Estimands in oncology

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What is specific to oncology?

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Time-to-event endpoints.

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Inertia?

"DFS" in adjuvant trials

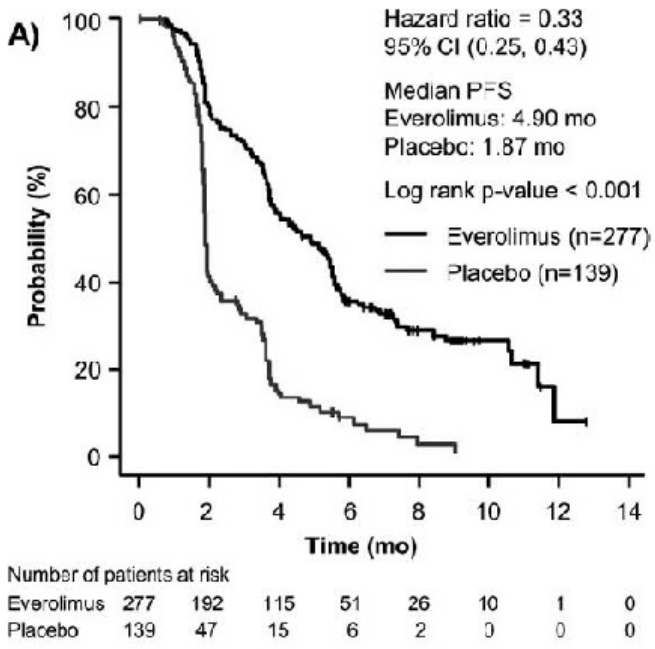
Table 1. Example of Inconsistent Definitions of Disease-Free Survival

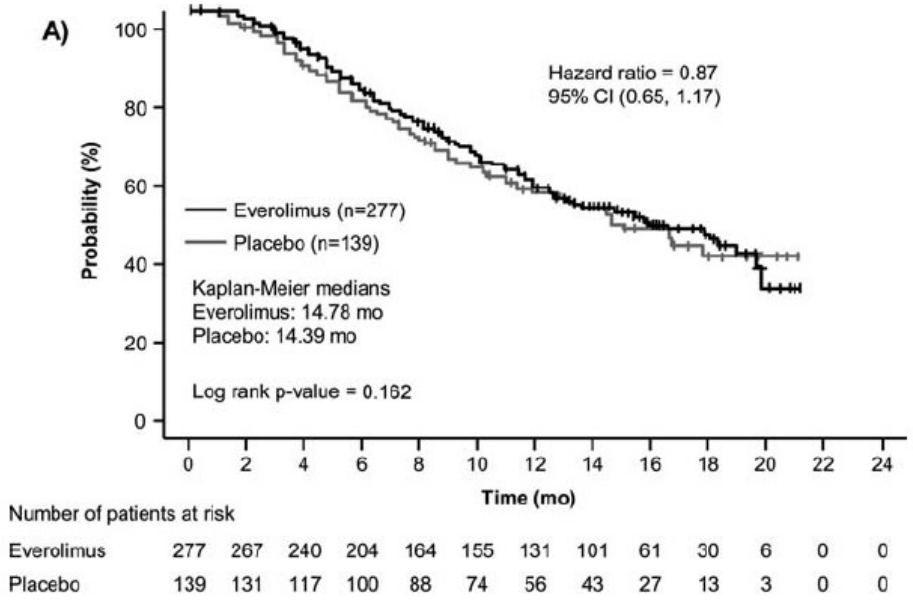
Trial	Local/Regional Recurrence	Distant Metastasis	Death From Any Cause	Invasive Contralateral Breast Cancer	Second Primary Invasive Cancer (nonbreast)	Ipsilateral DCIS	Contralateral DCIS	Ipsilateral LCIS	Contralateral LCIS
BIG 1-98[4]	X	X	X	X	X				
MA-17[1]	X	X		X		X	X	X	X
ATAC[2]	X	X	X	X		X	X		
IES[3]	X	X	X	X					
ARNO[5]	X	X		X					

NOTE: Event-free survival used by ARNO.
Abbreviations: DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; BIG, Breast International Group; MA, National Cancer Institute of Canada Clinical Trials Group MA-17; ATAC, Arimidex, Tamoxifen Alone, or in Combination; IES, Intergroup Exemestane 031; ARNO, Arimidex, Nolvadex 95 Study.

