Hematology Development Unit
Biostatistics

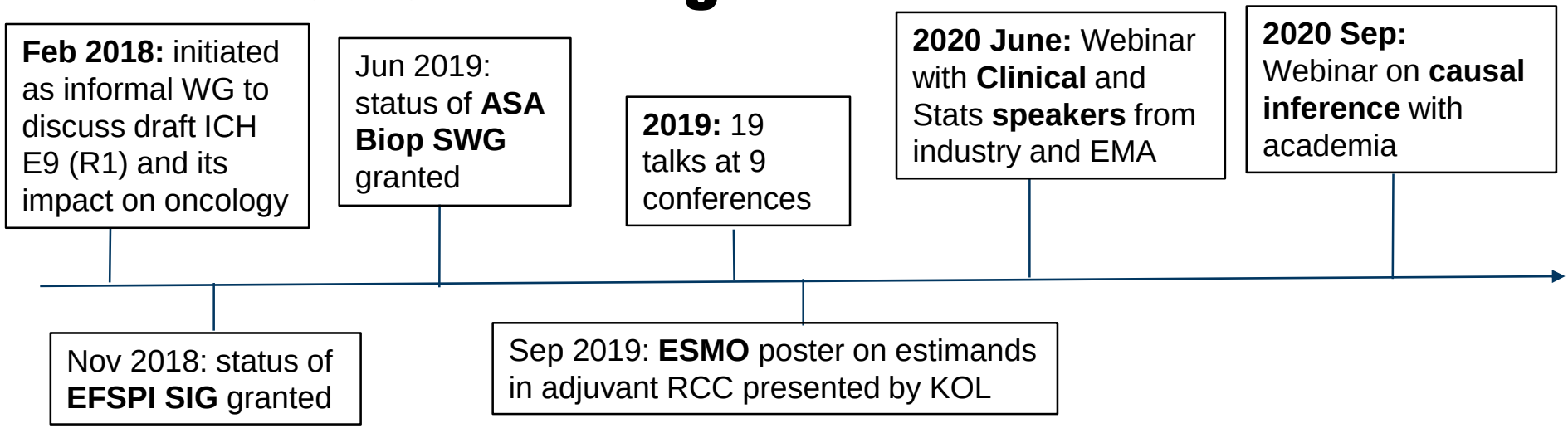
Estimand framework: What are the opportunities in oncology?

Evgeny Degtyarev

ASA BIOP/PSI/EFSPI Webinar, Nov 2020

NOVARTIS | Reimagining Medicine

Industry Working Group on Estimands in Oncology
www.oncoestimand.org



- 27 companies from Europe, US and Asia (pharmaceutical, biotech and CRO)
- in dialogue with HAs from Canada, China, Europe, Japan, Switzerland, Taiwan, UK and USA
- Recordings of the webinars, slides from all presentations as well as published papers available on our homepage

Oncology drug development today

Advanced therapies improving outcomes for patients

New therapeutic modalities:

- Immunotherapies
- Cell&Gene Therapies
- Radioligand Therapies

Great for patients!

- durable responses
- many ongoing clinical trials

Oncology drug development today

Regulators, sponsors and payers criticized

THE MILBANK QUARTERLY
A MULTIDISCIPLINARY JOURNAL OF POPULATION HEALTH AND HEALTH POLICY

Original Scholarship | Open Access

Approval of Cancer Drugs With Uncertain Therapeutic Value: A Comparison of Regulatory Decisions in Europe and the United States

MAXIMILIAN SALCHER-KONRAD, HUSEYIN NACI, COURTNEY DAVIS

First published: 06 October 2020 | https://doi.org/10.1111/1468-0009.12476

Conclusions: US and European regulators often deemed early and less complete evidence on benefit-risk profiles of cancer drugs sufficient to grant regular approval, raising questions over regulatory standards for the approval of new medicines. Even when imposing confirmatory studies in the postmarket-

ELSEVIER
European Journal of Cancer
Volume 136, September 2020, Pages 176-185

Original Research

Progression-free survival is a suboptimal predictor for overall survival among metastatic solid tumour clinical trials

