Estimands update: Summary of world-wide authority interaction

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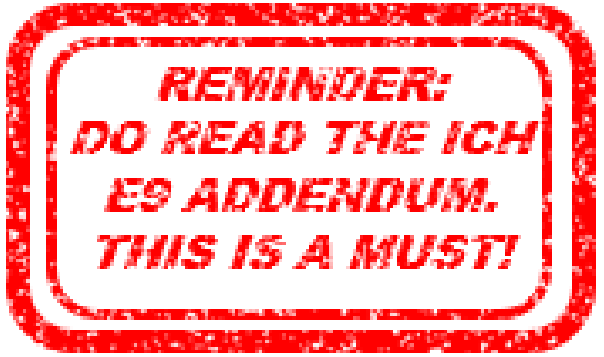
Head of Biostatistics, Staburo GmbH

Agenda

- Introduce European special interest group “Estimands in oncology”
- Summary of world-wide authority interaction
- Principal Stratum
- Treatment Switching

Estimands and the ICH E9



- The need for the Addendum on Estimands and Sensitivity Analysis in Clinical Trials E9 (R1) was identified due to recurrent issues with a lack of clarity in trial objectives and related treatment effect of interest
- Risk of different interpretation by relevant stakeholders, e.g. regulators, payers, patients.

- In November 2019, the ICH released an Addendum to E9 guideline on Statistical Principles for Clinical Trials
  - introduced structured framework for clinical trial design
  - defined intercurrent events: occur after treatment initiation and affect either the existence or interpretation of the measurement
  - highlighted the difficulty of assessing treatment effect in the presence of intercurrent events

Oncology estimand working group

As of 07 November 2020, the European special interest group “Estimands in oncology”, which is sponsored by PSI and EFSPI and ASA scientific working group of the ASA biopharmaceutical section

- has 41 members (14 from Europe and 26 from US) representing 25 companies,
- regularly interacts with seven Health Authorities globally,
- regularly organizes sessions and presents at conferences,
- has started to interact with academic colleagues.

- www.oncoestimand.org


NOVARTIS
Roche
Pfizer
MERCK
janssen
PHARMACEUTICAL COMPANIES OF Johnson&Johnson
SANOFI
gsk
abbvie
AstraZeneca
BeiGene
BAYER
Takeda
Celgene
astellas
SERVIER
MERCK
PPD
NEKTAR
Merus battling cancer
statburo
Statistical Consulting
AMGEN
ICON
A Symbol of Excellence
Boehringer Ingelheim
Adelphi
ADELPHI VALUES
Daiichi-Sankyo
MERCK SERONO

There are several papers 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.
- 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 | arxiv
- 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. doi

There are several papers under review:

- Sun, S., Weber, J., Butler, E., Rufibach, K., Roychoudhury, S. *Estimands in Hematology Trials* (2020). Under revision. arxiv
- 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 for Overall Survivla 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 | github | markdown

Many thanks to everybody within the subteams!

New task forces

- Clinical engagement
- Principal stratum application for treatment switching
- Estimands and PRO
- Time to Response and DOR
- Follow-up Quantification
- Estimands and RWD
- Conditional vs Marginal
- Time-to-event endpoints with prognostic or predictive biomarker subgroups (potentially some overlapping content with conditional vs marginal)

Agenda

- Introduce European special interest group “Estimands in oncology”
- **Summary of world-wide authority interaction**
- Principal Stratum
- Treatment Switching

World-wide authority interactions

- **The European special interest group “Estimands in oncology” organized world wide authority interactions in Sep 2020:**
  - FDA
  - Health Canada + Swissmedic
  - CFDA
  - PMDA
  - MHRA
  - Taiwan

  - *EMA ?*

- **Within the one hour meetings the different subteams presented their work:**
  - solid tumours
  - treatment switching
  - hematology
  - patient reported outcomes (PRO)
  - principal stratification
  - censoring
  - COVID-19

The presentation can be found on: http://www.oncoestimand.org

Summary from world-wide authority interactions

Many questions were asked especially about:

- PRO (how to handle death?)
- principal stratification
- treatment switching
- How to quantify effect for T2E endpoints in absence of PH, causal interpretation

Probably because they had faced issues around these topics before

- Generally very positive feedback and interest in further exchange.
- Framework of estimand considered to be very helpful! For agency-industry interaction but also for within agency communication!
- Except FDA regulatory stats departments small → capacity issue. They appreciate industry collaboration to assess new methodologies etc.

Learnings in setting up these collaborations

- You cannot talk to regulators as an individual or a company.
- Build industry consortia, get formal status.
- Onco estimand WG:
  - November 2018: European special interest group “Estimands in oncology”, sponsored by PSI and EFSPI.
  - June 2019: ASA scientific working group of ASA biopharmaceutical section.
- With this setup and a topic of common interest, regulators are **very open** to talk to us.
- You can make an impact:
  - MHRA presented our COVID-19 paper to their staff.
  - FDA asks us for examples of hypothetical estimands.
- Be aware: building such a group and maintain momentum needs a **lot of work and energy**.

Agenda

- Introduce European special interest group “Estimands in oncology”
- Summary of world-wide authority interaction
- **Principal Stratum**
- Treatment Switching

"... The target population might be taken to be the "principal stratum" in which an **intercurrent event would occur**. Alternatively, the target population might be taken to be the principal stratum in which an intercurrent event **would not occur**. The clinical question of interest relates to the treatment effect only within the principal stratum..."

2-arm RCT experimental (E) vs. control (C)

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Do patients with low exposure in E have lower treatment effect?

2-arm RCT experimental (E) vs. control (C)

Do patients with low exposure in E have lower treatment effect?

"Subgroup" built by post-randomization event!

How can we make valid causal statements?

How can we make valid causal statements?

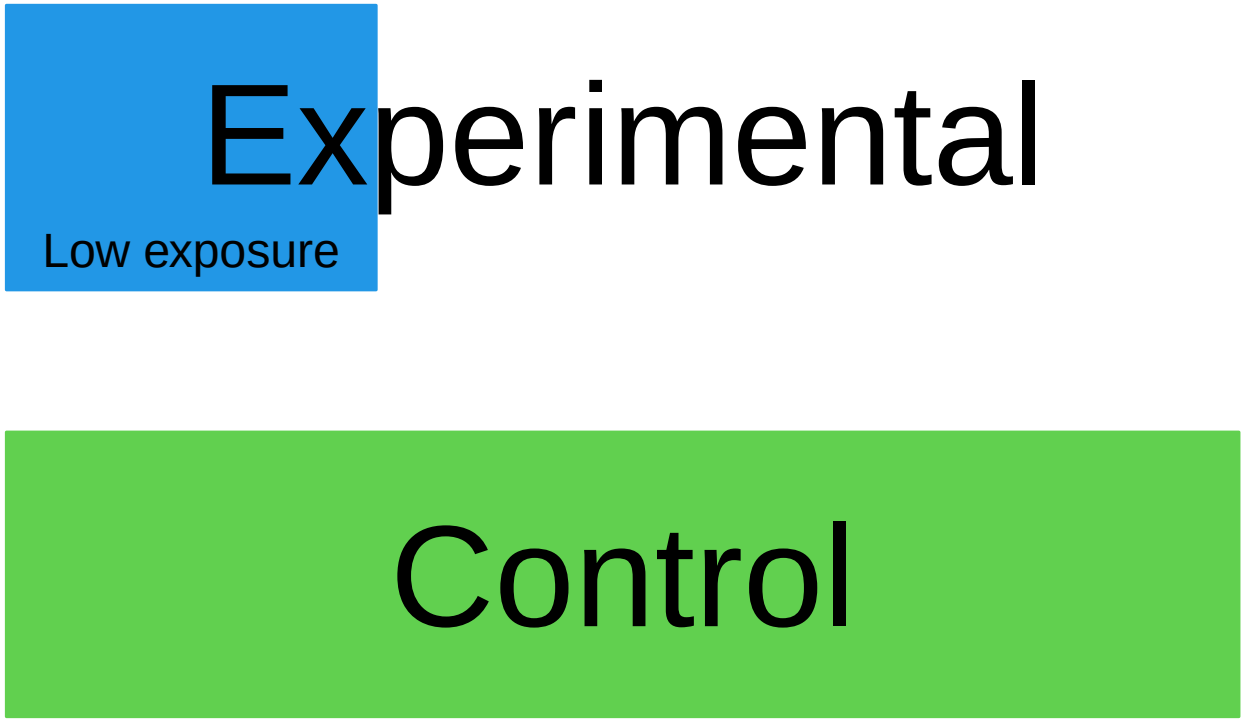
Need "matched control patients"!

