Estimands in clinical trials with treatment switching

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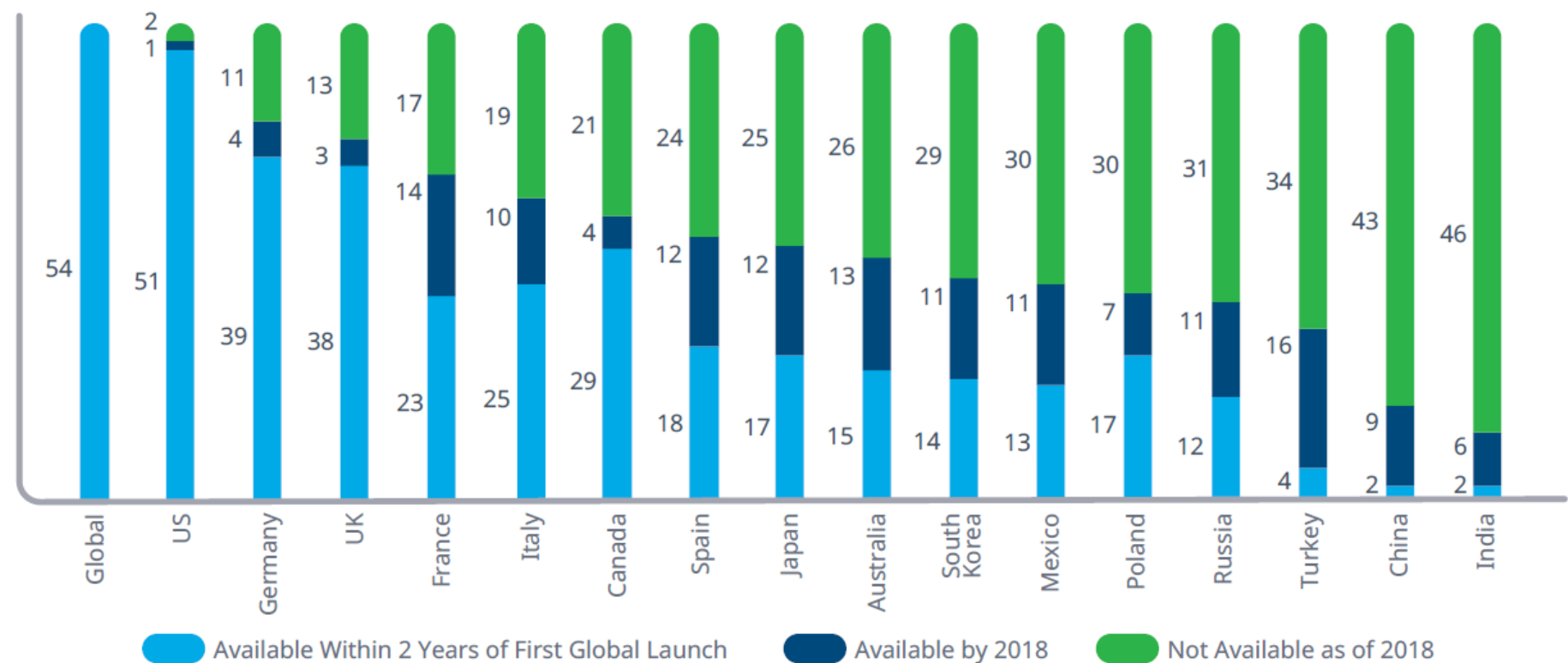
1) Isabary et al, Value in Health 21 (2018), 698-706
2) Latimer, Expert Rev. Pharmacoecon Outcomes Res. 15 (2015), 561-564

