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

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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

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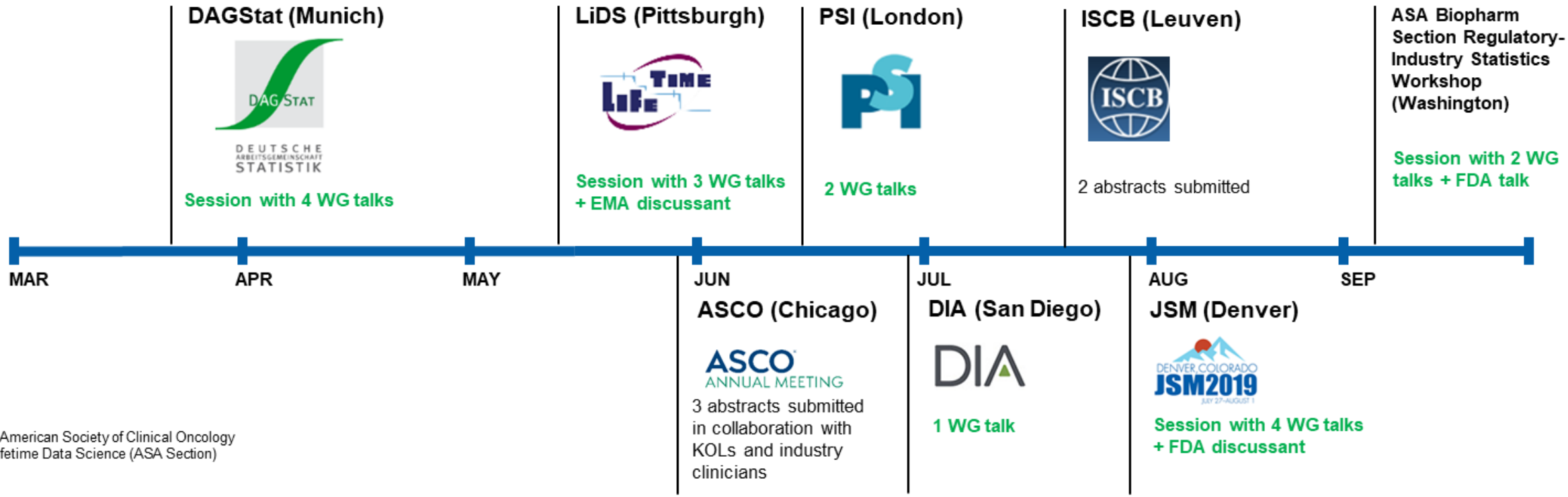
Estimands in Oncology WG
Communication plan for 2019

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

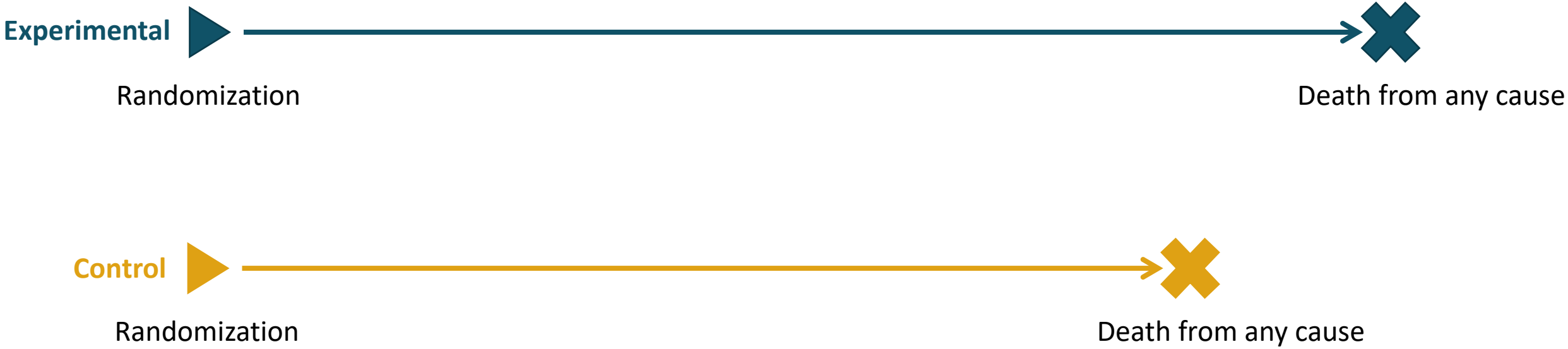


ASCO: American Society of Clinical Oncology
LiDS: Lifetime Data Science (ASA Section)