Experimental

Control


Experimental
Low exposure
High exposure

Patients randomized to E experiencing low exposure had they received control


Experimental
Low exposure
Control


Experimental
Low exposure


Control


Experimental
Low exposure
High exposure

Naive analyses are misleading and do not answer causal question

Naive analyses are misleading and do not answer causal question

Principal stratification: "subgroup analysis for post-baseline subgroups"

Naive analyses are misleading and do not answer causal question

Principal stratification: "subgroup analysis for post-baseline subgroups"

randomization + assumptions

Assumptions are unverifiable

Assumptions are unverifiable

Scientific knowledge + sensitivity analyses

Example	Scientific question	Primary endpoint	Intercurrent event	Stratum of interest
Multiple Sclerosis	Treatment effect on confirmed disability progression in the subpopulation of relapse-free patients	Time to confirmed disability progression	Post-randomization relapse	Patients who would be relapse-free under both treatments
Treatment effect in early responders	Predict treatment effect on long-term primary endpoint based on early biomarker-type readout	Time-to-event	Biomarker value above or below a prespecified threshold	Patients who would respond early under treatment vs. those that would not
Antidrug antibodies (ADA) for targeted oncology drugs	Do patients that develop ADAs on either arm still benefit from the drug?	Time-to-event	Development of antidrug antibodies because of receiving experimental drug	Patients who would be ADA+ under treatment
Impact of exposure on OS	Do patients with insufficient exposure have lower treatment effect?	Time-to-event	Exposure below a prespecified threshold	Patients with low vs. non-low exposure under treatment
Prostate cancer prevention	Assess effect of treatment to prevent prostate cancer on severity of prostate cancer among those men who would be diagnosed with prostate cancer regardless of their treatment assignment	Time-to-event	Getting prostate cancer	Patients who get prostate cancer irrespective of treatment

Herceptin

Atezolizumab

Satralizumab

Interest on side of HAs

Statistics > Applications

[Submitted on 12 Aug 2020]

Principal Stratum Strategy: Potential Role in Drug Development

Björn Bornkamp, Kaspar Rufibach, Jianchang Lin, Yi Liu, Devan V. Mehrotra, Satrajit Roychoudhury, Heinz Schmidli, Yue Shentu, Marcel Wolbers

A randomized trial allows estimation of the causal effect of an intervention compared to a control in the overall population and in subpopulations defined by baseline characteristics. Often, however, clinical questions also arise regarding the treatment effect in subpopulations of patients, which would experience clinical or disease related events post-randomization. Events that occur after treatment initiation and potentially affect the interpretation or the existence of the measurements are called intercurrent events in the ICH E9(R1) guideline. If the intercurrent event is a consequence of treatment, randomization alone is no longer sufficient to meaningfully estimate the treatment effect. Analyses comparing the subgroups of patients without the intercurrent events for intervention and control will not estimate a causal effect. This is well known, but post-hoc analyses of this kind are commonly performed in drug development. An alternative approach is the principal stratum strategy, which classifies subjects according to their potential occurrence of an intercurrent event on both study arms. We illustrate with examples that questions formulated through principal strata occur naturally in drug development and argue that approaching these questions with the ICH E9(R1) estimand framework has the potential to lead to more transparent assumptions as well as more adequate analyses and conclusions. In addition, we provide an overview of assumptions required for estimation of effects in principal strata. Most of these assumptions are unverifiable and should hence be based on solid scientific understanding. Sensitivity analyses are needed to assess robustness of conclusions.

(with markdown)

(with markdown)

BBS seminar:

http://bbs.ceb-institute.org/?p=1587

Effective statistician podcast, together with Björn Bornkamp:

https://theeffectivestatistician.com/

a-deep-dive-into-principal-stratification-and-causal-inference

Agenda

- Introduce European special interest group “Estimands in oncology”
- Summary of world-wide authority interaction
- Principal Stratum
- **Treatment Switching**

Treatment switching is a reality and should accounted for

- Cross over maybe allowed for ethical reasons and/or practical considerations (can enhance trial participation), may be desirable and or undesirable, and may occur before any action can be taken by the monitoring committee

- The reality of varying access to innovative treatment across study centers and countries presents additional challenges **as access to**
  - **subsequent treatments** (including approved investigational drug in later lines), and
  - **diagnostic tests,** and
  - **standard of care** may be different.

  →**external validity of the trial in a specific decision context maybe be questionable**

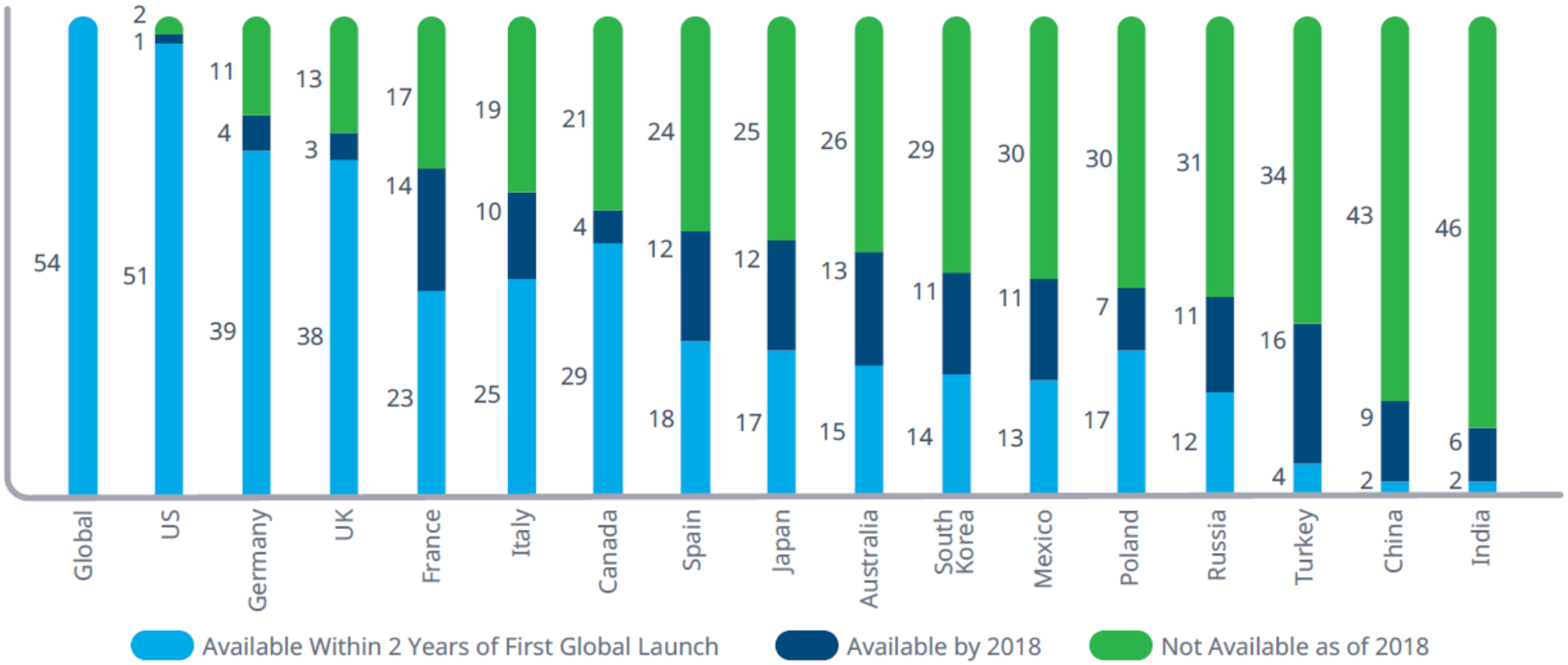
- Treatment switching has a non-negligible impact on decision making (in Germany led to an assignment of lower evidence levels[1] and in NICE UK over 50% of technology appraisal were affected by treatment switching[2])