ELSEVIER
Journal of Clinical Epidemiology
Volume 127, November 2020, Pages 1-8

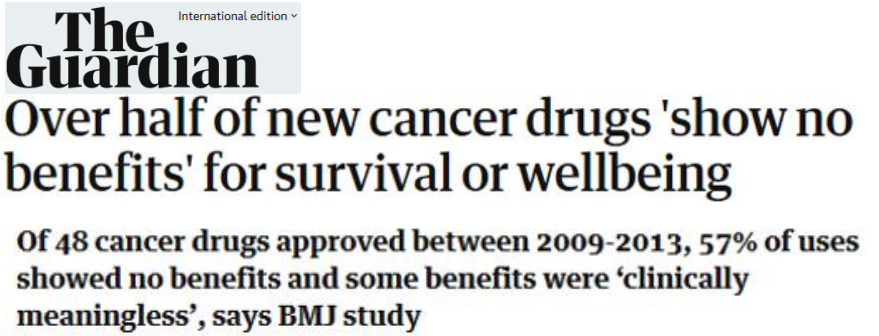
Original Article

Evidence of survival benefit was often ambiguous in randomized trials of cancer treatments

NOVARTIS | Reimagining Medicine

Oncology drug development today

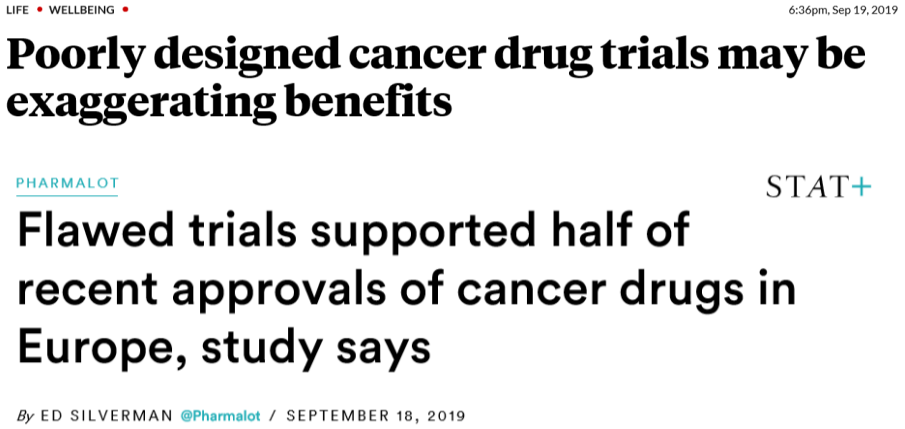
Regulators, sponsors and payers criticized



The Guardian International edition

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

PHARMALOT STAT+

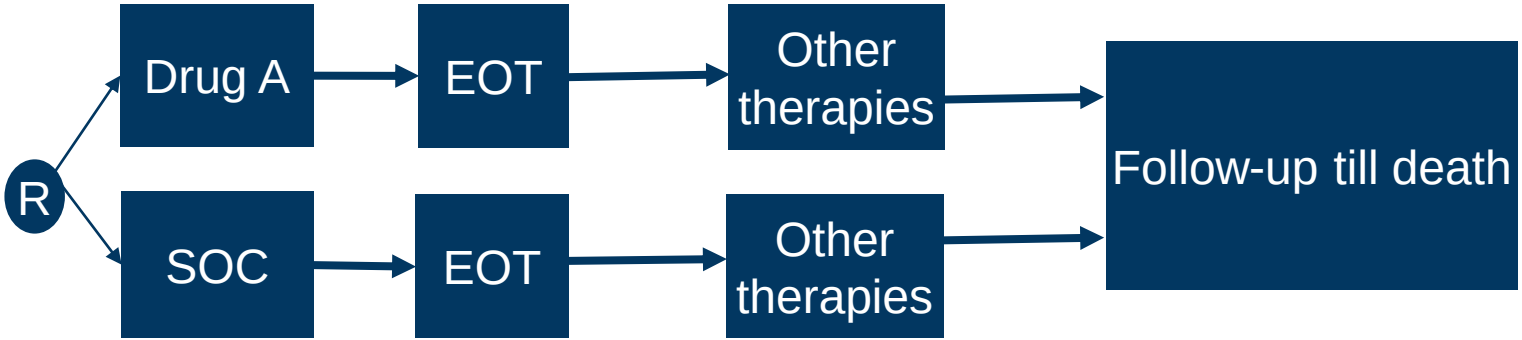
Flawed trials supported half of recent approvals of cancer drugs in Europe, study says

By ED SILVERMAN @Pharmalot / SEPTEMBER 18, 2019

Negative perception often **driven by** non-significant **result for overall survival,** often when subsequent therapies don't reflect clinical practice!