Treatment switching subteam

- Viktoriya 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



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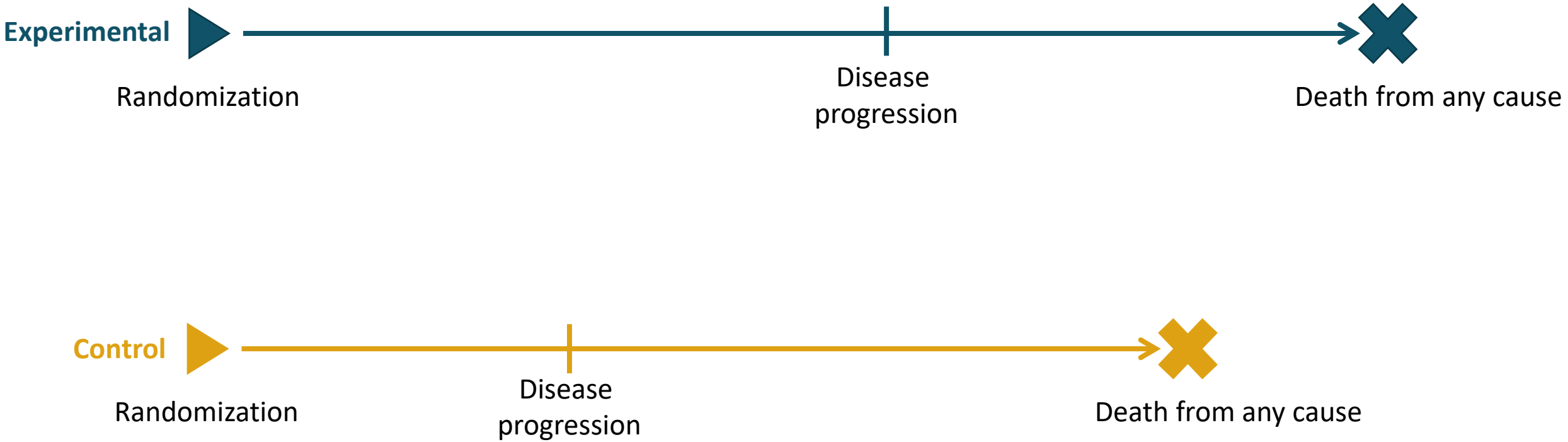
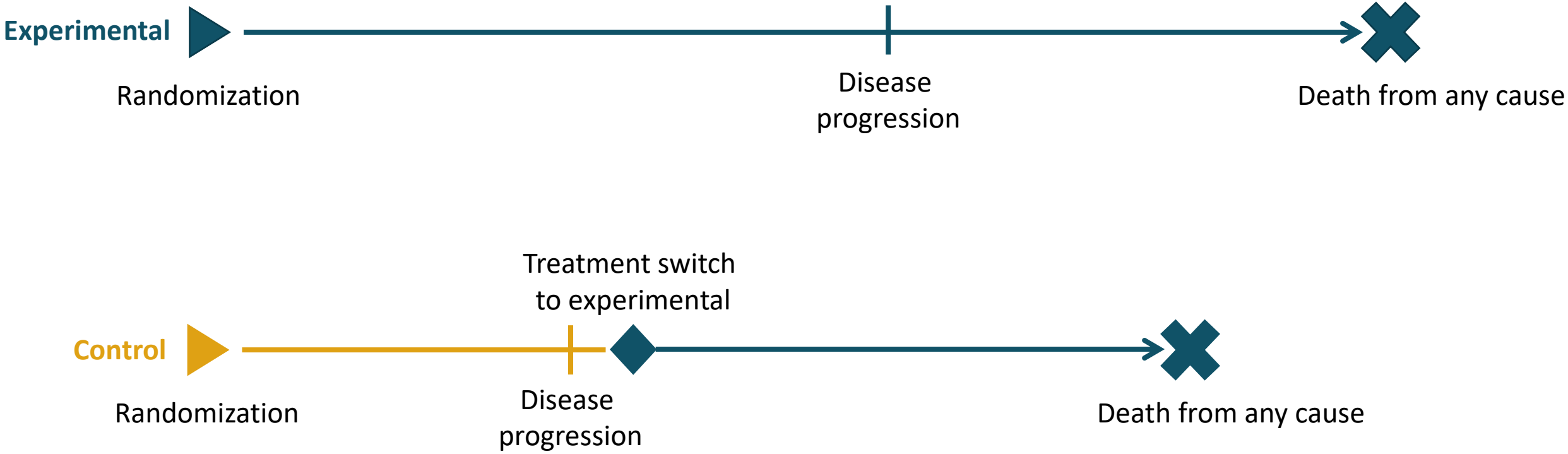
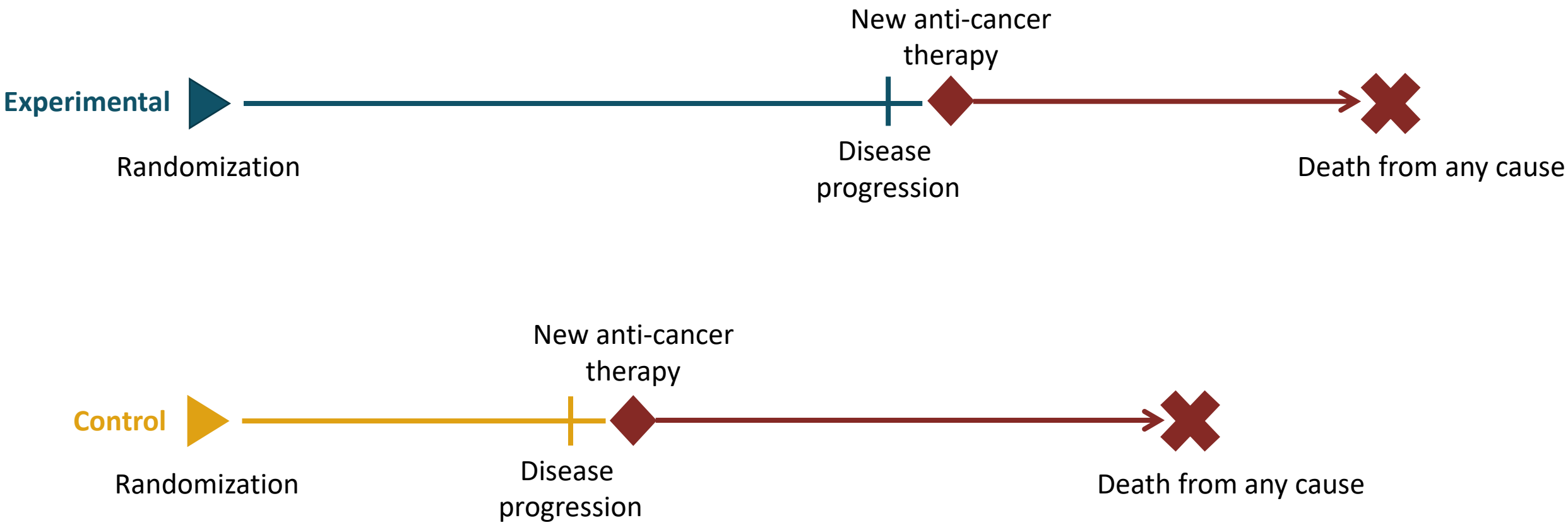
Disease progression often precedes death