1) Isabary et al, Value in Health 21 (2018), 698-706
2) Latimer, Expert Rev. Pharmacoecon Outcomes Res. 15 (2015), 561-564

Indeed, standard of care across countries may be different

Patients in only nine countries have access to more than half of recently launched global cancer medicines

Exhibit 24: Availability in 2018 of Oncology Medicines Launched in 2013–2017

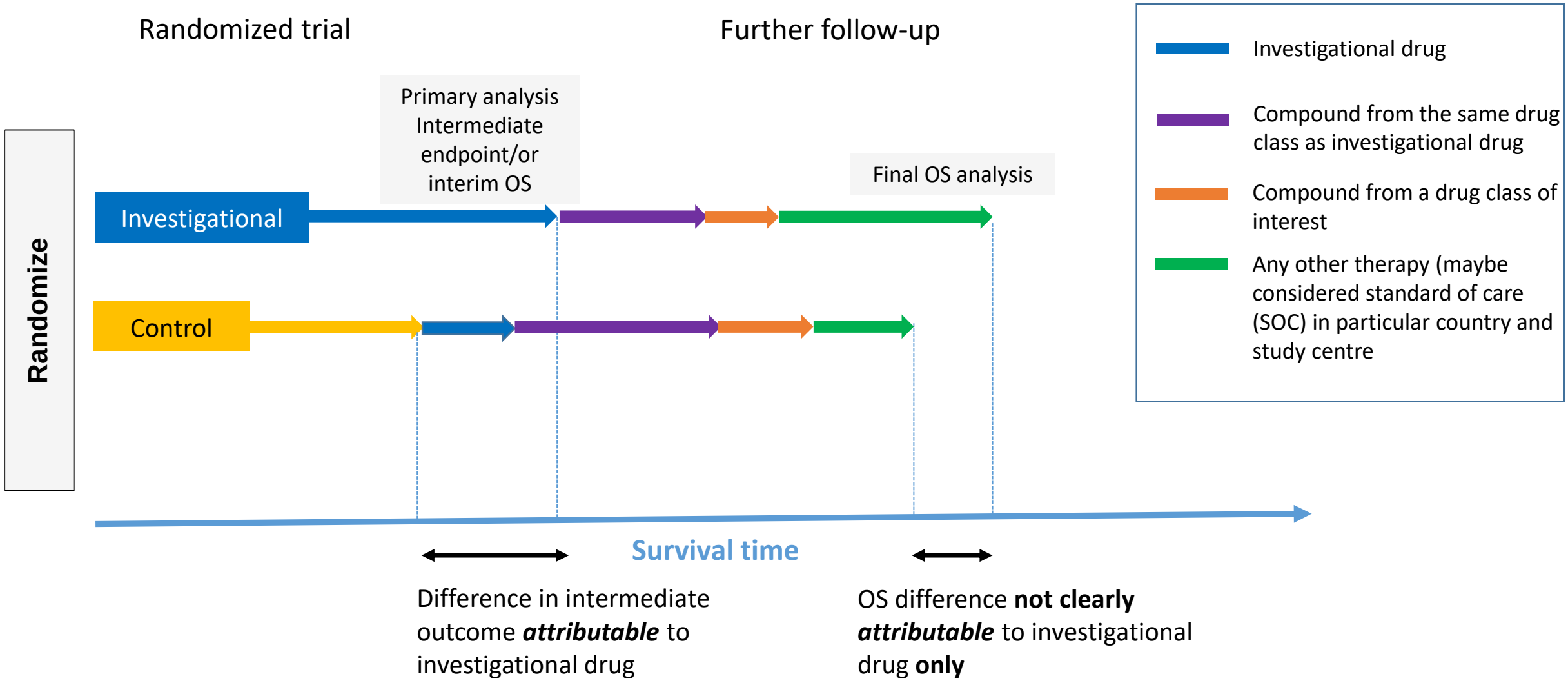


Source: IQVIA MIDAS, Dec 2018; ARK New Product Intelligence, IQVIA Institute, Apr 2019

Treatment switching is not just limited to one scenario…

Description of Treatment Switching	Type of Treatment Switching
From control arm to investigational arm	Cross-over
From control arm to same drug class as investigational arm	Treatment Switching, can be analyzed using cross-over methods
From control or investigational arm to drug (class) of interest	Treatment Switching

A more realistic scenario is a mix of treatment switching scenarios: what are we actually measuring?



What are the key questions?

- The traditional approach ignores treatment switching and rest on the following assumptions:
  - ✓ Subsequent therapy reflect clinical practice (including investigational drug in later line) **in particular decision context**
  - ✓ Patients receiving subsequent treatments (from same class as investigational drug and drug class of interest) and dose intensity as expected (as SOC) between investigational and control arm

- If these assumptions do not hold, we may consider to estimate the OS benefit that is attributable to the investigational drug

- The **Estimand** framework provides a coherent framework to make the arising issues of treatment switching explicit and offers a systematic and transparent approach for assessment

Estimands in clinical trials with treatment switching

OBJECTIVE		*Evaluate OS benefit assuming subsequent therapies represent clinical practice*	*Evaluate OS benefit adjusted for treatment switching*	*Evaluate OS benefit adjusted for treatment crossover*	*Evaluate OS benefit adjusted for treatment crossover at disease-related time-point*
ESTIMAND					
Population		Defined through appropriate I/E criteria to reflect the target patient population for approval			
Variable / Endpoint		Overall survival: Time from randomization to death			
Treatment condition of interest		Sequence of investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapies (including Investigational drug)	Investigational drug vs control (if there were no subsequent therapies)	Sequence of investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapy (excluding investigational drug)	Sequence of Investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapy (excluding investigational drug)
Handling of intercurrent events (IEs)	**IE: Start of subsequent therapy at any time**	Treatment policy	Hypothetical	Treatment policy	Treatment policy
	IE: Crossover to investigational drug at any time	Treatment policy	Hypothetical	Hypothetical	Treatment policy
	IE: Crossover to investigational drug at disease – related time point	Treatment policy	Hypothetical	Hypothetical	Hypothetical
Population - level Summary		Kaplan – Meier estimates; Hazard ratio (HR) with confidence interval (CI)			
ESTIMATION		Cox model and KM estimates using ITT approach	Adjusted HR and CI from IPCW – weighted Cox model; weighted KM estimates	HR from RSPFT model using adjusted survival times; bootstrapped CI; KM estimates using adjusted survival times; IPCW methods could also be used	HR from two – stage method using reconstructed survival; modified KM estimates using reconstructed survival times; IPCW and RPSFT methods could be used

Treatment switching / Crossover correction methods

- Several methods to account for treatment switching exist
- Most importantly:
  - RPSFT
  - IPCW
  - But also two stage methods

➢ However, they can only be applied if the necessary data is collected in the eCRF!!

Conclusions & Summary - treatment switching

- Treatment switching is a reality and should be accounted for!
- The estimand framework provides a coherent framework to make the issues of treatment switching explicit and offers a systematic and transparent approach for assessment
- The treatment switching part of the talk focused on OS but estimands for PROs including data collection beyond progression are currently heavily debated
- Think about possible scenarios during the planning phase of a trial!
  Do you expect the treatment landscape to change during your trial?
  Look into the examples!! Many things can happen!
- There are treatment switching methods which can be applied if the necessary data is collected in the eCRF. However, they do rely on assumptions!

