Statistical, clinical and ethical considerations when minimizing confounding for overall survival in cancer immunotherapy trials

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BBS / PSI CIT event 15-June-2017, Basel

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Non-Proportional Hazards (NPH): What does It mean?

- Most popular methods for analysis of time to event trials:
  - log-rank test (testing) – Proof of efficacy
  - Cox regression (estimation) – Quantify treatment effect
- Hazard ratio, naive median differences and milestone survival differences are standard way of summarizing treatment effect
- Are they appropriate summary measures when the treatment effect is not constant over time (eg NPH situation)?

Non-Proportional Hazards (NPH): What does It mean?

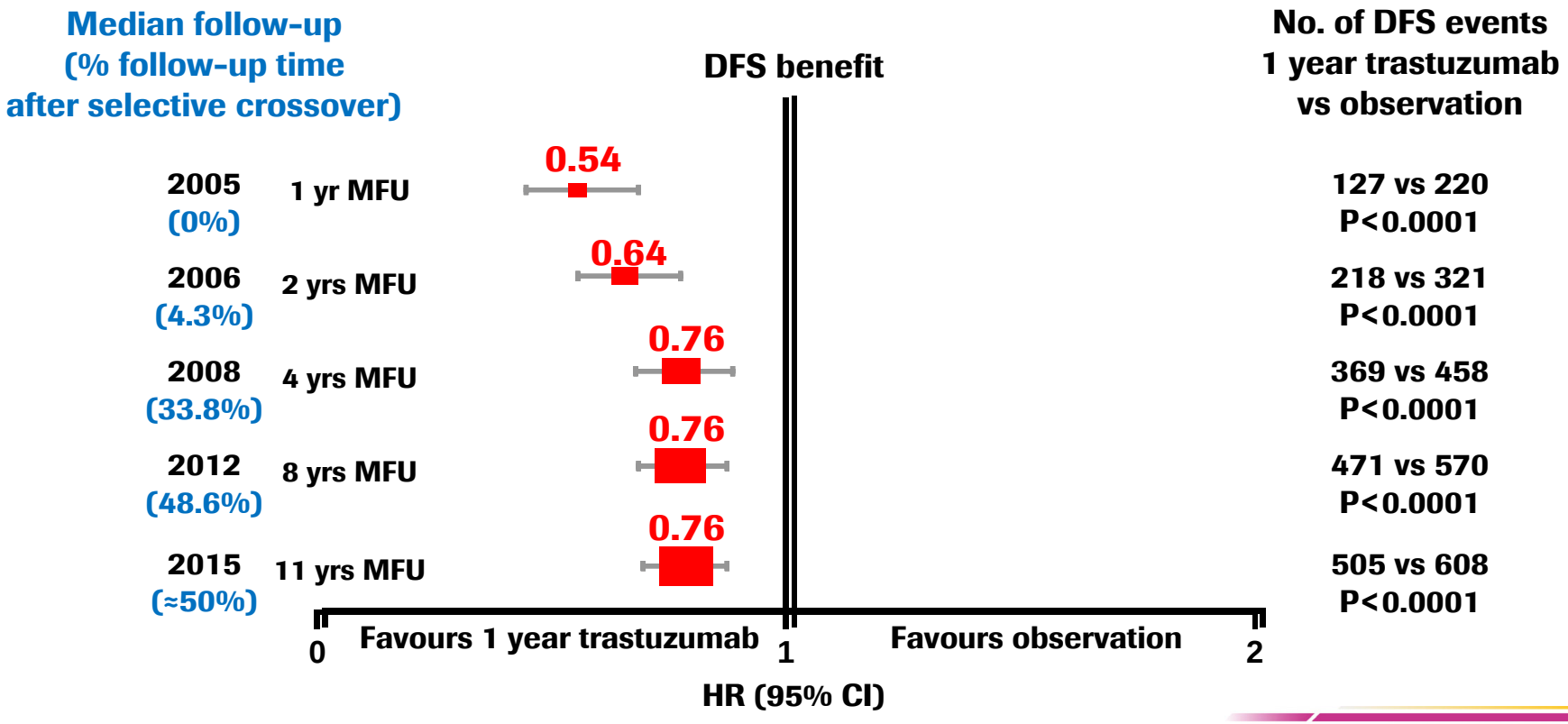
- **Different types of NPH**
  1. Delayed treatment effect
  2. **Diminishing treatment effect (eg treatment switch control arm)**
  3. Crossing Hazard
  4. Long term survivor (“cure” / long-term survival rate)
  5. Subgroup effect: NPH driven by particular subgroup

