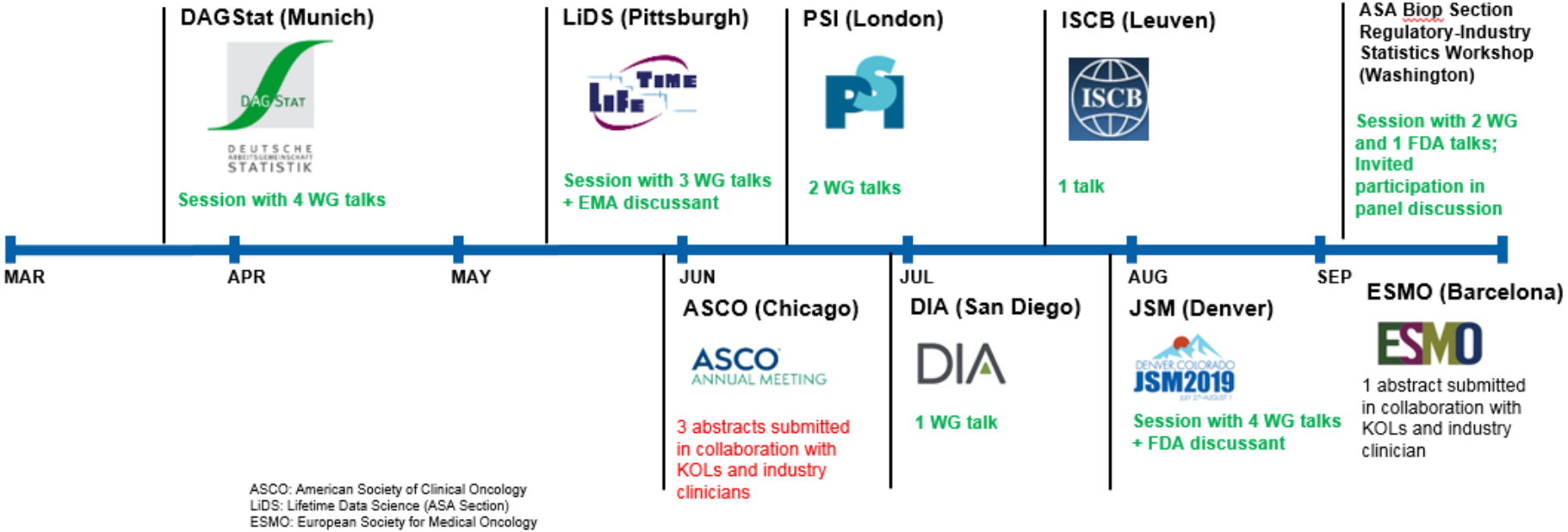
Estimands in Oncology WG

- 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
- 34 members (15 from Europe and 19 from US) representing 22 companies
- established as EFSPI SIG for Estimands in Oncology in Nov 2018 and ASA Biopharmaceutical Section SWG in Apr 2019
- collaboration with regulators from EMA, FDA, Japan, 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



ASCO: American Society of Clinical Oncology
LiDS: Lifetime Data Science (ASA Section)
ESMO: European Society for Medical Oncology