- **Different treatment switching methods can answer different scientific questions!!**

- *What is better?* If we do **strategic country selection or** if we apply methods to account for treatment switching?

Some of the content of this presentation was developed within the **European special interest group "Estimands in oncology"**, which is sponsored by PSI and EFSPI and ASA scientific working group of the ASA biopharmaceutical section.

There is also a paper submitted with the title:

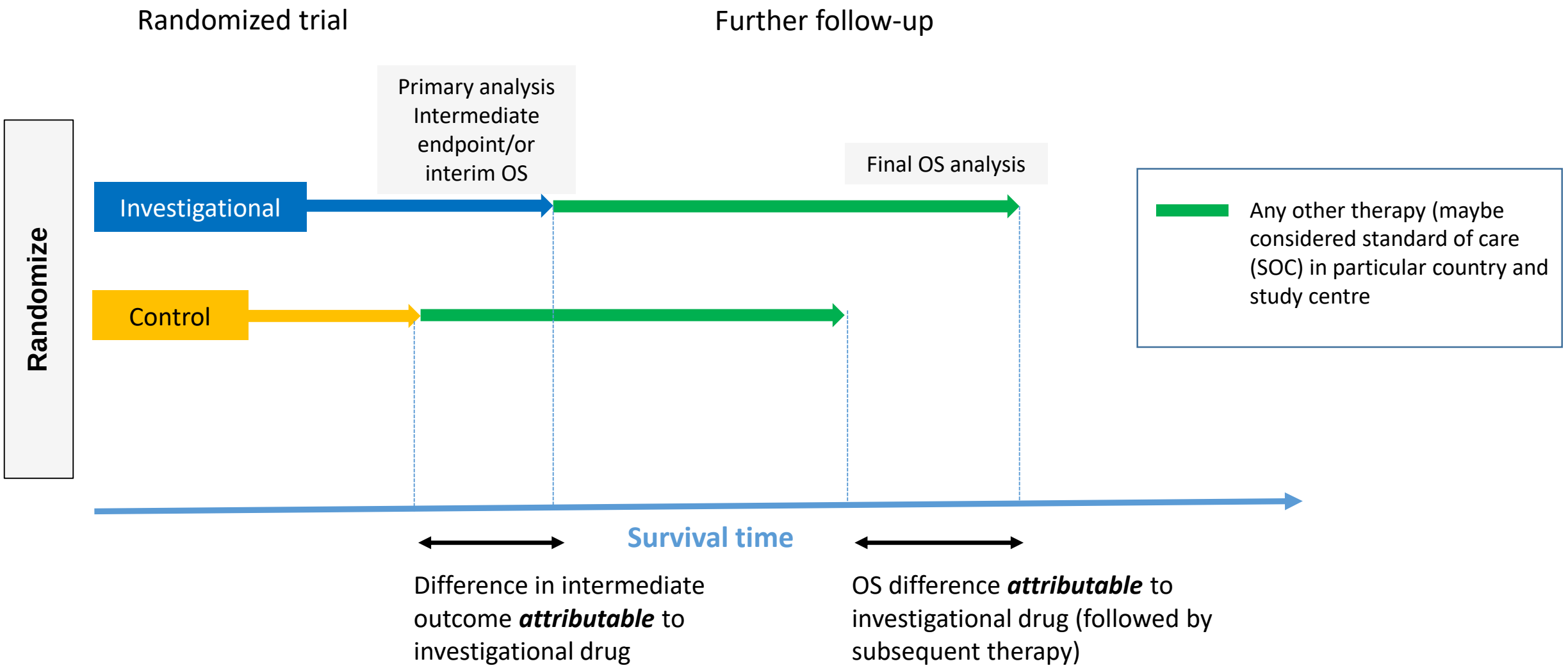
Estimands for Overall Survival in Clinical Trials with Treatment Switching

Many thanks to everybody within the treatment switching subteam:

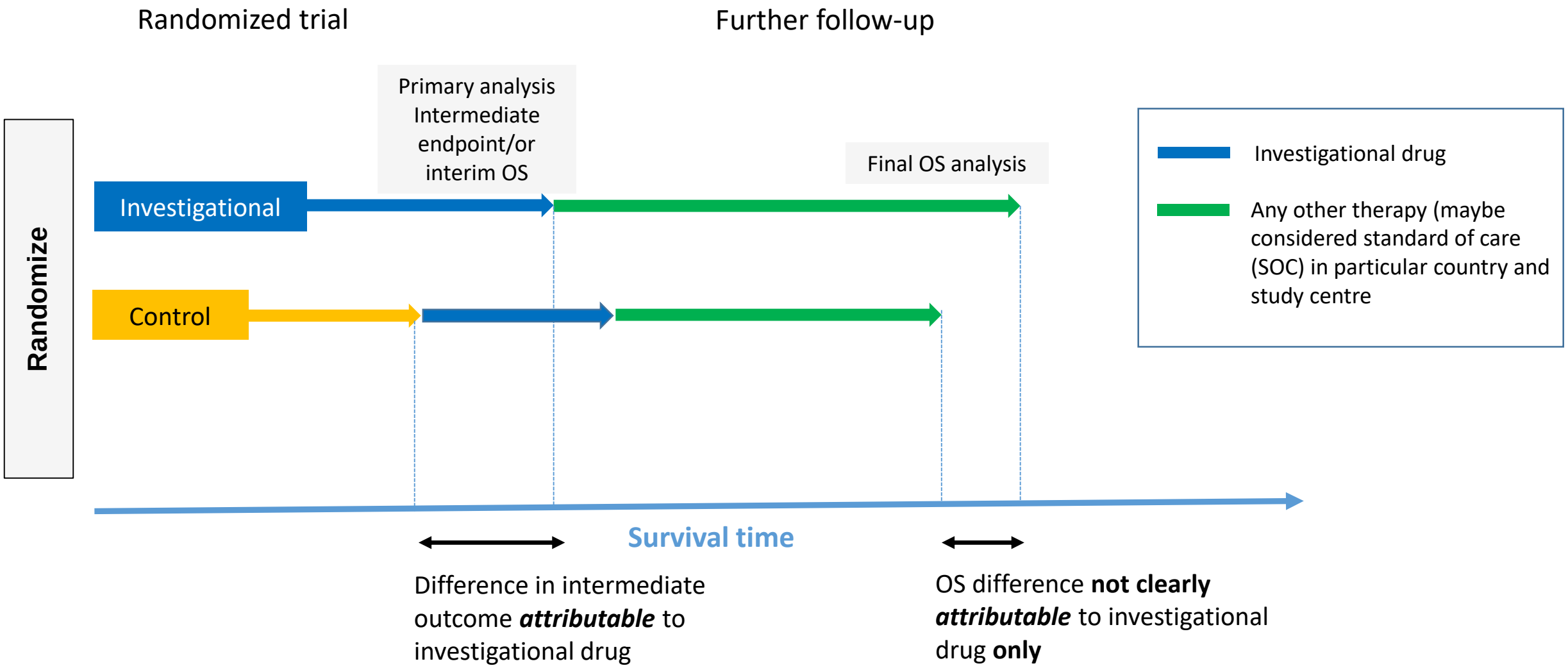
Juliane Manitz (EMD Serono), Natalia Kan-Dobrosky (PPD), **Hannes Buchner (Staburo GmbH),** Marie-Laure Casadebaig (Celgene), Evgeny Degtyarev (Novartis), Jyotirmoy Dey (AbbVie), Vincent Haddad (AstraZeneca), Fei Jie (Astellas Pharma Global Development), Emily Martin (EMD Serono), Mindy Mo (Amgen), **Kaspar Rufibach (F. Hoffmann-La Roche Ltd)**, Yue Shentu (Merck Sharp & Dohme), Viktoriya Stalbovskaya (Merus), Rui Tang (Servier Pharmaceuticals), Godwin Yung (Takeda Pharmaceuticals), Jiangxiu Zhou (GSK)

