Estimand framework: opportunity to rethink some old (and new) problems in Oncology trials?

Evgeny Degtyarev
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Oncology clinical trials today
Advanced therapies and highly competitive environment

Immunotherapies (IO)
Clinical trials with anti-PD1/PDL1 agents:
• 1 in 2006
• 1502 in September 2017
• 2250 in September 2018

Cell therapies
New trials with CAR-T therapies:
• 13 in 2013, >100 in 2017

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Great for patients!
- durable responses
- many ongoing clinical trials

But what does it mean for clinical trials?
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- Blinding often not feasible → many open-label studies
- Patients not interested in SOC (often chemo) and withdraw consent after randomization to control arm
- Intercurrent event: Patients randomized to control, but not treated
  - Quantum-R trial (2019): 23% (vs 1.6% on investigational arm)
  - Checkmate-37 trial (2015): 20% (vs 1.5% on investigational arm)

→ Primary analysis (Overall survival in all randomized patients) not interpretable!
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- R.Pazdur, director of FDA Oncology Center of Excellence, on Quantum-R: “That is quite bothersome, I’ve been here 20 years. I haven’t seen this discrepancy of randomized-but-not-treated to this extent.”

- Possible to anticipate understanding competitive landscape and discussing intercurrent events!
  - new approaches for study design and analysis required?
Non-proportional hazards (NPH)
- already frequently observed in IO trials
- expected in ongoing and future CAR-T trials
- durable responses possibly resulting in cure rate

Suggested analyses for NPH: weighted log-rank, milestone analyses, RMST etc.
- power often used for comparison, but they all target different questions!

\( \rightarrow \) opportunity to focus on interpretation

RMST: Restricted Mean Survival Time
Checkmate-057, Borghaei (2015)
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Treatment as sequence of interventions

- Studying effect of each part vs whole sequence?

**FDA:** «study not designed to test the effectiveness of Drug A as maintenance, since there was no rerandomization prior to start of maintenance»

→ approved only as induction and consolidation therapy in US

**EMA:** «added value of maintenance therapy difficult to establish [...] clear scientific rationale for following the induction and consolidation phases by a period of maintenance therapy»

→ approved as induction, consolidation and maintenance therapy in EU
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Overall survival (OS) and treatment switching

OS usually analyzed using treatment policy strategy
- using time from randomization to death regardless of patient’s journey
- captures effect on the choice and impact of subsequent therapies
- assumption: choice of subsequent therapies after EOT reflect clinical practice

SOC: Standard of Care; EOT: End of treatment
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Overall survival (OS) and treatment switching

Drug A → EOT → SOC
SOC → EOT → Other available therapies

Smiley choice of subsequent therapies after EOT reflects clinical practice

→ Treatment policy OS estimand interpretable

SOC: Standard of Care; EOT: End of Treatment
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Overall survival (OS) and treatment switching

Drug A approved as next-line therapy after SOC

(choice of subsequent therapies after EOT reflects clinical practice)

→ Treatment policy OS estimand interpretable

SOC: Standard of Care; EOT: End of Treatment
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Overall survival (OS) and treatment switching

Drug A and drugs with the same MoA not approved as next-line therapy after SOC

Drug A (cross-over) or investigational drugs with the same MoA

ście choice of subsequent therapies after EOT does not reflect clinical practice

→ Treatment policy estimand comparing vs SOC followed by Drug A relevant? Benefit on OS without cross-over possibility more informative? (hypothetical estimand)
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Overall survival (OS) and treatment switching: misinterpretation

- Sponsors, regulators, payers criticized for approvals and pricing
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Overall survival (OS) and treatment switching: misinterpretation

- Summary of product characteristics for Nivolumab:

There was no statistically significant difference between nivolumab and chemotherapy in the final OS analysis. The primary OS analysis was not adjusted to account for subsequent therapies, with 54 (40.6%) patients in the chemotherapy arm subsequently receiving an anti-PD1 treatment. OS may be confounded by dropout, imbalance of subsequent therapies and differences in baseline factors.

→ Negative perception driven by non-significant result for treatment-policy OS estimand when subsequent therapies don’t reflect clinical practice!

- Possible to anticipate non-informative treatment-policy estimand

→ Opportunity to discuss alternatives for main OS analysis (e.g. hypothetical estimand targeted by RPSFT, IPCW etc.) and to communicate added value of approved drugs better!

RPSFT: Rank Preserving Structural Failure Time models
IPCW: Inverse Probability of Censoring Weighting
Estimands in Oncology
Need for Industry Working Group

Many other open questions requiring discussions:

- Causality for time-to-event endpoints
- Censoring
- Supplementary vs Sensitivity analyses
- Competing risks

etc.
Estimands in Oncology WG

- Purpose: common understanding and consistent definitions for key estimands in Oncology across industry
- initiated in Feb 2018, 35 members (Europe/US: 16/19) representing 22 companies
  - subteams: causal; treatment switching; censoring mechanisms; hema and solid tumor case studies
- established as EFSPi SIG (Nov 2018) and ASA Biopharmaceutical Section SWG (Apr 2019)
- collaboration with regulators from EMA, FDA, Japan, China, Taiwan and Canada
- ongoing discussions to define the scope for collaboration with academia
Conclusions

- More dialogue in future between all stakeholders about questions of interest
- Clarity in interpretation of results and discussions about added value of the drugs
- Alternative approaches to avoid non-informative treatment policy estimand if its assumption very likely to be violated
- Less analyses in future, but more value for all stakeholders!
  - Critical discussion of various rules in HA guidelines & protocol/SAP templates needed!
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