- Combination of different types is possible (e.g., Type 4 can occur in combination with 1)

Treatment switch situation with CIT

- For many CIT trials, patients can only be enrolled if they **did not obtain previous CIT**
- Hence only control arm patients from e.g. a first line CIT trial could participate in subsequent line CIT trials, impacting on the likelihood to capture the benefit of CIT (if it exists).
- For **blinded** trials (mainly combination trials), this issue may become an ethical dilemma, as keeping the blinding prevents control arm patients to access **experimental** clinical CIT studies

Illustrative example: HERA trial (non CIT)



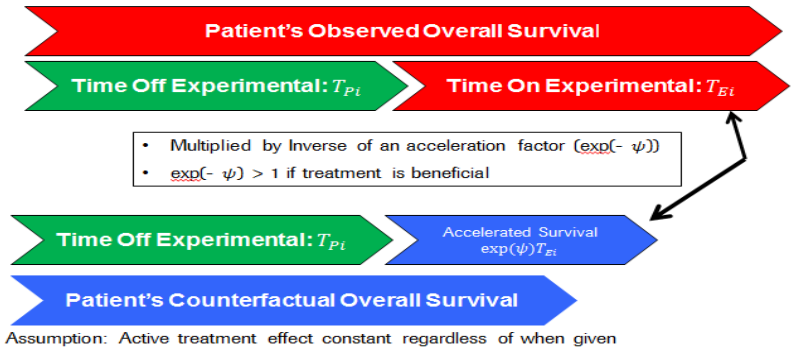
Adjust for switch?

1) **[Naïve] Censoring patients** at time of switch (biased decision to switch is usually not independent of prognosis)

2) **Inverse Probability Censoring Weighting (IPCW)**
   a) Creates a scenario of **missing follow-up data** by censoring the follow-up of each patient at the time of crossover
   b) BUT patients are weighted according to their probability to cross-over
   c) A patient will be assigned a weight of > 1 if other patients with similar characteristics crossed over to "re-create" the population that would have been observed without crossover
   d) Weights are based on factors affecting a patient's decision to cross over or prognostic of survival

   Challenge: Assumes no unmeasured confounders (i.e. everything predicting switch / OS is collected)

3) **Rank-preserving structural failure time model (RPSFT)**
   a) It works by "re-creating" the survival time of patients, as if they had never received experimental treatment, i.e. patient who switches treatment has a **counterfactual event time** – the time-to-event if no experimental treatment had been received