Treatment switching subteam

- Viktoriya Stalbovskaya
- Juliane Manitz
- Marie-Laure Casadebaig
- Emily Martin
- Rui (Sammi)Tang
- Godwin Yung
- Vincent Haddad
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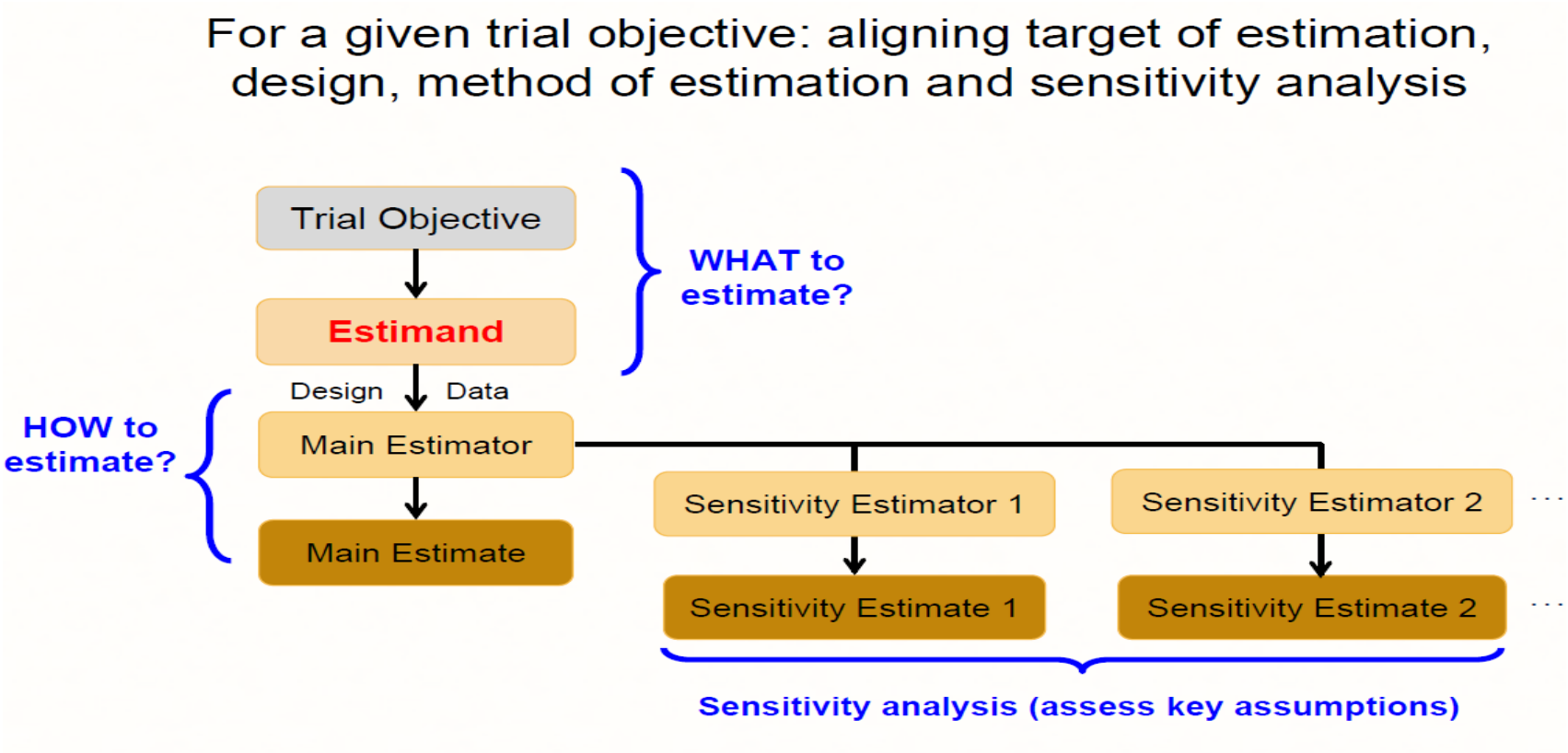
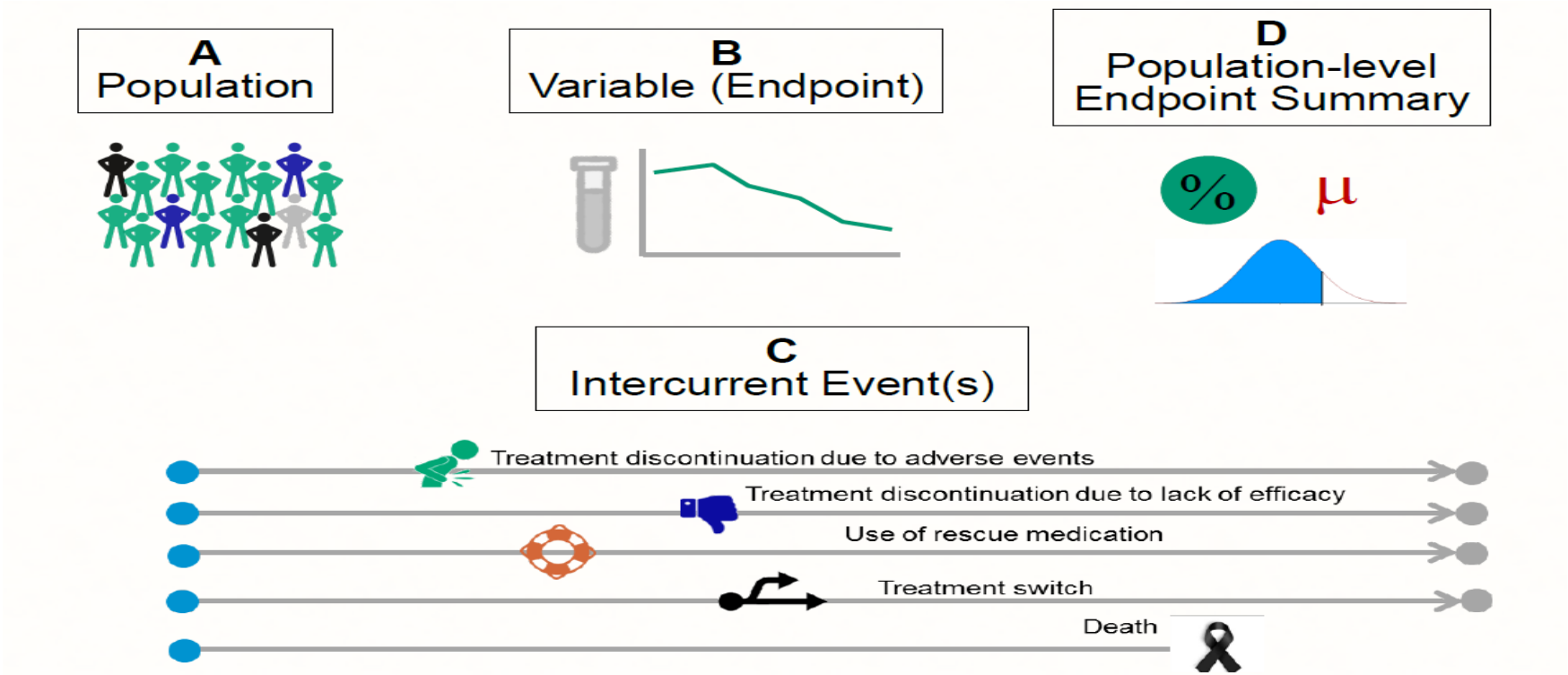
- Evgeny Degtyarev
- Hannes Buchner