Disease progression may allow initiation of experimental therapy



… or a start of new anti-cancer therapy



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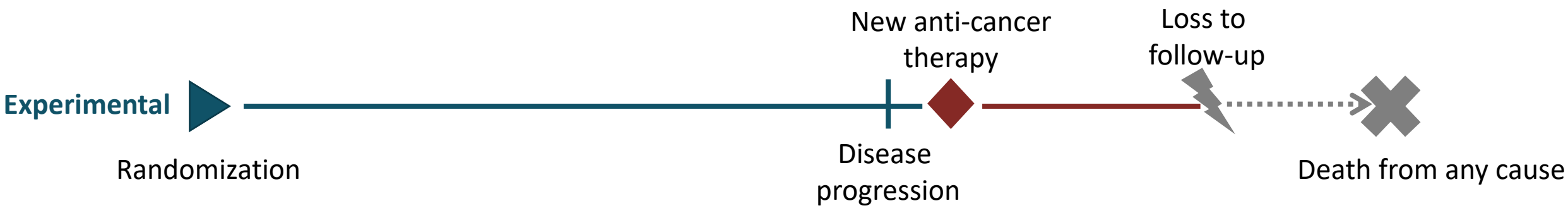
How about events that are not observed?



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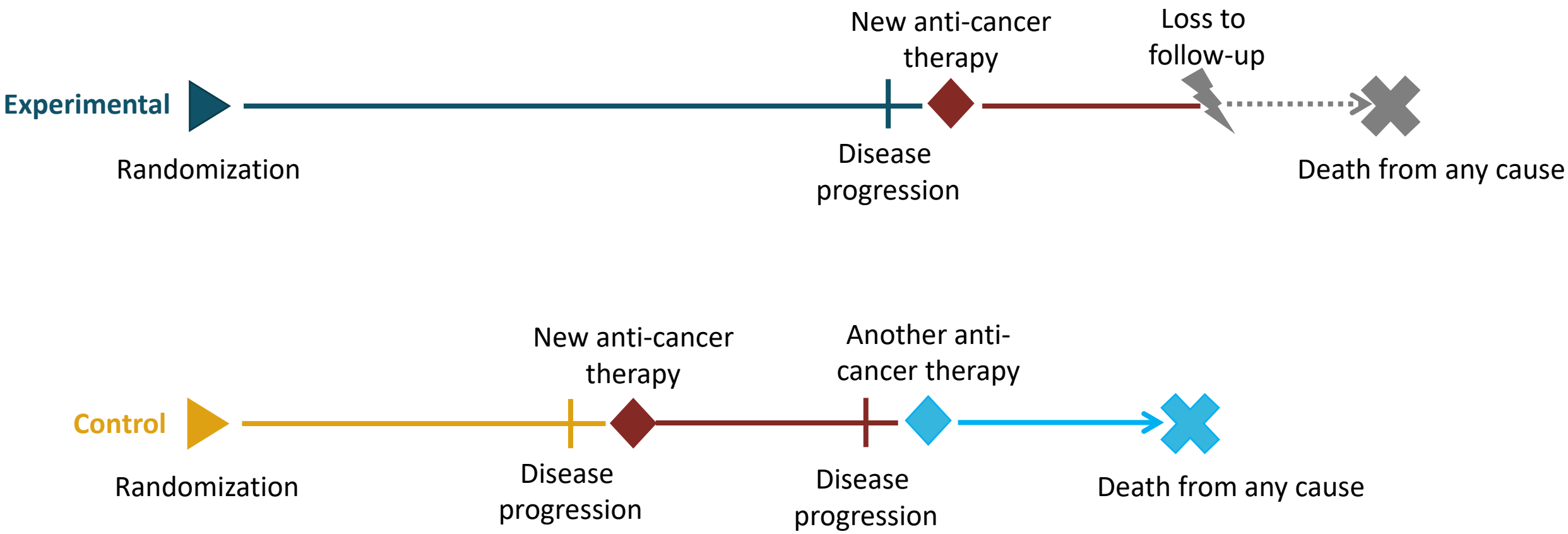

