Oncology Biostatistics

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

Evgeny Degtyarev

EFSPI Workshop on Regulatory Statistics, Basel, September 24, 2019

NOVARTIS | Reimagining Medicine

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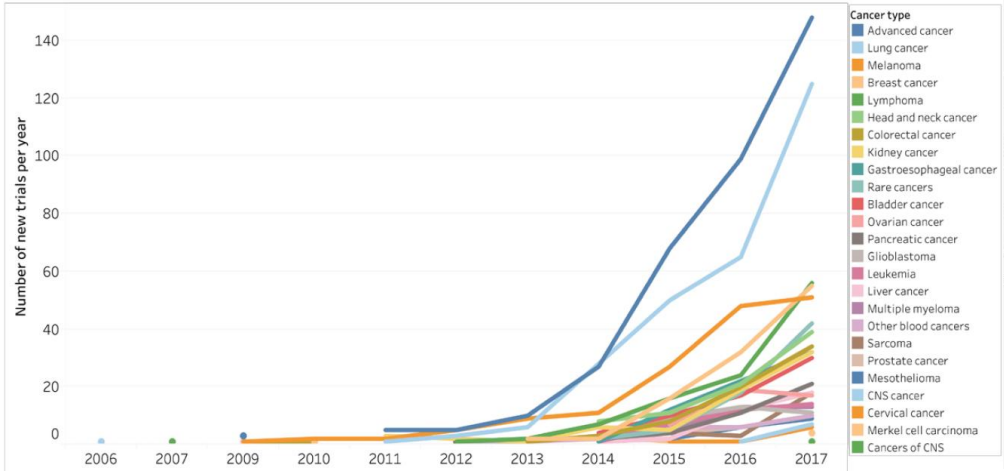
Advanced therapies and highly competitive environment

Immunotherapies (IO)

Clinical trials with anti-PD1/PDL1 agents:

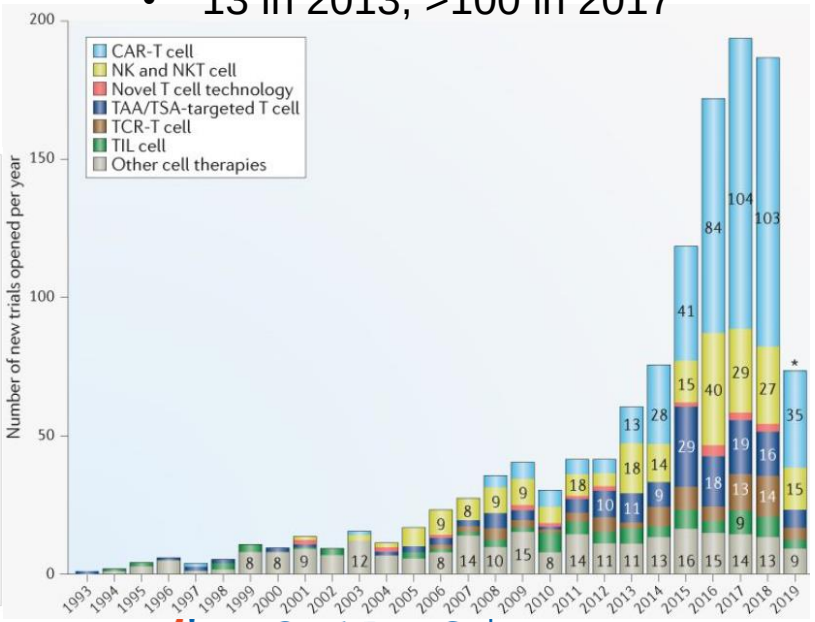
- 1 in 2006
- 1502 in September 2017
- 2250 in September 2018



Cell therapies

New trials with CAR-T therapies:

- 13 in 2013, >100 in 2017



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Jia Xin Yu et al. (2019) The global pipeline of cell therapies for Cancer, Nature Reviews Drug Discovery, Tang et al. (2018) The clinical trial landscape for PD1/PDL1 immune checkpoint inhibitors. Nature Reviews Drug Discovery volume 17, p854–855

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Advanced therapies and highly competitive environment

Great for patients!