IHC E9/R1: Estimand Framework



ICH E9/R1: Component of Defining an Estimand



Source: Devan V. Mehrotra ASA-BIOP presentation 2018

ICH E9 addendum and oncology

- Why this addendum?
  - **Lack of alignment** of trial objectives and effect estimates.
  - Addendum and many (early) publications focus on **longitudinally** measured endpoints, especially with missing data.
- What about **time-to-event** (T2E) endpoints?
- Anticipated impact on **oncology** clinical trials?

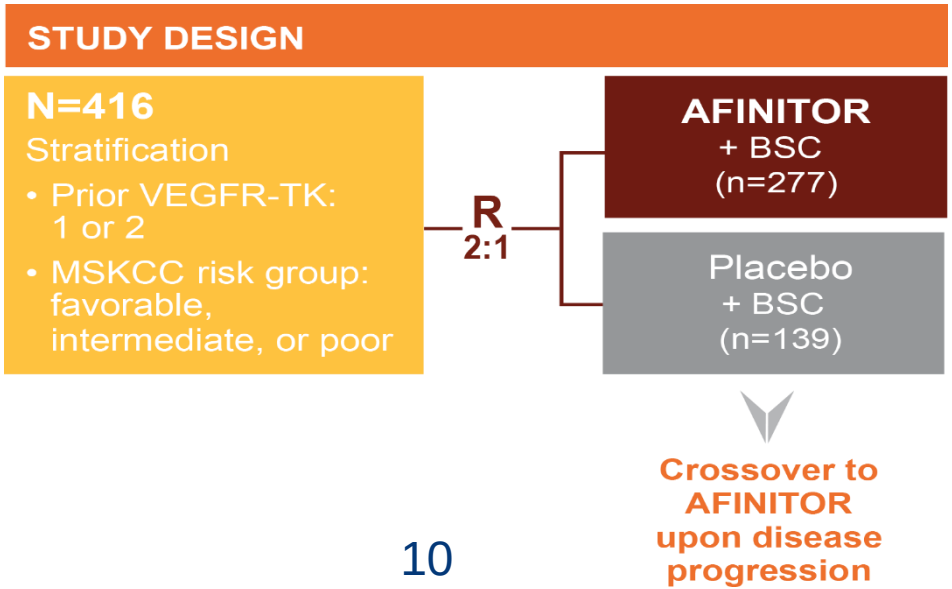
Key questions

- Key **intercurrent** events, endpoints, and estimands in oncology?
- How do five proposed strategies to handle intercurrent events apply to T2E endpoints?
- How can established methods in oncology, e.g.
  - **censoring** schemes or
  - treatment **switching**

  be embedded in addendum framework?
- What estimands are targeted by «**standard**» analyses?
- «**Missing data**» often highly informative. What implicit assumptions are we making when simply censoring?

Example: study RECORD-1

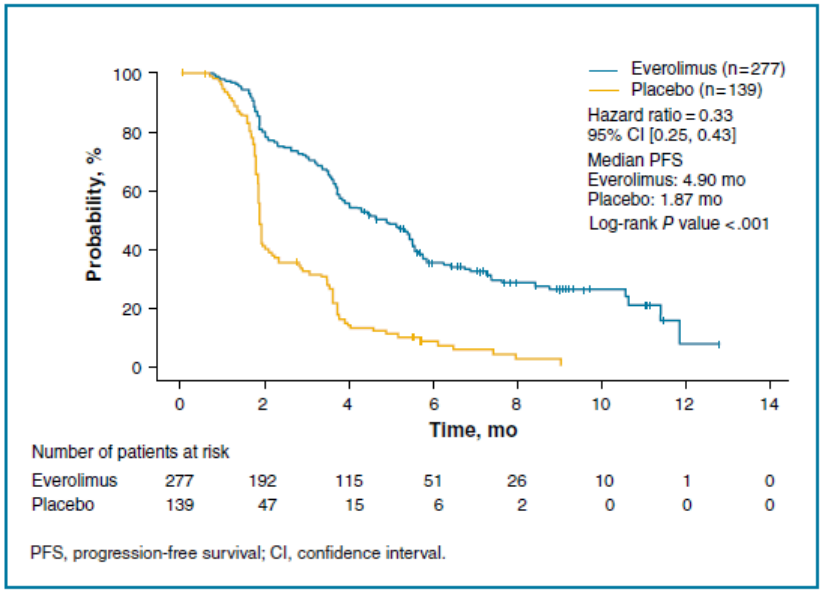
- Phase III study of everolimus in metastatic renal cell carcinoma Motzer et al (2008, 2010)
  - Double-blind, multicenter study with patients randomized to receive either everolimus (n = 277) or placebo (n = 139)
  - Primary endpoint – Progression-free survival defined as time from randomization until disease progression or death



Motzer et al (2010)

Example: study RECORD-1

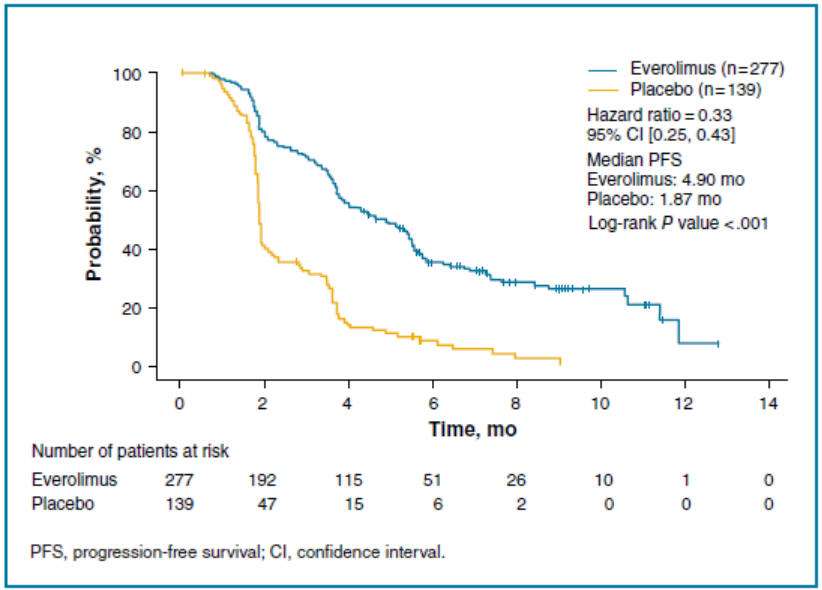
- Positive study with clinically meaningful improvement in PFS (HR=0.33, 95% CI: 0.25, 0.43, p-value < 0.001)