Back-up

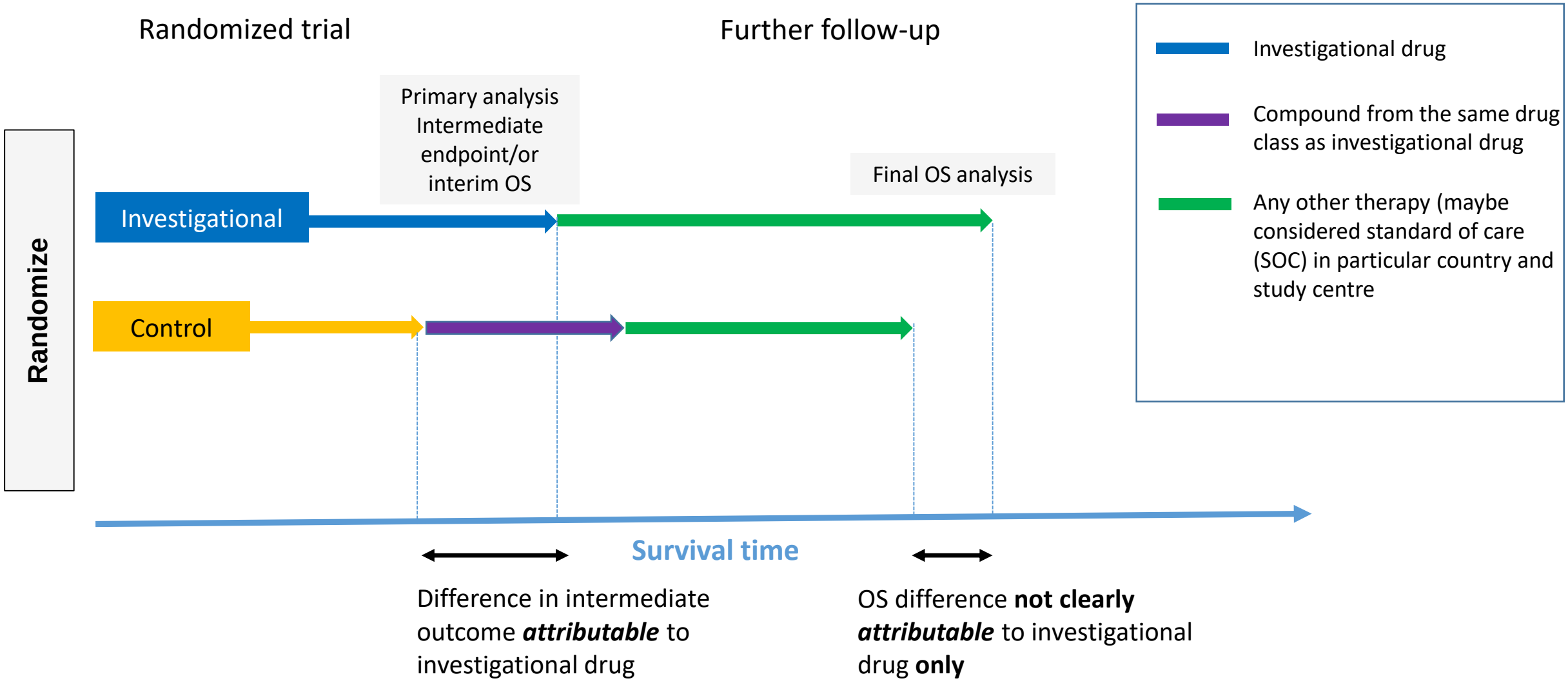
A stylized example of a randomized clinical trial in Oncology with primary and final overall survival analysis



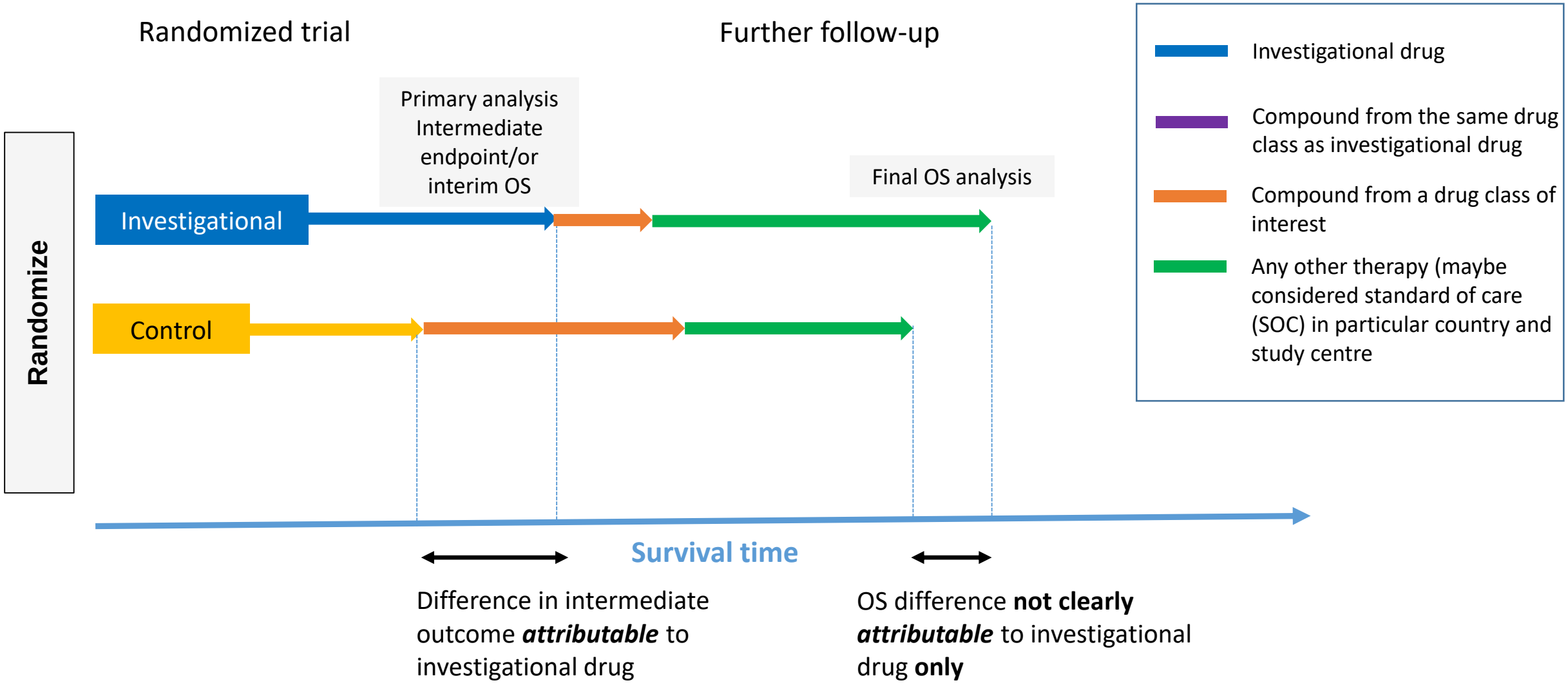
A Treatment switching scenario 1: Cross over



Treatment switching scenario 2: from control arm to same drug class as of investigational arm