… or observed after a sequence of therapies?

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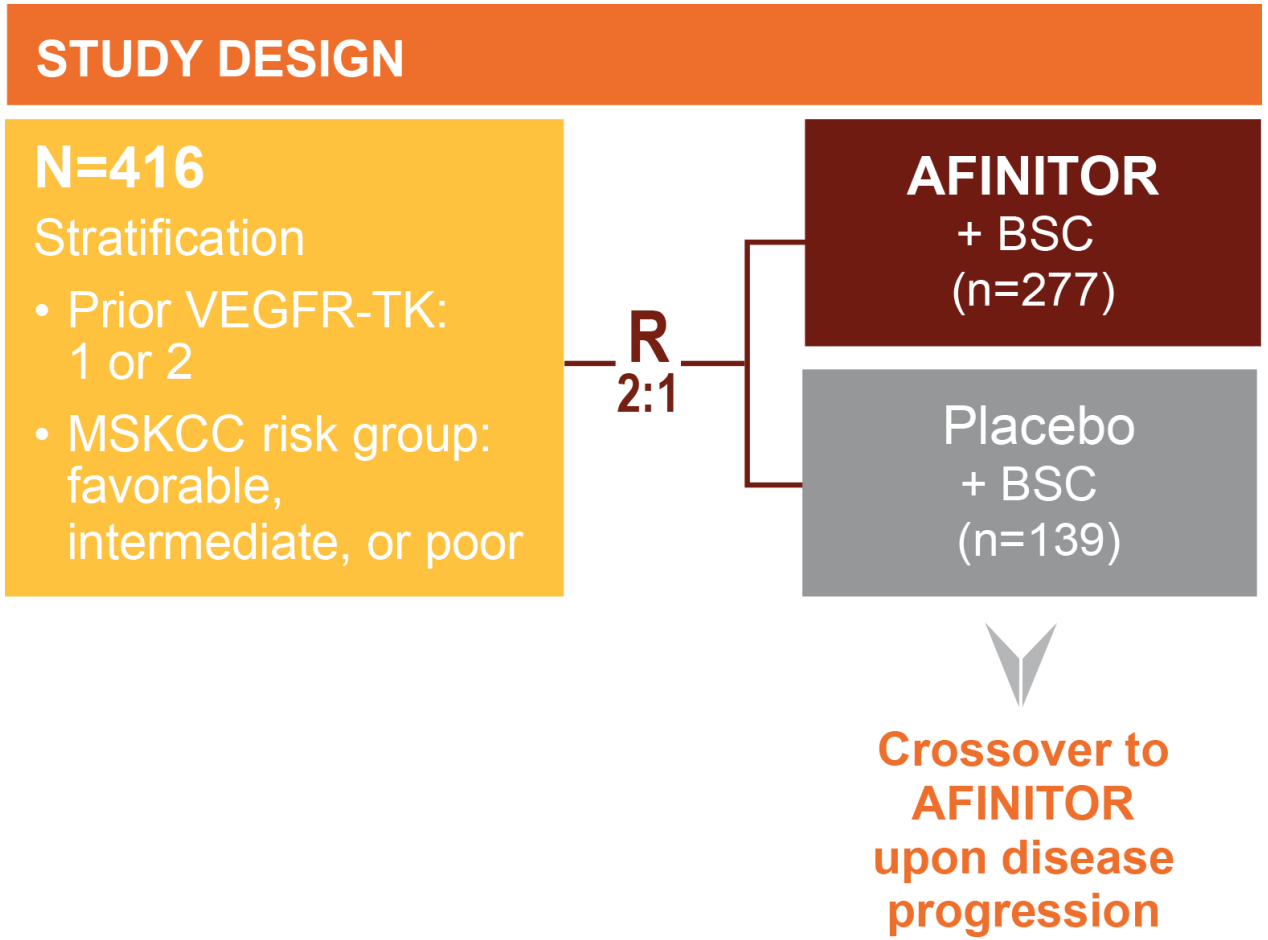
Example: study RECORD-1