- durable responses
- many ongoing clinical trials

But what does it mean for clinical trials?

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Advanced therapies and highly competitive environment

- 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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Advanced therapies and highly competitive environment

- 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?

https://pink.pharmaintelligence.informa.com/PS125338/Daiichis-Quizartinib-And-The-Quintessential-Pazdur-Moment;

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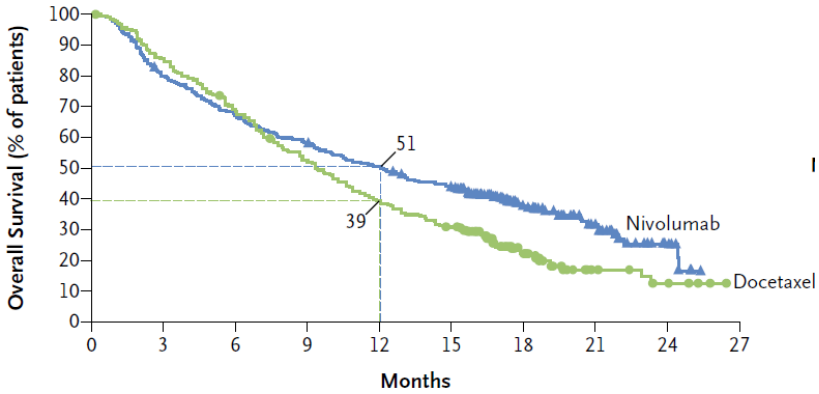
Advanced therapies and non-proportional hazards

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!

→ opportunity to focus on interpretation

RMST: Restricted Mean Survival Time

Checkmate-057, Borghaei (2015)

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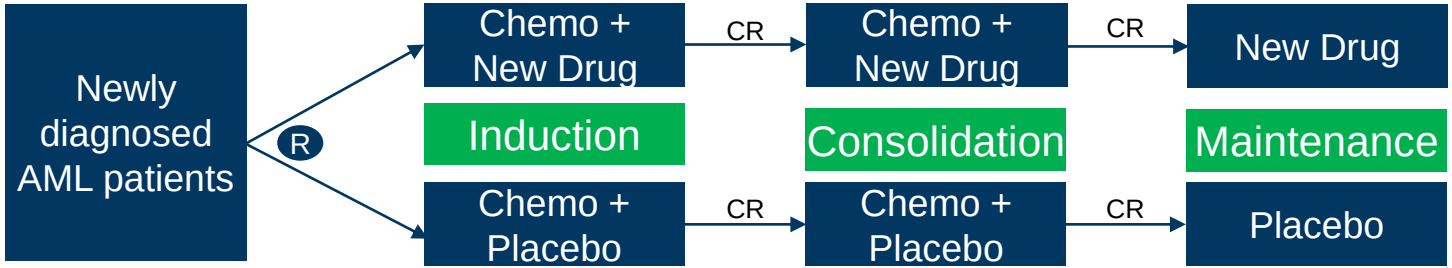
Treatment as sequence of interventions

- 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

CR: Complete Response

FDA Review: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/207997Orig1Orig2s000CrossR.pdf

EMA Review: https://www.ema.europa.eu/en/documents/assessment-report/rydapt-epar-public-assessment-report_en.pdf