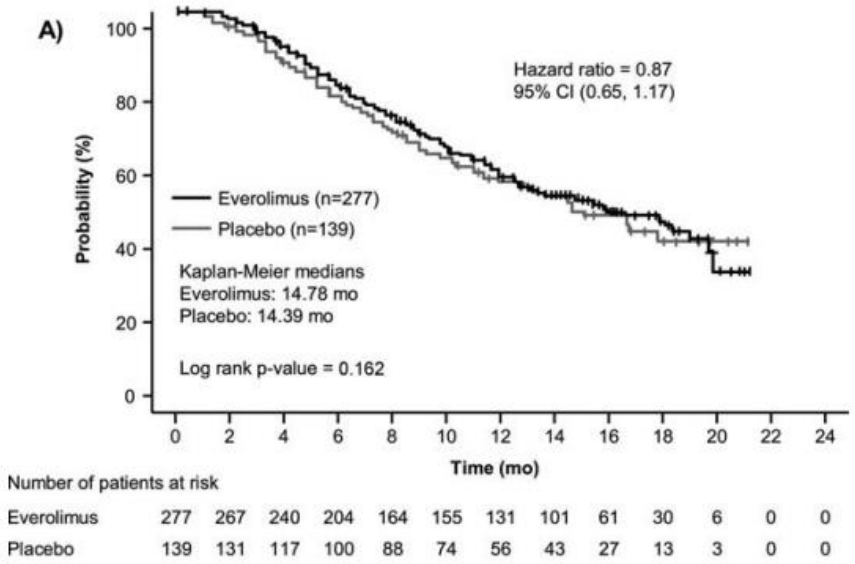


Motzer et al (2010)

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)
- 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)