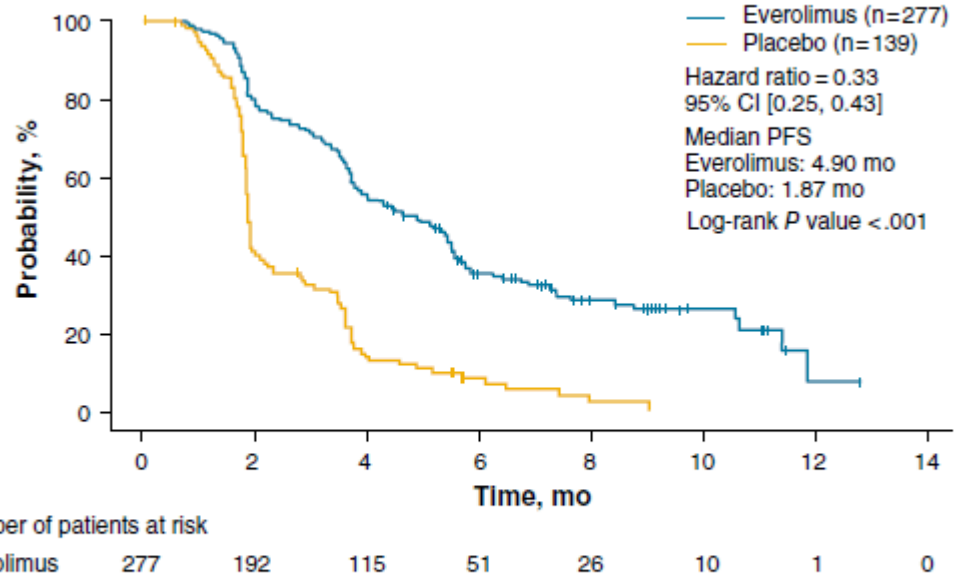
- Phase III study of everolimus in metastatic renal cell carcinoma Motzer et al (2008, 2010)
  - Double-blind, multicenter study with patients randomized to receive either everolimus (n = 277) or placebo (n = 139)
  - Primary endpoint – Progression-free survival defined as time from randomization until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



Number of patients at risk

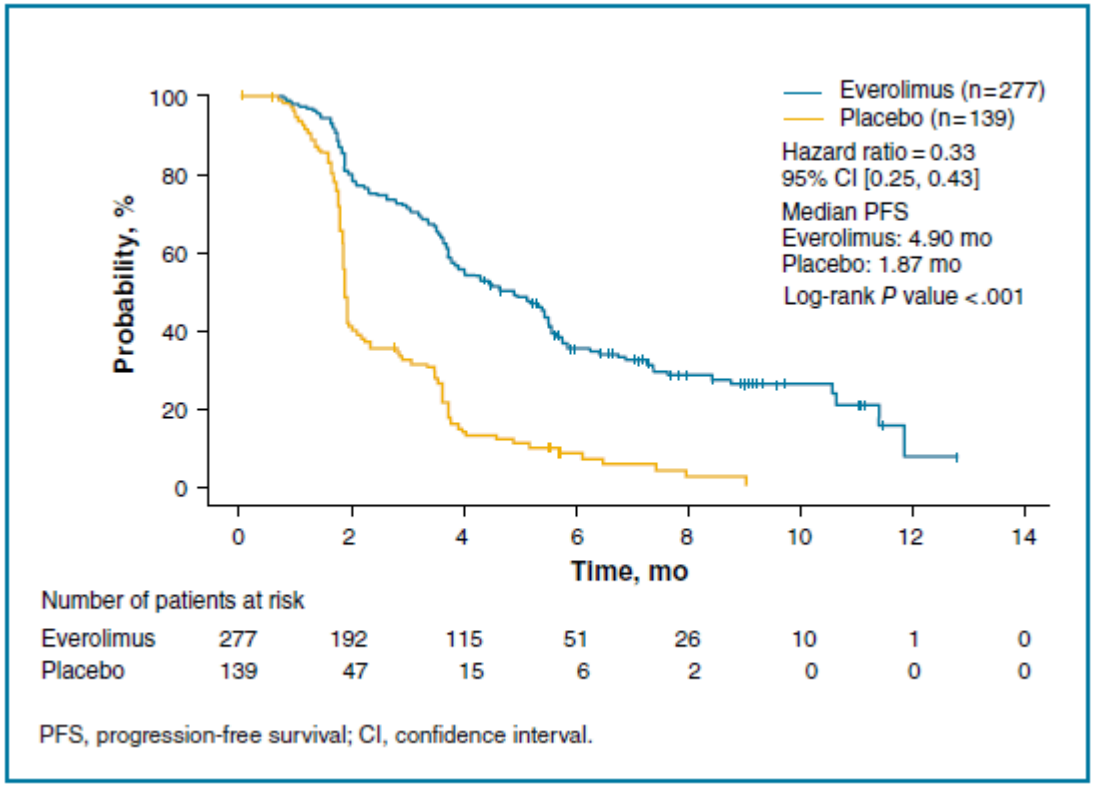
Everolimus	277	192	115	51	26	10	1	0
Placebo	139	47	15	6	2	0	0	0