Hudis et al. (2007)

Treatment switching





RECORD-1: Motzer et al. (2010).

- Some trials **X-over** from control to experimental arm upon PD.
- Switching from control to drugs with same MoA in **other trial** $\Rightarrow$ I/O therapies.

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).

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"ITT" effect really what we are interested in?

What do these findings have in common?

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They can all be anticipated!

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Clear formulation of
clinical trial objective is key.

Impact

Pre-addendum:

- "ITT" primary.
- Attempts to "rescue" failed OS with ad-hoc treatment switching analyses.
- Likely not all data collected that "proper modelling" requires.
- Post-hoc.

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Post-addendum:

- Estimand of interest: **hypothetical**.
- EMA Q&A document that opens door to such analyses **IF**:
  - **Preplan**.
  - Ensure **quality** throughout protocol, proper data collection, and analysis.
- **Assumptions** transparent.

COVID-19: Estimand framework allowed for rapid assessment of impact.

Degtyarev et al. (2020): *Assessing the impact of COVID-19 on the objective and analysis of oncology clinical trials - application of the estimand framework*, **available online**.

"ITT" not always effect of interest.

Time invested at design stage **pays off** later.

Estimand framework = **opportunity**

- for better designed trials,
- transparent assumptions,
- **leadership of statisticans**.

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Also in oncology.

Industry working group on estimands in oncology:

- Founded November 2018.
- European special interest group "Estimands in oncology", sponsored by PSI and EFSPI.
- ASA scientific working group of ASA biopharmaceutical section.
- **37** members representing **22** companies.
- Regularly interacts with **7 health authorities**.

www.oncoestimand.org

Thank you for your attention.

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Backup slides

General implications of the addendum

Broader impact

Aligning drug developers and regulatory bodies' expectations for target treatment effect **upfront** has potential to give:

- More **meaningful** descriptions of treatment effects for licensing and prescribing decisions.
- Clinical trials with designs that are **aligned to agreed objectives**.
- Increased **transparency** with respect to data analysis and inference.
- More **predictable** regulatory assessment procedures.
- More **flexibility** from regulators.
- **Reduction in total number of analyses** (primary + secondary + sensitivity).
- Clear language to describe and discuss different estimands required by different stakeholders.
- **Shift of resources** from analysis / filing to design.

Framework and language

- Promote alignment between trial objectives, design, data collection, conduct, analysis and inference.
- Promote understanding that trial objectives cannot be translated into estimands without reflecting how potential intercurrent events are addressed in scientific question of interest.
- Promote discussion of different strategies to handle intercurrent events to identify and describe treatment effects that reflect scientific questions of interest.
- Define treatment effect of interest - before a trial is designed and conducted - that is relevant in clinical practice.
- Highlight importance of considering whether main analysis provides estimate which is reliable for inference.
- Re-define missing data.
- Re-define sensitivity analysis and regulatory assessment of robustness.
- Introduce supplementary analysis as any other analysis to fully investigate and understand trial data.

Impact on documentation

Protocols	Study population	Derive population from estimand definition
	Study intervention	Derive intervention from estimand definition, including rescue medicine
	Discontinuation	Derive discontinuation actions from intercurrent event strategies in estimand definition
	Statistical considerations	Hypothesis, analysis sets, sample size, endpoints follow from estimand definition Separate sensitivity from supplementary analyses.
Additonally for SAPs	Sample Size	Optionally provide (even) more details how intercurrent events are taken into account in sample size computation
Additonally for CSRs	Discontinuation	Tabulate observed intercurrent events.
	Changes in Planned Analyses Prior to Unblinding or DB lock	Discuss how intercurrent events that were not foreseen at the design stage, or identified during the conduct of the trial, were handled. Discuss not only the choices made for the analysis, but the effect on the estimand.

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Post-addendum: **Principal stratum** estimand $\Rightarrow$ meaningful estimand, assumptions transparent.

Doing now what patients need next

R version and packages used to generate these slides:

R version: R version 4.0.0 (2020-04-24)

Base packages: stats / graphics / grDevices / utils / datasets / methods / base

Other packages:

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