Overall survival (OS) in clinical trials

Treatment Switching



OS usually analyzed using **treatment policy** strategy

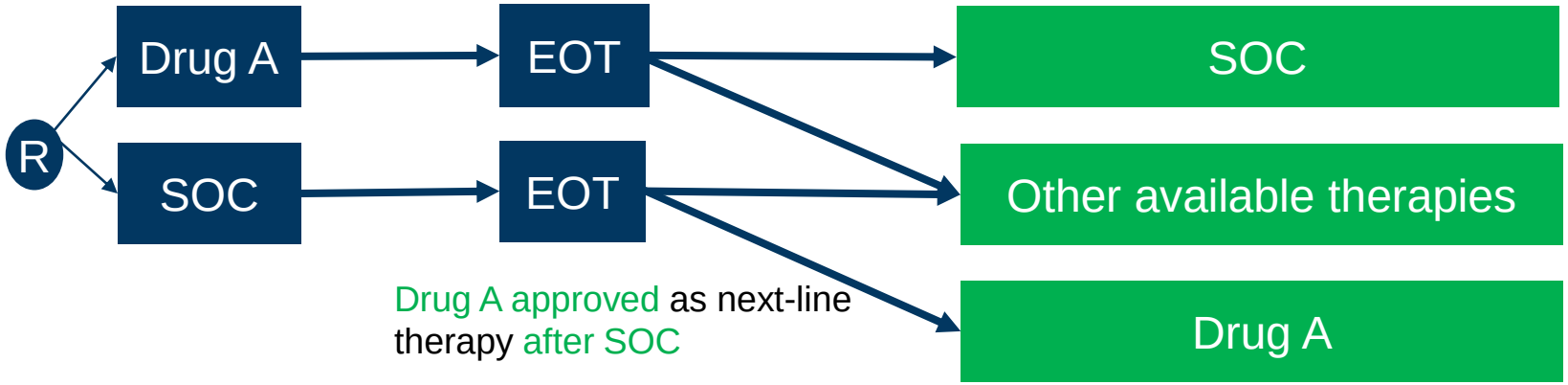
- using time from randomization to death regardless of patient's journey
- captures effect on the choice and impact of subsequent therapies
  - note: balance in subsequent therapies generally not expected as physician choose subsequent therapy in light of previously administered therapies
- **Clinically meaningful if choice of subsequent therapies after EOT reflects clinical practice**