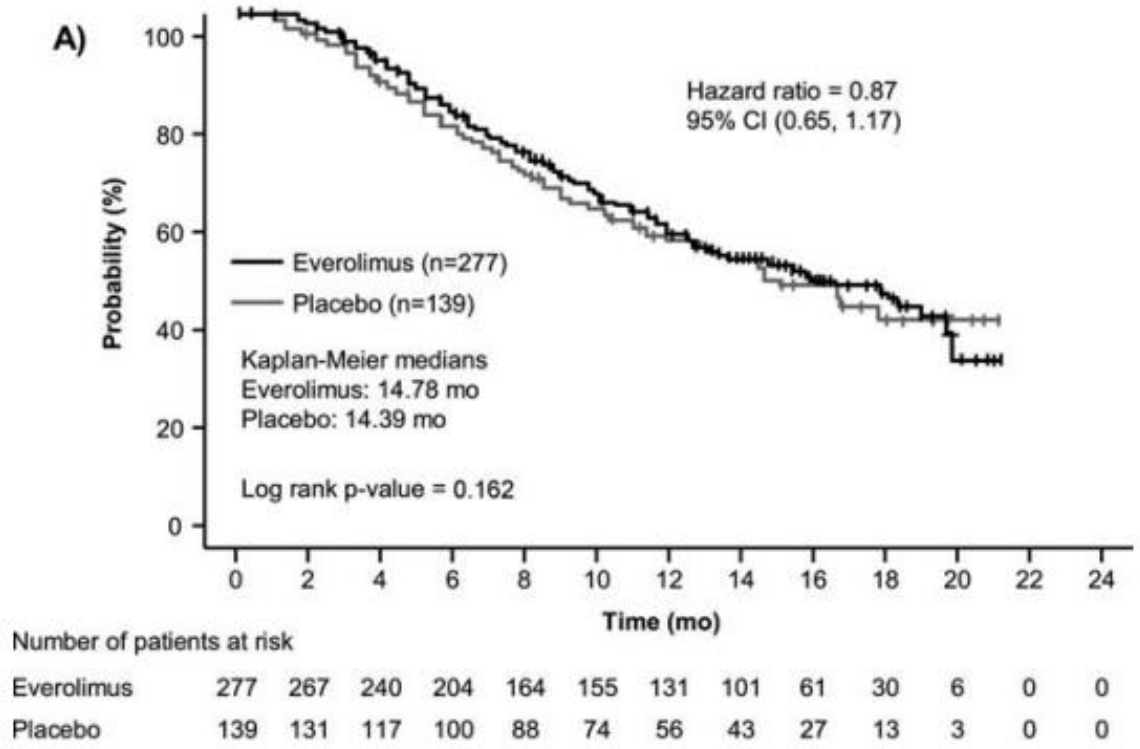
PFS, progression-free survival; CI, confidence interval.

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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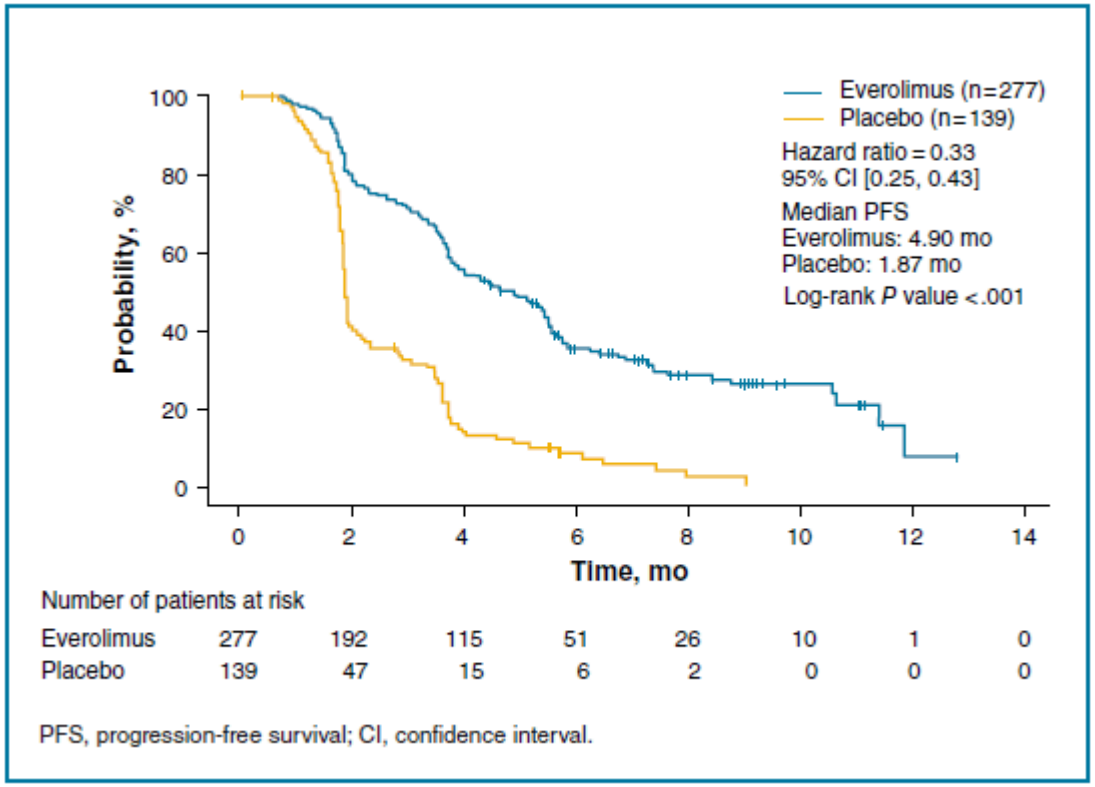