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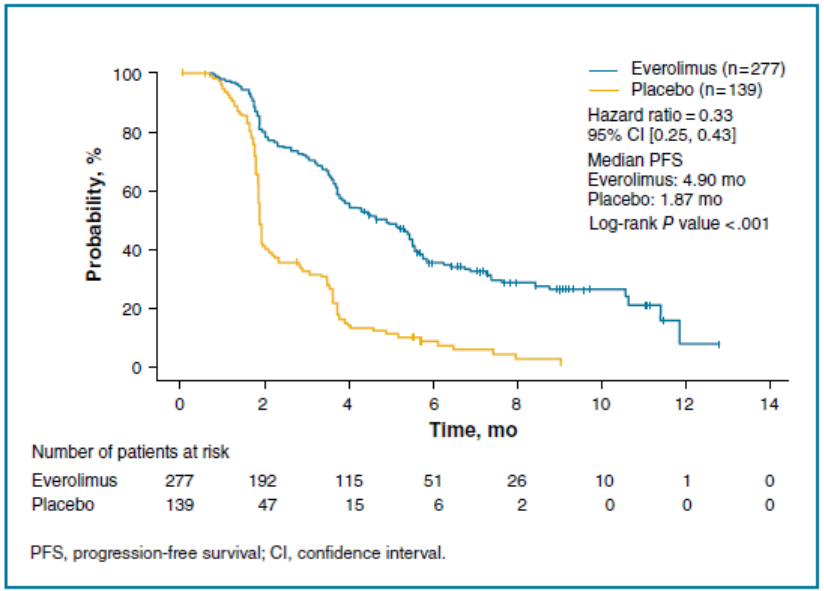
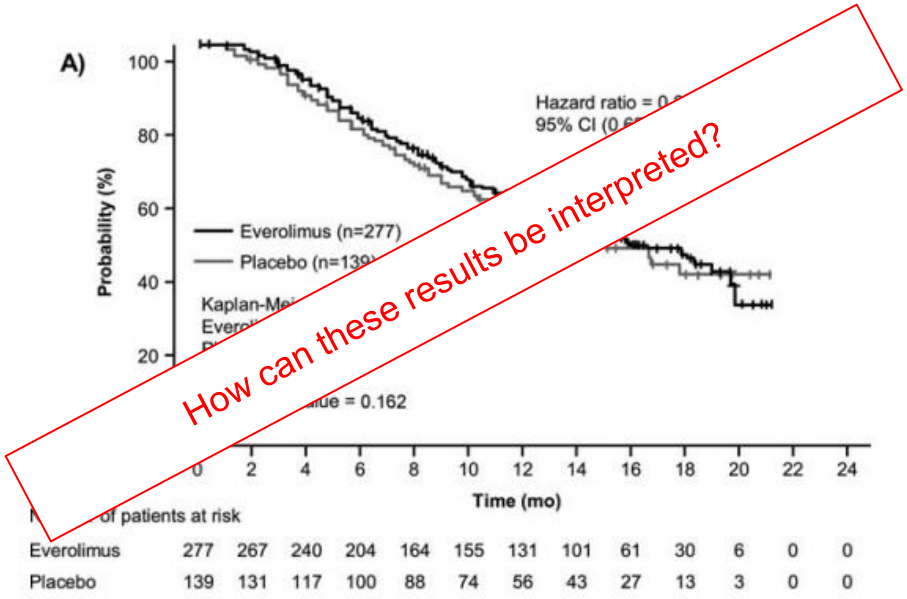
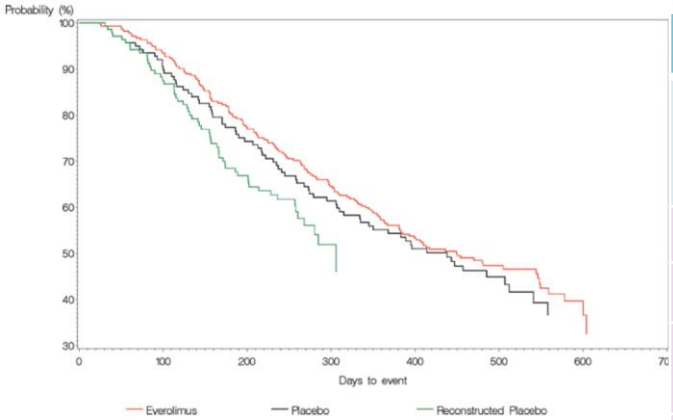




Motzer et al (2010)

Revisiting RECORD – 1

Two different estimands for OS



Everolimus
Placebo
Re-constructed Placebo using RPSFT* model

	Estimand 1	Estimand 2
Scientific question: Does experimental drug prolongs survival…	**… regardless of crossover**	**…had cross-over not occurred**
Population	Targeted population	Targeted population
variable	OS	OS
Intercurrent event: Cross-over to Everolimus	*Treatment Policy*	*Hypothetical*
Population-level summary	Hazard Ratio	Hazard Ratio
Analysis	Estimate HR using Cox model (**Red** vs **Black**)	Estimate HR from RPSFT model (**Red** vs **Green**)
Additional data collection	-	Date of crossover, information needed for the model

These are not different sensitivity analysis, but different estimands!