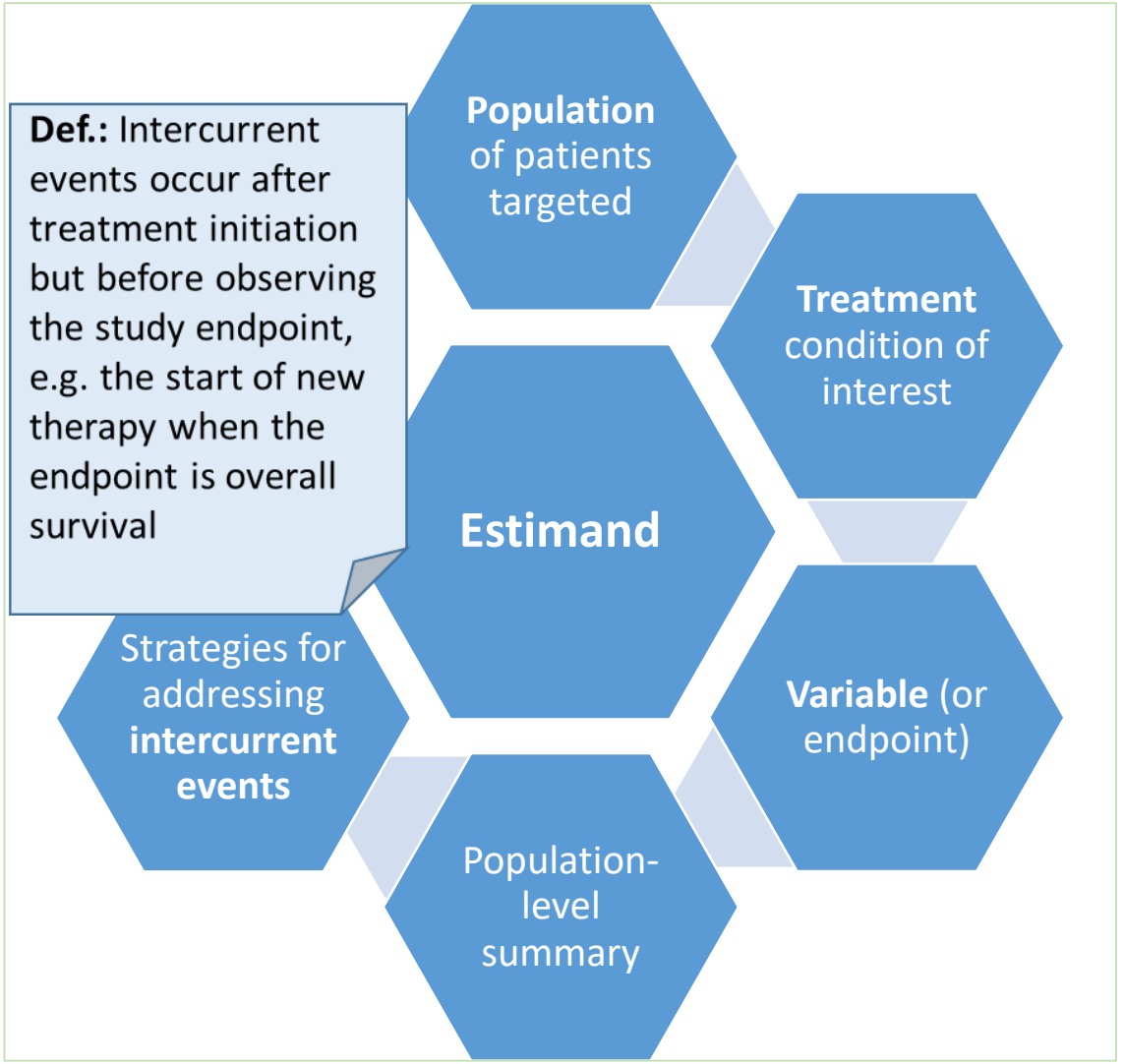
Treatment switching scenario 3: from control arm to drug class of interest



What is an Estimand?

- **Estimand** is the target of estimation to address the scientific question of interest posed by the study objective.
- An estimand is described by five attributes, defining together the treatment effect of interest.

- ➢ Increase transparency with respect to data analysis and inference
- ➢ Align trial **objectives** and statistical analyses by requiring a precise definition of the population quantity of interest
- ➢ Strengthen the dialogues between disciplines involved in the formulation of clinical study objectives, design, conduct, analysis and interpretation



Types of Estimands

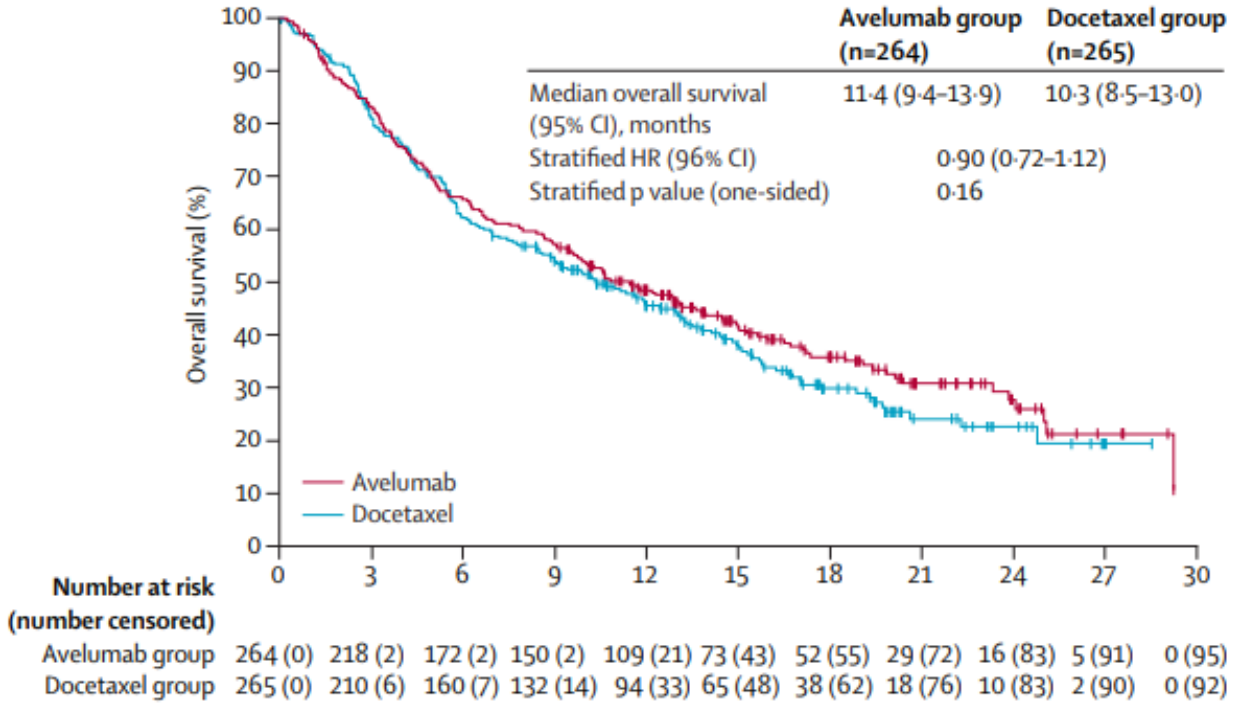
- ICH E9(R1) considers 5 general ‘types’ of estimand:
  - **Treatment policy** (‘effectiveness’)
  - **Hypothetical** (‘efficacy’)
  - **Composite**
  - **While On Treatment**
  - **Principal Stratum**

- Each has a different impact on the five attributes…
  - … but in most cases it is just different ways of handling ICEs

Now let us switch to the different presenter ...