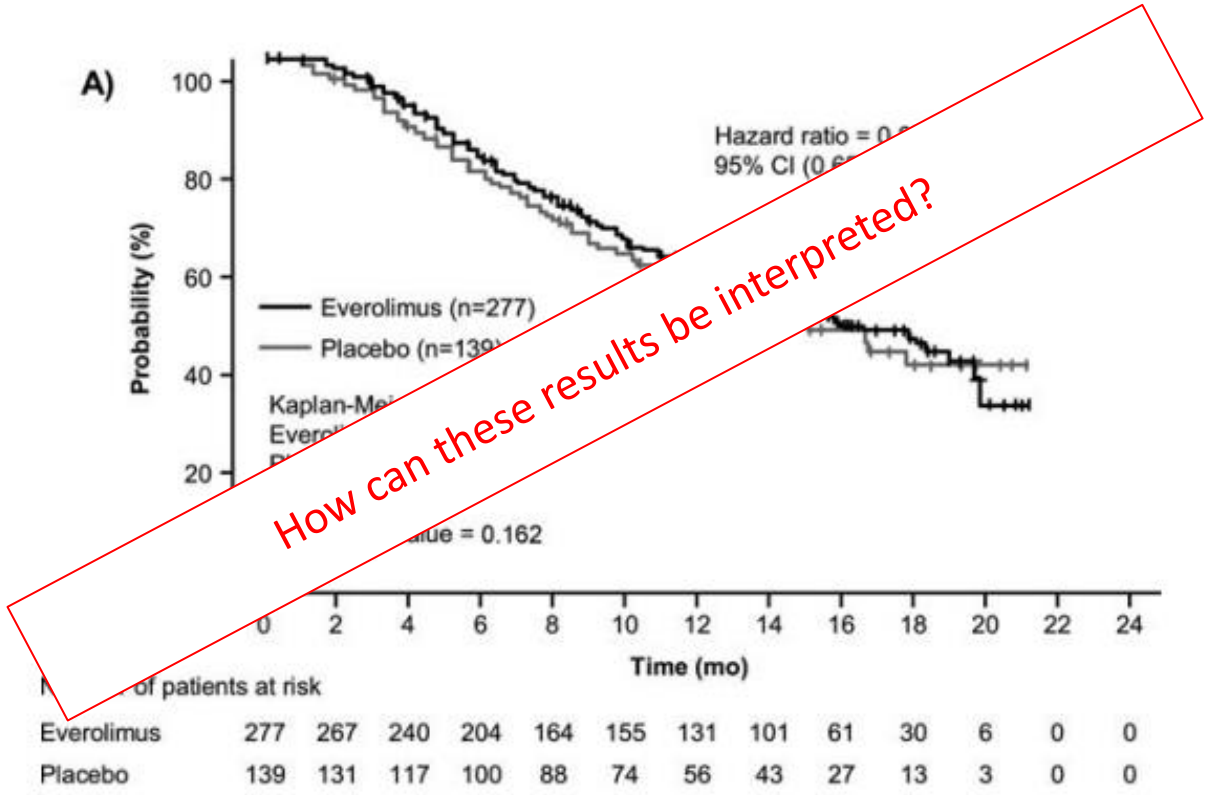

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Our focus

- 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 prolongs survival …	… regardless of crossover or new therapies
Population	All randomized patients
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 prolongs survival …	... regardless of crossover or new therapies	… in patients who did not cross-over
Population	All randomized patients	All randomized patients excluding patients who cross-over
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