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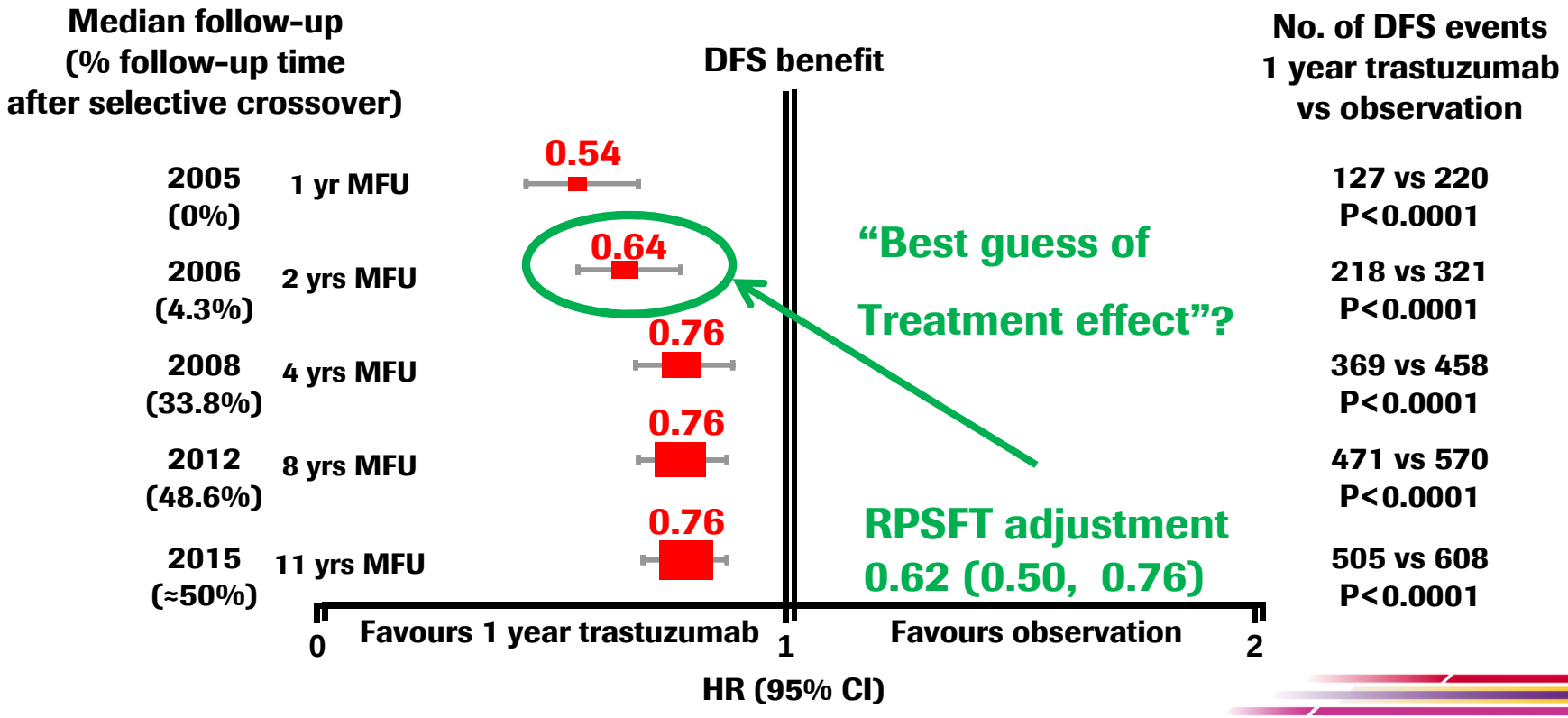

Wait a minute – What is the estimand?

- **Intercurrent events:** Causing missing information as to the situation when patients would have adhered to randomized treatment and to assessment as per protocol until end of trial
- Change in protocol treatment: **Treatment switching**
- **Hypothetical estimand:** Effect “when no control patient would have switched to experimental treatment”
- For OS, always subsequent therapies
  - Hence “non-adherence” really intercurrent events?
- In such cases intervention effect: **Treatment policy estimand**

Wait a minute – What is the estimand?

- Current CIT landscape, deal with **experimental** CIT treatments in subsequent lines
- So back to: **Hypothetical estimand?**
- OR avoid switch (keep blinding to avoid entering later line CIT trials)
  - **“Clear” estimand?**

- **Remark:** Complicated if we have different CIT approvals in later lines in different regions (eg US vs EU)
  - “Clear”/hypo estimand relevant for one region, treatment policy estimand for other region(s)

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Effect magnitude of endpoints with CITs

Study name	Indication	Control	Experimental	HR PFS	HR OS	ORR
Checkmate 017	NSCLC 2L	Docetaxel	Nivolumab	0.63 (0.48,0.83)	0.62 (0.48, 0.81)	9% vs 20%
Checkmate 057	NSCLC 2L non-sq	Docetaxel	Nivolumab	**0.92** (0.77,1.11)	**0.72** (0.60, 0.88)	19% vs 12%
CHECKMATE 026	NSCLC 1L PDL1+ enriched	Chemo	Nivolumab	1.15 (0.91, 1.45)	1.02 (0.80,1.30)	
KEYNOTE 010	NSCLC 2L	Docetaxel	Pembrolizumab	**0.88** (low dose) 0.79 (high dose)	**0.71** 0.61	9% vs 18% 9% vs 18%
KEYNOTE 024	NSCLC 1L PDL1 enriched	Platinum-containing chemo	Pembrolizumab	0.50 (0.37,0.68)	0.60 (0.41,0.89)	28% vs 45%
POPLAR	NSCLC 2L	Docetaxel	Atezolizumab	**0.94**	**0.73**	12% vs 19%
OAK	NSCLC 1L	Docetazel	Atezolizumab	**0.95** (0.62,0.87)	**0.73** (0.62,0.87)	13% vs 14%

Remark: Suggestive that PFS may not be the optimal (most sensitive) endpoint?