NOVARTIS | Reimagining Medicine

SOC: Standard of Care; EOT: End of treatment

Overall survival (OS) in clinical trials

Treatment Switching

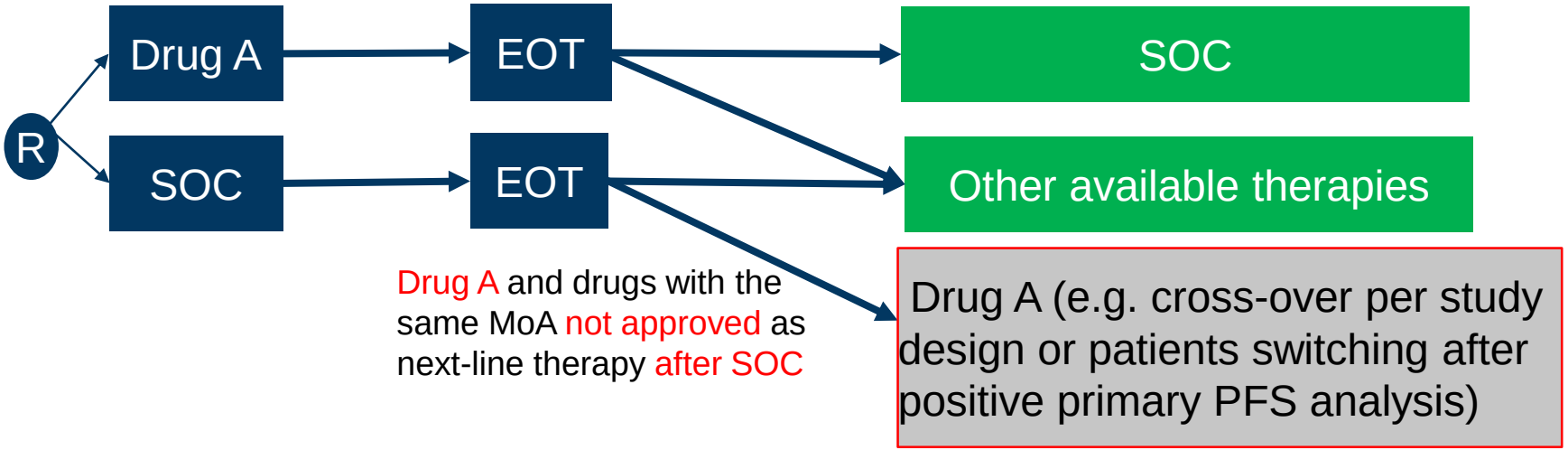


☺ choice of subsequent therapies after EOT reflects clinical practice

→ Treatment policy OS estimand interpretable at the time of the readout

Overall survival (OS) in clinical trials

Treatment Switching



☹ choice of subsequent therapies after EOT does **not** reflect clinical practice

→ Treatment policy estimand comparing Drug A followed by SOC or other available therapies vs SOC followed by Drug A or other available therapies relevant?

Benefit on OS without cross-over possibility more informative? (hypothetical estimand)

NOVARTIS | Reimagining Medicine

SOC: Standard of Care; EOT: End of Treatment; PFS: Progression-Free Survival

Oncology clinical trials today

Estimand framework: Opportunity to improve communication!

- Opportunity to
  - discuss alternatives for main OS analysis addressing relevant questions for patients and prescribers (e.g. **hypothetical estimand** evaluated by RPSFT, IPCW ...)
  - **communicate** added **value of** approved **drugs better** in publications
  - **improve OS description in the labels**?

At the protocol-specified final analysis of OS, the median OS was 114.6 weeks for the SUTENT arm and 94.9 weeks for the IFN-α arm [HR= 0.821, 95% CI (0.673, 1.001)]. The median OS for the IFN-α arm includes 25 patients who discontinued IFN-α treatment because of disease progression and crossed over to treatment with SUTENT as well as 121 patients (32%) on the IFN-α arm who received post-study cancer treatment with SUTENT.

Sutent US Prescribing Information in RCC (>10 years ago!)

Nivolumab Summary of Product Characteristics

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.

Few thoughts on the Hypothetical estimand

- ICH E9(R1) addendum acknowledges that some hypothetical scenarios are likely to be of more clinical or regulatory interest than others
- Hypothetical estimands often targeted as primary analysis in pivotal trials
  - PFS analysis censoring new anticancer therapies per FDA guideline
  - proposed in EMA guidelines for Alzheimer or Diabetes
- «What would be the effect on OS if patients from the SOC arm had not the possibility to receive Drug A subsequently?» key question for patients and prescribers if Drug A is not available after SOC
  - statistical methods such as IPCW can answer this question if properly planned (incl. data collection)
  - facing some headwinds as the methods rely on assumptions
- **Opportunity for sponsors and regulators to learn together and to collaborate with academia to address important questions for patients!**

Improved HA interactions ensuring that we get the questions right

- Case study in CAR-T setting presented in a recent webinar* on causal inference:
  - Commenting on the protocol FDA stated that the analysis plan «should prospectively create rules for appropriately censoring» certain observations in supplementary analysis
  - Sponsor realized that this censoring would target a hypothetical scenario that is likely not of clinical or regulatory interest
  - Sponsor suggested that principal stratum estimand would address FDA's actual question of interest
  - FDA agreed to use the principal stratum strategy as supplementary analysis instead of censoring

→ Improved interactions **discussing questions of interest** and not censoring rules resulting in **more meaningful analyses**

- Principal stratum: another opportunity to learn together and to collaborate with academia
  - addressing important questions – many examples of practical relevance in drug development (Bornkamp** et al. (2020))

NOVARTIS | Reimagining Medicine

* «RCTs meeting causal inference: principal stratum strategy and beyond» http://bbs.ceb-institute.org/?p=1587

** Bornkamp et al. *Principal Stratum Strategy: Potential Role in Drug Development* (2020). Under revision. arXiv:2008.05406

Other opportunities

- Harmonization of therapeutic guidances between regulators?!
  - More focus on questions of interest than censoring rules in future?