Several estimands for overall survival (not an exhaustive list)

	Estimand 1	Estimand 2	Estimand 3
Scientific question: does experimental therapy prolongs survival ...	... regardless of crossover or new therapies	… in patients who did not cross-over	... in patients while they remained on randomized treatment or no treatment
Population	All randomized patients	All randomized patients excluding patients who cross-over	All randomized patients
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

Several estimands for overall survival (not an exhaustive list)

	Estimand 1	Estimand 2	Estimand 3	Estimand 4
Scientific question: does experimental therapy prolongs survival ...	... regardless of crossover or new therapies	… in patients who did not cross-over	... in patients while they remained on randomized treatment or no treatment	... had cross-over not occurred and regardless of new therapies
Population	All randomized patients	All randomized patients excluding patients who cross-over	All randomized patients	All randomized patients
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

A hypothetical estimand

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

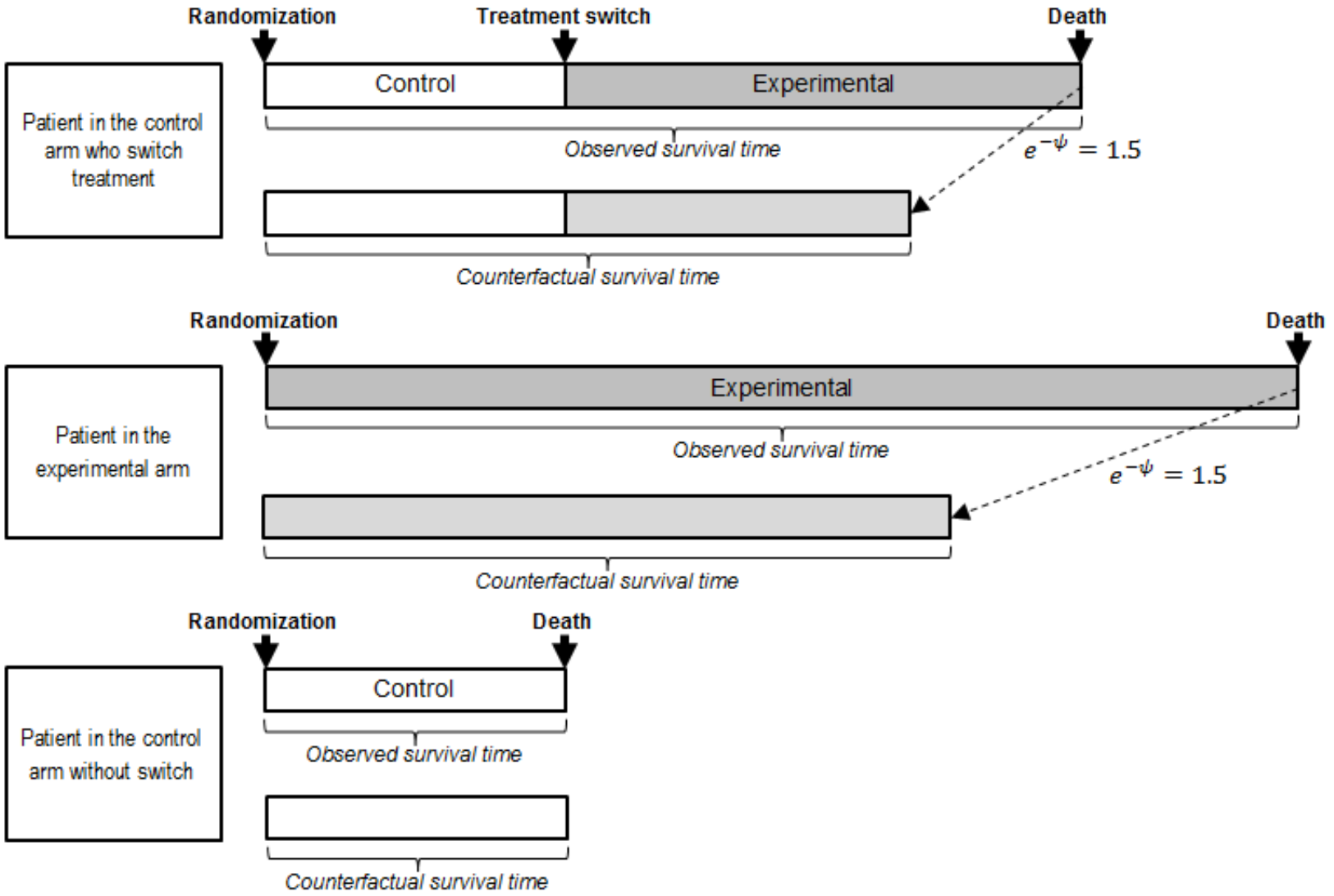
New antineoplastic therapy with the same class of drugs as experimental arm: follow treatment policy approach and not account for it

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

Observed and counterfactual survival times



- 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.

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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)

Current status and future outlook

- 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

References

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