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)

	Estimand 1
Scientific question: does experimental therapy prolong	... survival regardless of crossover or new therapies
Population	Targeted indication
Variable	OS
Intercur. event: cross-over to experimental therapy	Treatment Policy
Intercur. event: switch to new anticancer therapy excl. cross-over	Treatment Policy
Population-level summary	Hazard ratio
Analysis	Estimate HR using Cox model and reported survival times
Additional data collection	--

Several estimands for overall survival (not an exhaustive list)

	Estimand 1	Estimand 2
Scientific question: does experimental therapy prolong	... survival regardless of crossover or new therapies	… survival in patients who did not cross-over
Population	Targeted indication	Targeted indication
Variable	OS	OS
Intercur. event: cross-over to experimental therapy	Treatment Policy	Exclude switchers
Intercur. event: switch to new anticancer therapy excl. cross-over	Treatment Policy	Treatment policy
Population-level summary	Hazard ratio	Hazard ratio
Analysis	Estimate HR using Cox model and reported survival times	Estimate HR using Cox model excluding patients who switched
Additional data collection	--	Indicator for treatment switch

Note: caution to use Estimand 2: breaks down randomization and potentially biased

Several estimands for overall survival (not an exhaustive list)

	Estimand 1	Estimand 2	Estimand 3
Scientific question: does experimental therapy prolong	... survival regardless of crossover or new therapies	… survival in patients who did not cross-over	... survival in patients while they remained on randomized treatment or no treatment
Population	Targeted indication	Targeted indication	Targeted indication
Variable	OS	OS	OS
Intercur. event: cross-over to experimental therapy	Treatment Policy	Exclude switchers	While on treatment
Intercur. event: switch to new anticancer therapy excl. cross-over	Treatment Policy	Treatment policy	Treatment policy
Population-level summary	Hazard ratio	Hazard ratio	Hazard ratio
Analysis	Estimate HR using Cox model and reported survival times	Estimate HR using Cox model excluding patients who switched	Estimate HR using Cox model censoring survival time at the time of switch
Additional data collection	--	Indicator for treatment switch	Indicator for treatment switch, verification that no additional treatment had started

Note:
Estimand 3
Informative censoring

Several estimands for overall survival (not an exhaustive list)

	Estimand 1	Estimand 2	Estimand 3	Estimand 4
Scientific question: does experimental therapy prolong	... survival regardless of crossover or new therapies	… survival in patients who did not cross-over	... survival in patients while they remained on randomized treatment or no treatment	... survival had cross-over not occurred and regardless of new therapies
Population	Targeted indication	Targeted indication	Targeted indication	Targeted indication
Variable	OS	OS	OS	OS
Intercur. event: cross-over to experimental therapy	Treatment Policy	Exclude switchers	While on treatment	Hypothetical
Intercur. event: switch to new anticancer therapy excl. cross-over	Treatment Policy	Treatment policy	Treatment policy	Treatment Policy
Population-level summary	Hazard ratio	Hazard ratio	Hazard ratio	Hazard ratio
Analysis	Estimate HR using Cox model and reported survival times	Estimate HR using Cox model excluding patients who switched	Estimate HR using Cox model censoring survival time at the time of switch	Estimate HR using RPSFT and re-calculate survival times based on time spent on experimental treatment
Additional data collection	--	Indicator for treatment switch	Indicator for treatment switch, verification that no additional treatment had started	Start and stop dates on experimental therapy for patients who switched

Note: For each estimand, analysis approach relies on different assumptions. This is important to define and discuss those assumptions with clinicians

A hypothetical estimand

A. Population

Targeted indication*: 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

e.g. Crossover to experimental therapy in control arm patients: survival time will be re-calculated based on time spent on experimental therapy using RPSFT *and*

New antineoplastic therapy with the same class of drugs as experimental arm: follow treatment policy approach and not account for it

Other approach: i.e. IPCW

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

Conclusions

- Addendum aims to bring more transparency around
  - connection of trial objective to estimand and estimator,
  - bias-variance trade-off of a given estimator,
  - handling of «missing» data,
  - interpretation of trial results and added value of drugs.
- More **dialogues** anticipated between all **stakeholders** ensuring key questions understood and addressed in study design and study conduct (e.g. data collection).
- Reduce overall number of (unfocused) analyses.
- Addendum has potential to change the way we design and analyze trials.
- **Leadership opportunity** for statisticians that are able to connect clinical to statistical questions.
- Streamline planned sensitivity/supplemental analysis and reduce overall number of (unfocused) analyses.

Current status and future outlook

- Preparation of the position paper with the estimands, strategies for handling intercurrent events, recommendations on 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

Thank you!

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