Change in treatment landscape: a lung cancer example

Overall survival in the PD-L1-positive population at the ≥1% cutoffs
Figure was adjusted for multiple comparisons



The JAVELIN Lung 200 trial

- randomized
- open-label
- phase III study

→ did not meet its primary endpoint of significantly improving OS with avelumab vs docetaxel in patients with PD-L1+ NSCLC

- Subsequent IO treatments with **similar MoA** were approved during trial conduct and changed the respective treatment landscape for lung cancer
- A large proportion of patients in the chemotherapy arm (docetaxel arm, 26.4%) crossed over to immune checkpoint inhibitors (like nivolumab, pembrolizumab, etc.) outside the study

Furthermore, the approval status of new drugs within a rapidly changing treatment landscape vary across countries

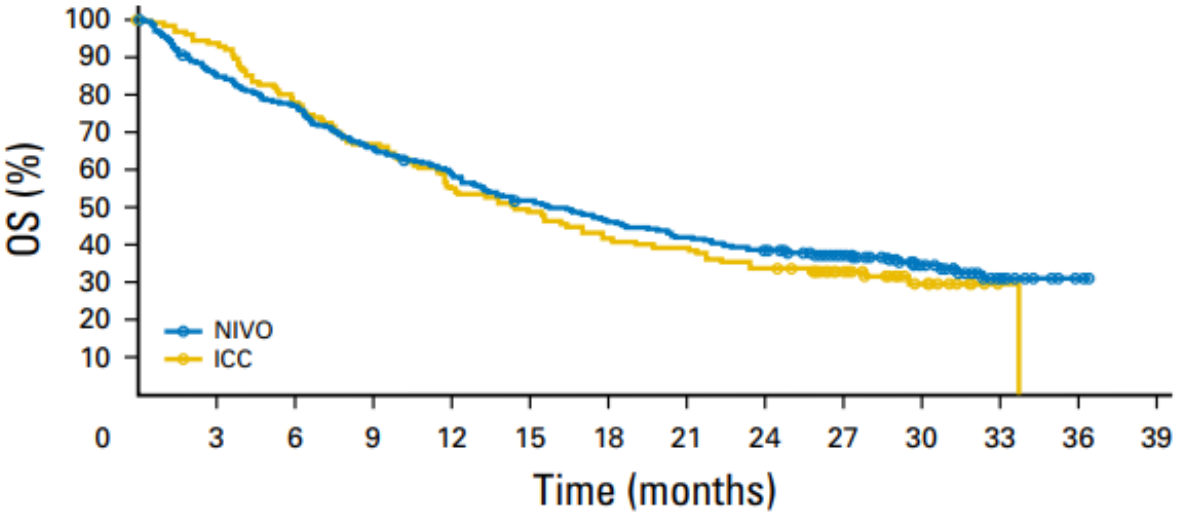
➢ **The estimand framework structures the discussion about intercurrent events (here start of new therapy) and allows granular considerations with regard to the type of therapy**

Barlesi F., Özgüroğlu M., Vansteenkiste J.F., Spigel D., Yang J. C-H., Bajars M., Ruisi M., Manitz J., Park K., Assessing the impact of subsequent checkpoint inhibitor (CPI) treatment on overall survival: Post hoc analyses from the phase III JAVELIN Lung 200 study of avelumab vs docetaxel in platinum-treated locally advanced/metastatic non-small cell lung cancer (NSCLC), Annals of Oncology, Volume 30, Issue Supplement_5, October 2019, mdz260.014, https://doi.org/10.1093/annonc/mdz260.014
https://www.researchgate.net/publication/327855792_Avelumab_versus_docetaxel_in_patients_with_platinum-treated_advanced_non-small-cell_lung_cancer_JAVELIN_Lung_200_an_open-label_randomised_phase_3_study

Treatment switching in open label trials

Open-label studies have the risk that patients stop randomized treatment after randomization in the control arm and seek the opportunity to receive an investigational therapy in another clinical trial, possibly even from the same class as the investigational drug in the previous trial (similar to scenario 2).

OS in all randomly assigned patients (hazard ratio for death, 0.95; 95.54% CI, 0.73 to 1.24; P = .716)



No. of patients at risk

NIVO	272	230	208	178	158	138	123	112	103	71	44	16	3	0
ICC	133	119	99	85	70	62	53	49	43	28	14	2	0	0

Example:

Checkmate-37, comparing Nivolumab vs chemotherapy where 20% of the patients from the control arm withdrew consent immediately after they learned that they were randomized into the control arm

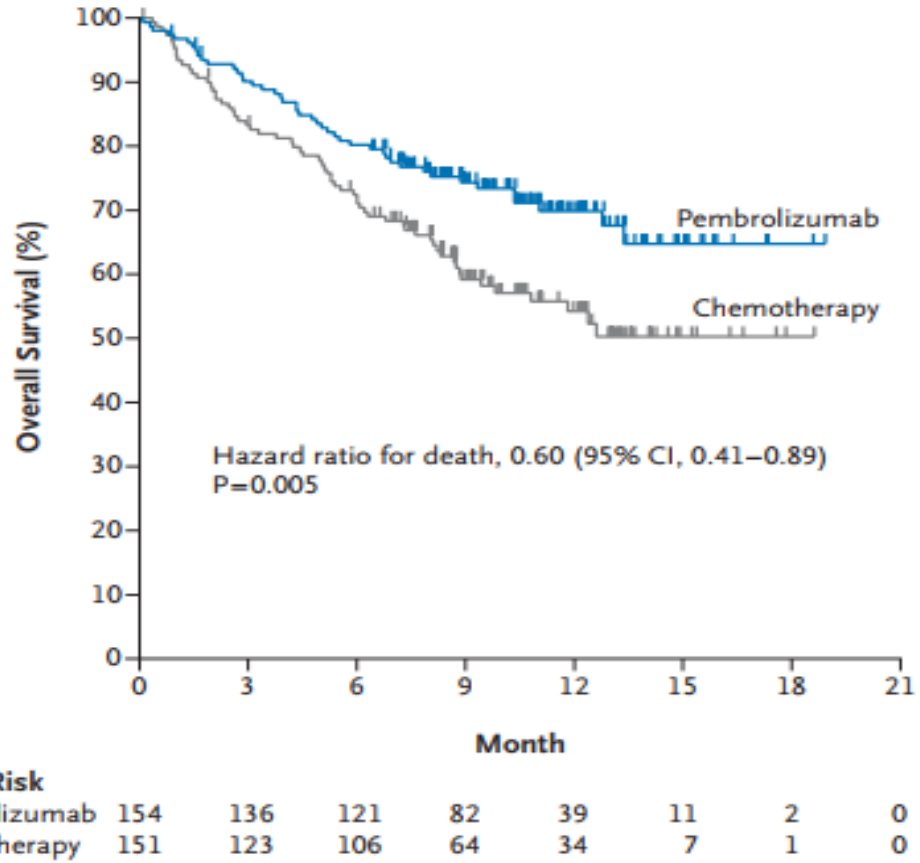
- Switching to products with a similar mode of action as the investigational product is considered in certain situations - but careful definition is necessary
- In immunoncology (IO), for example, the therapy could be either any IO therapy or only specific checkpoint inhibitors

➢ The estimand frameworks helps to anticipated those intercurrent events in advance. Defining different estimands and/or different estimators can in certain cases provide a fruitful solution

Larkin J., Minor D., D'Angelo S., Neyns B., Smylie M., Miller W.H. Jr., Gutzmer R., Linette G., Chmielowski B., Lao C.D., Lorigan P., Grossmann K., Hassel J.C., Sznol M., Daud A., Sosman J., Knushalani N., Schadendorf D., Hoeller C., Walker D., Kong G., Horak C., Weber J., Overall Survival in Patients With Advanced Melanoma Who Received Nivolumab Versus Investigator's Choice Chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial. J Clin Oncol. 2018; 36(4):383–390. doi:10.1200/JCO.2016.71.8023