- RWE
  - structured discussion about the question of interest and planned comparison between single arm trials and RWD with regard to population, endpoint, handling of intercurrent events etc (or when supplementing control arm in randomized trial)
  - transparent description of potential limitations and uncertainties to decide whether RWD source is suitable for comparison
  - similar to target trial framework*

*Danaei G, García Rodríguez LA, Cantero OF, Logan RW, Hernán MA. Electronic medical records can be used to emulate target trials of sustained treatment strategies. J Clin Epidemiol. 2018 Apr;96:12-22. doi: 10.1016/j.jclinepi.2017.11.021.

Just some topics requiring discussions

New task forces of the industry WG on Estimands in Oncology:

- Clinical engagement
- Principal stratum use for treatment switching
- Estimands and PRO
- Estimands and time to response/duration of response
- Follow-up quantification
- Estimands and RWE
- Conditional and marginal effects
- Time to event endpoint with prognostic or predictive biomarker subgroups

Conclusions

- Opportunity to improve perception that approved drugs do not provide benefit with more **patient-focused drug development**
  - addressing questions relevant to patients
  - ensuring clarity in interpretation of results and added value of the drugs
    - impact on labels and publications
  - more dialogue in future between all stakeholders about questions of interest

- Opportunity for **sponsors and regulators** to **learn together** and to **collaborate with academia** to address important questions for patients!
  - Successfully done before, e.g. Bayesian designs for dose-finding in Oncology instead of traditional 3+3

Acknowledgements

Thanks for many discussions on estimands in Oncology over the last years to:

- Kaspar Rufibach and many other members of the industry working group
- Frank Bretz and many other colleagues at Novartis

Industry Working Group on Estimands in Oncology Webinars and Publications

EFSPI/BBS Webinar: Estimands addendum is final: Anything new for oncology? (June 29) http://bbs.ceb-institute.org/?p=1453

BBS Webinar: RCTs meeting causal inference: principal stratum strategy and beyond September (September 7) http://bbs.ceb-institute.org/?p=1587

Accepted or published

- Lawrence, R., Degtyarev, E., Griffiths, P., Trask, P., Lau, H., D'Alessio, D., Griebsch, I., Wallenstein, G., Cocks, K., Rufibach, K. *What is an estimand & how does it relate to quantifying the effect of treatment on patient-reported quality of life outcomes in clinical trials* (2020). Journal of Patient-Reported Outcomes, 4(1):68. DOI: 10.1186/s41687-020-00218-5
- Degtyarev, E., Rufibach, K., Shentu, Y., Yung, G., Casey, M., Englert, S., Liu, F., Liu, Y., Sailer, O., Siegel, J., Sun, S., Tang, R., Zhou, J. *Assessing the impact of COVID-19 on the objective and analysis of oncology clinical trials – application of the estimand framework* (2020). Statistics in Biopharmaceutical Research. DOI: 10.1080/19466315.2020.1785543
- Casey M., Degtyarev E., Lechuga M.J., Aimone P., Ravaud A., Motzer R., Liu F., Stalbovskaya V., Tang R., Butler E., Sailer O., Halabi S., George D. *Estimand framework: Are we asking the right question? A case study in the solid tumor setting* (2020). Pharmaceutical Statistics, accepted.

Under review

- Sun, S., Weber, J., Butler, E., Rufibach, K., Roychoudhury, S. *Estimands in Hematology Trials* (2020). Under revision. arXiv:2010.00957
- Manitz, J., Kan-Dobrosky, N., Buchner, H., Casadebaig, M.L., Degtyarev, E., Dey, J., Haddad, V., Fei, J., Martin, E., Mo, M., Rufibach, K., Shentu, Y., Stalbovskaya, V., Tang, R., Yung, G., Zhu, J. *Estimands in clinical trials with treatment switching* (2020). Under revision.
- Bornkamp, B., Rufibach, K., Lin, J., Liu, Y., Mehrotra, D., Roychoudhury, S., Schmidli, H., Shentu, Y., Wolbers, M. *Principal Stratum Strategy: Potential Role in Drug Development* (2020). Under revision. arXiv:2008.05406

Further publications are currently being written within the working group.