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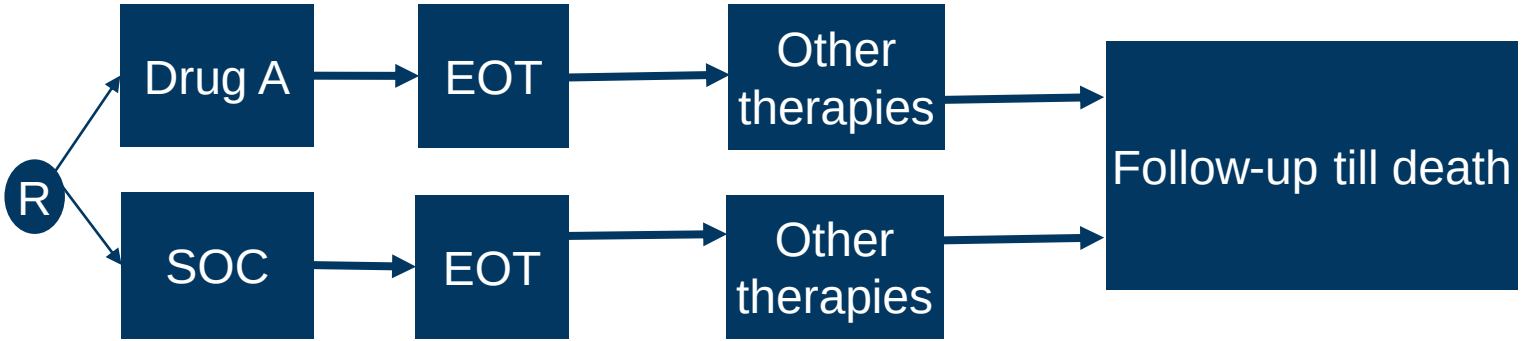
Overall survival (OS) and treatment switching



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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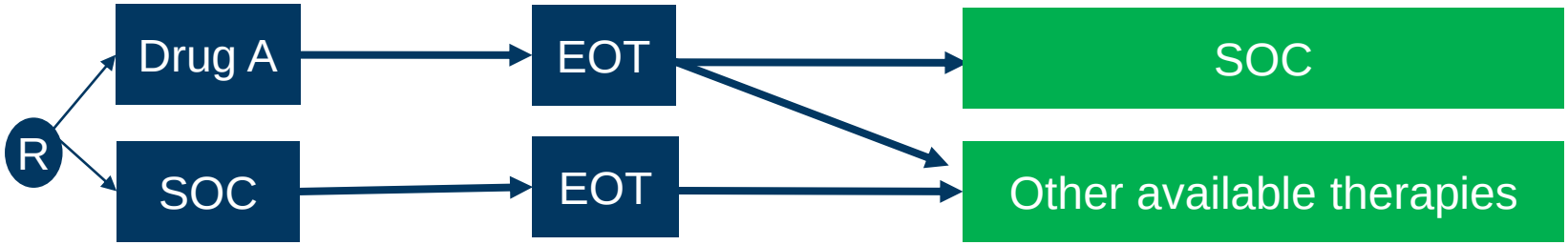
Overall survival (OS) and treatment switching



☺ 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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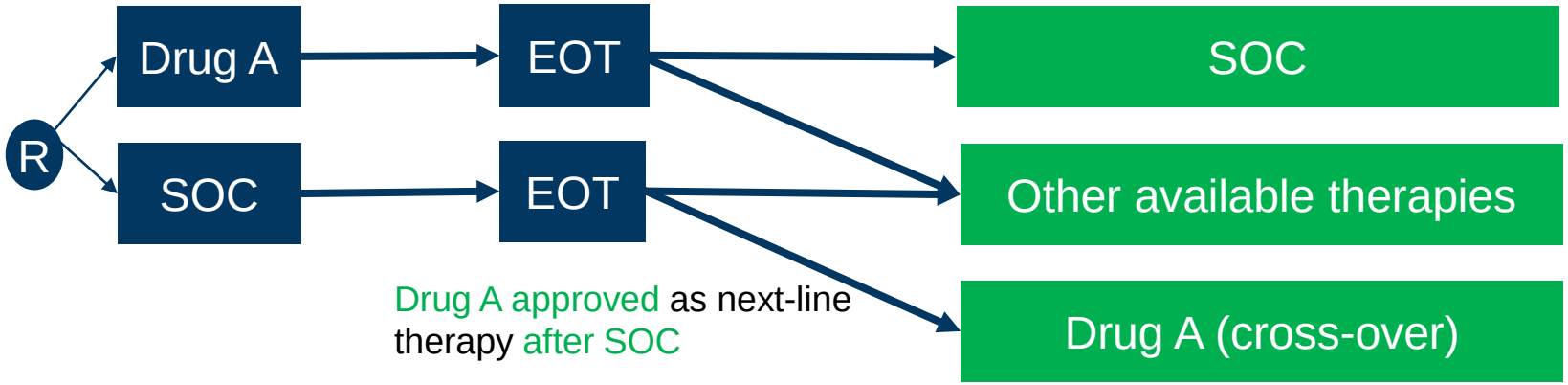
Overall survival (OS) and treatment switching