Treatment Switching but nevertheless good results…

Kaplan–Meier estimates of overall survival, according to treatment group

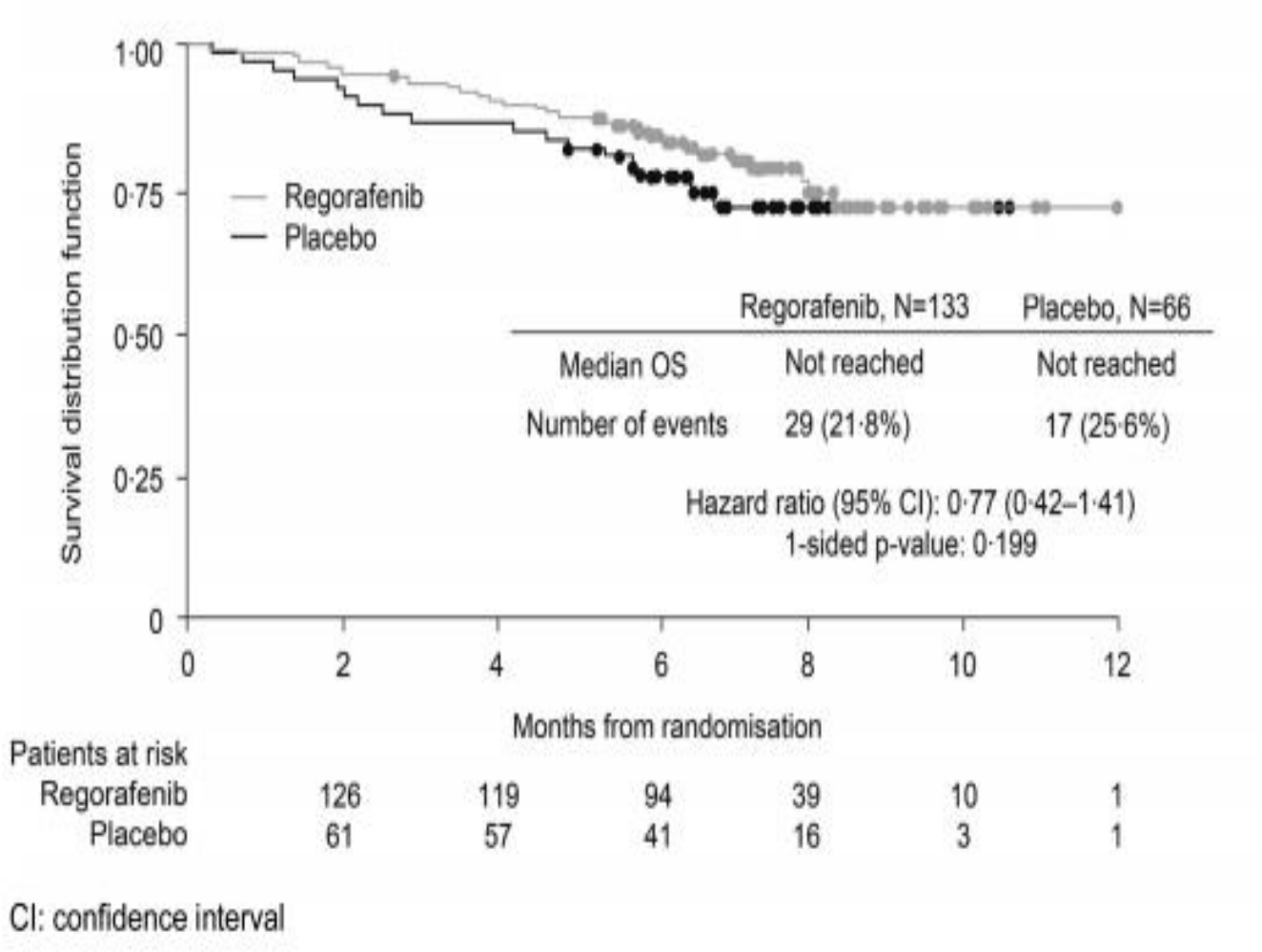


- **Tick marks:** Data censored at the last time the patient was known to be alive
- **Intention-to-treat population:** All patients who underwent randomization

At the time of data cutoff, 35.4% of the enrolled patients had died and 43.7% of the patients in the chemotherapy group had crossed over to receive pembrolizumab.

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu et al.,Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer, The New England Journal of Medicine, October 9, 2016, at NEJM.org.,

Further interesting example (1/2)



The placebo-controlled GRID trial with a high rate of crossover of placebo patients to regorafenib (85%) at progression **were crossover was allowed per protocol**

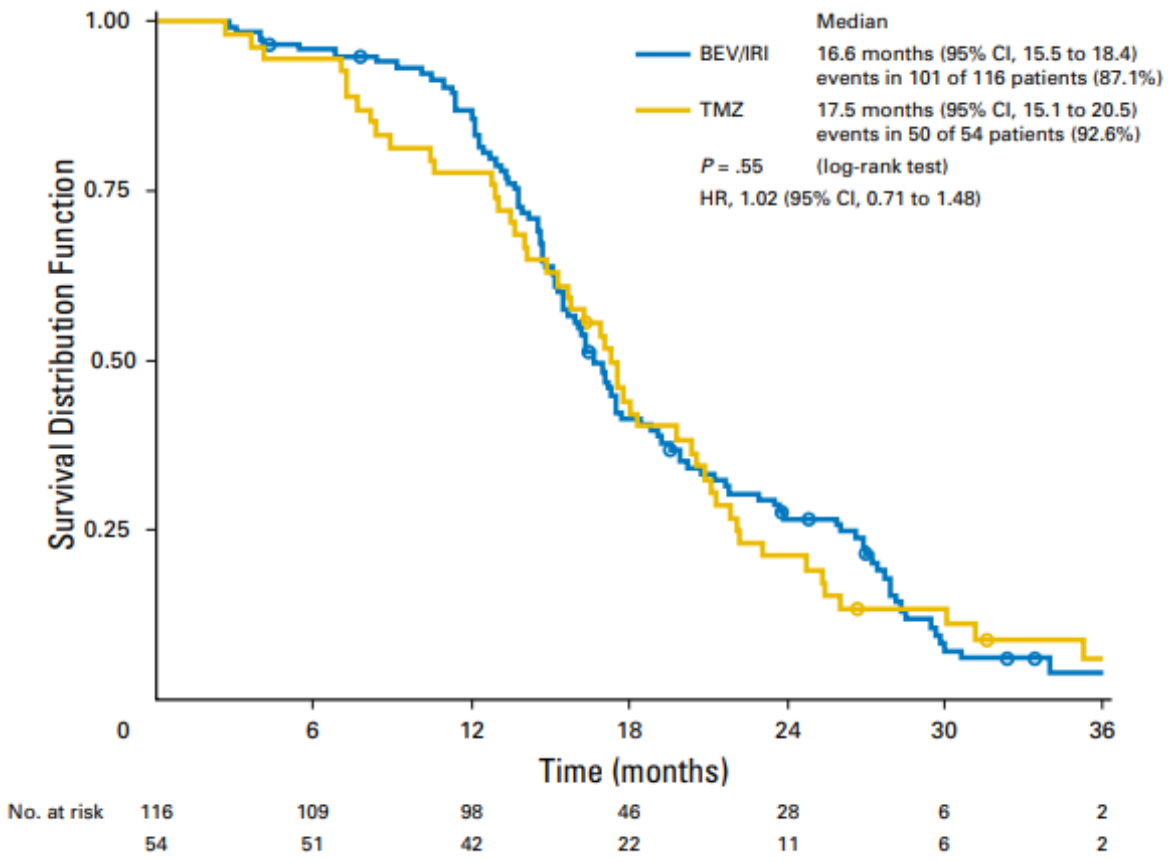
→At primary analysis (ITT), it was shown that regorafenib improved PFS but not OS

Demetri G.D., Reichardt P., Kang Y-K., Blay J-Y., Joensuu H., Wagner A., Kappeler., Casali P.G., Final overall survival (OS) analysis with modeling of crossover impact in phase III GRID trial of regorafenib vs placebo in advanced gastrointestinal stromal tumors (GIST). Journal of Clinical Oncology 34 (4_suppl): 156-156, DOI: 10.1200/jco.2016.34.4_suppl.156.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3819942/pdf/nihms-516975.pdf/?tool=EBI

Further interesting example (2/2)

Overall survival in the modified intention-to treat population (n = 170)



The GLARIUS trial which compared standard temozolomide (TMZ) versus bevacizumab plus irinotecan (BEV+IRI) in patients with newly diagnosed glioblastoma

- Crossover to BEV+IRI therapy was given to 81.8% of all patients who received any sort of second-line therapy in the TMZ arm, affecting OS

➢ Within such settings (similar to scenario 1) it can even happen that, on average, patients in the control arm have a similar exposure to the investigational treatment as the patients in the investigational arm

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