OS only reliable EP? – Trial implications

- For many CIT trials, patients can only be enrolled if they did not obtain previous CIT
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OS only reliable EP? – Trial implications

Scenario	Percentage of switchers (after PFS)	Resulting diminished power
No switch	**0%**	–
Low Switch	**30%**	**-16%**
Medium Switch	**50%**	**-33%**
High Switch	**80%**	**-58%**

Summary impact on OS

- OS results likely heavily impacted by treatment switch of control arm patients to experimental next-line CIT trials (significant power decrease by 16-58%)
- Study would be underpowered for co-primary endpoint OS

OS only reliable EP? – Trial implications

Prohibiting unblinding -> "Clear" estimand

1. Affects the ability of patients/physicians to determine eligibility for participation in subsequent-line **experimental** CIT trials
2. Does not affect options for treatment with **standard-of-care agents**
3. Preserves the ability of the CIT study to detect OS and hence provide a new treatment option

Permitting unblinding -> Hypothetical or treatment policy estimand?

1. Compromises ability of the CIT study to detect OS (due to imbalances in subsequent line-therapies between the two arms), potentially negating a future treatment option
2. Maximizes the treatment options (including experimental treatment options) available for each individual patient

Other CIT specific consideration…

1. Treatment beyond progression ("pseudo-progression")
   - Unethical to treat blinded (placebo &chemo) after RECIST progression
   - Pseudo-progression not entirely objective assessment, cannot be fully controlled (eg may be misused to determine eligibility for subsequent CIT trials)

Interactions with health authorities

Questions:

- (1) blinded? -> *“Clear” estimand*
- (2) if not adjust model-based adjustment for treatment switch -> *Hypothetical estimand*
  - Inverse Probability Censoring Weighting (IPCW)
  - Rank-preserving structural failure time model (RPSFT)

General feedback:

- “… but final decision remains with sponsor…”
- Neither FDA nor EMA agreed to use any currently available methods to “adjust” for treatment switch as primary analysis for OS -> *not hypothetical estimand*

Interactions with external ethics consultants

- **General comment:** Clinical trials are conducted in general to investigate *experimental treatments*. Enrolled patients do no have a guaranteed benefit for themselves, but potentially help future patients.
- **Trial shall be blinded,** but that the *Informed Consent Form* shall clearly state that participation in the trial may prohibit patients to join experimental CIT trials in subsequent lines.
- **Rational:** Ethical requirements that
  - clinical research must lead to improvements in health or advancements in generalizable knowledge
  - clinical research must produce reliable and valid data that can be interpreted.
  - Invalid research includes underpowered studies and studies with biased endpoints

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Outlook

- One may observe more and more approvals of CITs in a shorter time frame (eg through breakthrough and AA in US, PRIME and CMA in EU…)
- What if different CITs (eg PD-1 after PD-L1…) are used across lines, is there a hope to still being able to measure benefit in a trial?
  - PFS for combo sensitive? We need to await data…
  - OS prolonged and confounded by subsequent (approved) CITs…
- Other endpoints?
  - Immune RECIST since clinical response to immune therapies can manifest after conventional progressive disease (PD) – “pseudoprogression”
  - Tumor growth kinetics as surrogate for response to check-point inhibitors?

Conclusions

- Blinding in CIT trials is a controversial topic
- Important to link the discussion to precise definition of the treatment effect that your clinical trial will estimate (addendum of ICH E9)
  - Facilitates interactions with clinicians, regulators and other stakeholders
- Desire for alternative endpoints… not that easy
- **Remark:** FDA / cross-industry initiative on NPH ongoing, white paper to be expected Q4 2017 / Q1 2018

Doing now what patients need next