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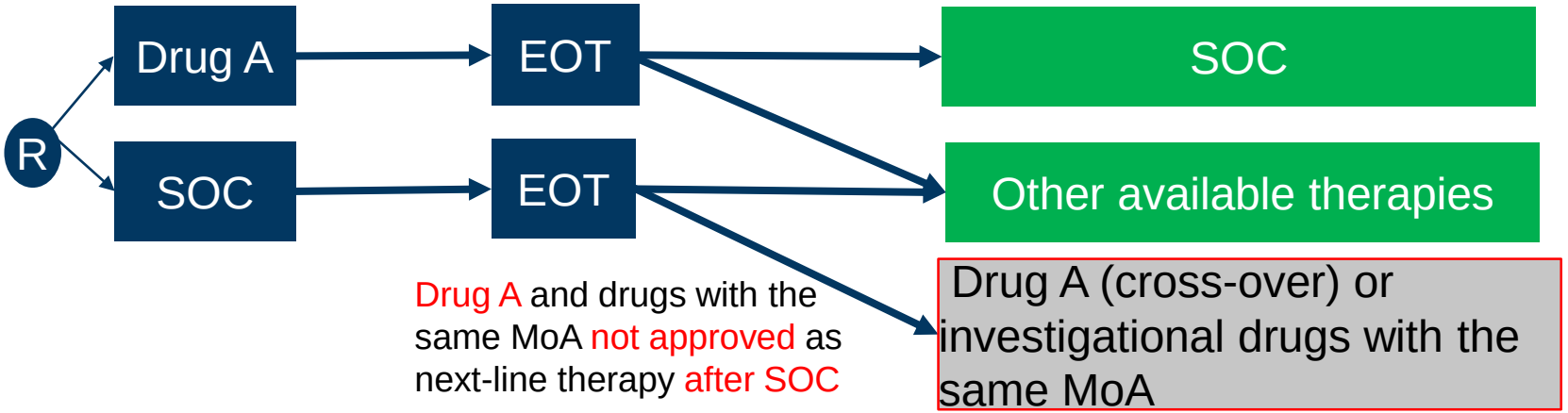
Overall survival (OS) and treatment switching



☹ 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)

SOC: Standard of Care; EOT: End of Treatment

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Overall survival (OS) and treatment switching: misinterpretation

Over half of new cancer drugs 'show no benefits' for survival or wellbeing

Of 48 cancer drugs approved between 2009-2013, 57% of uses showed no benefits and some benefits were 'clinically meaningless', says BMJ study

LIFE • WELLBEING •

6:36pm, Sep 19, 2019

Poorly designed cancer drug trials may be exaggerating benefits

HEALTH NEWS OCTOBER 13, 2017 / 8:44 PM / 7 MONTHS AGO

Little evidence new cancer drugs improve survival

PHARMALOT

STAT+

Flawed trials supported half of recent approvals of cancer drugs in Europe, study says

By ED SILVERMAN @Pharmalot / SEPTEMBER 18, 2019

- 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.

CheckMate 037: Nivolumab Improved Responses, Not Survival in Advanced Melanoma

By Leah Lawrence
Monday, July 17, 2017

→ 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!

Acknowledgements

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