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

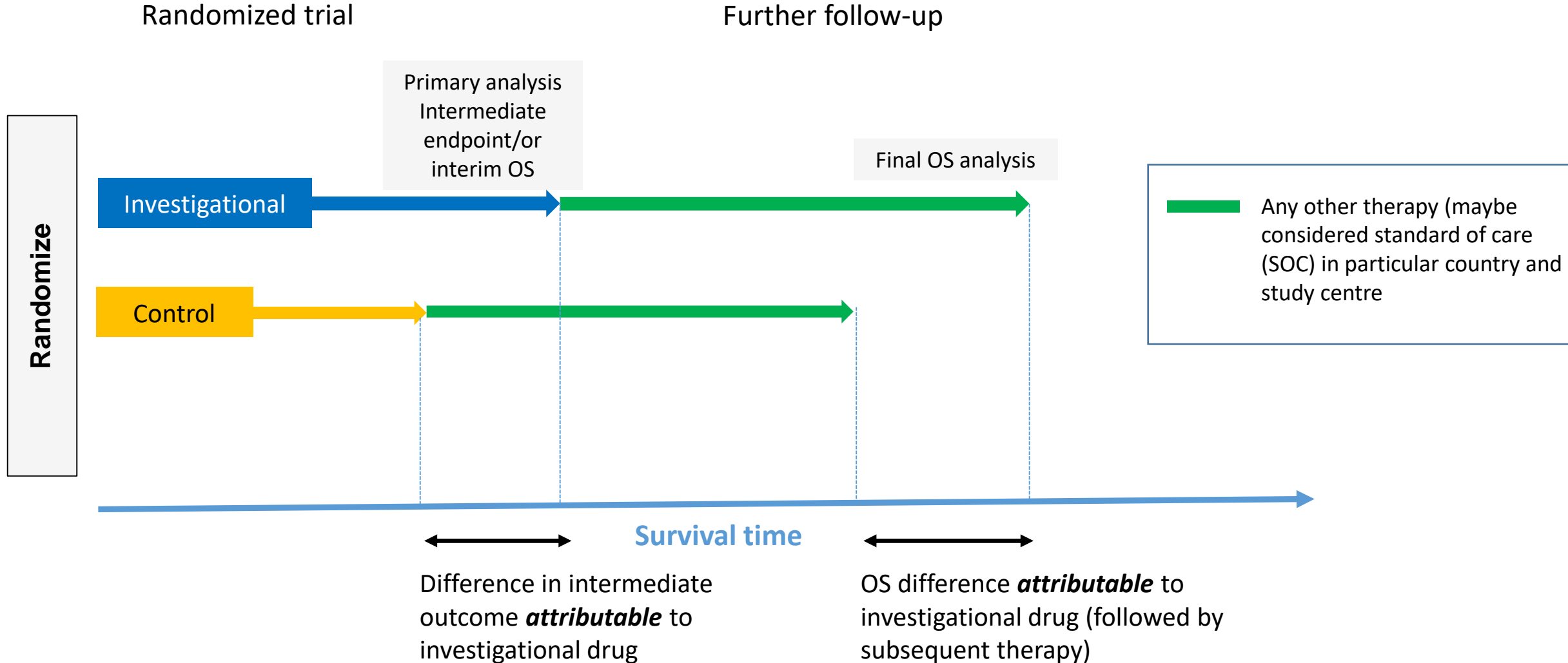Exhibit 24: Availability in 2018 of Oncology Medicines Launched in 2013–2017

Legend: Available Within 2 Years of First Global Launch | Available by 2018 | Not Available as of 2018
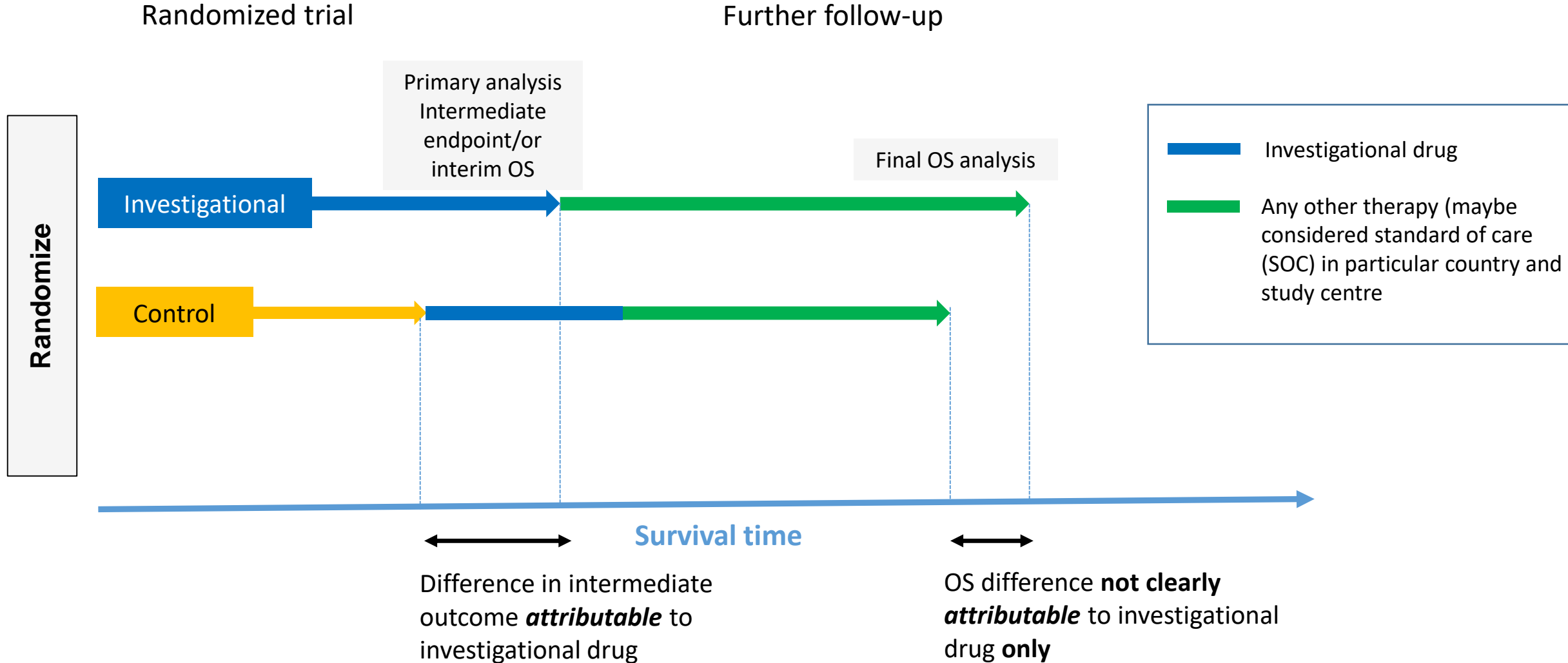
Treatment switching is not just limited to one scenario...

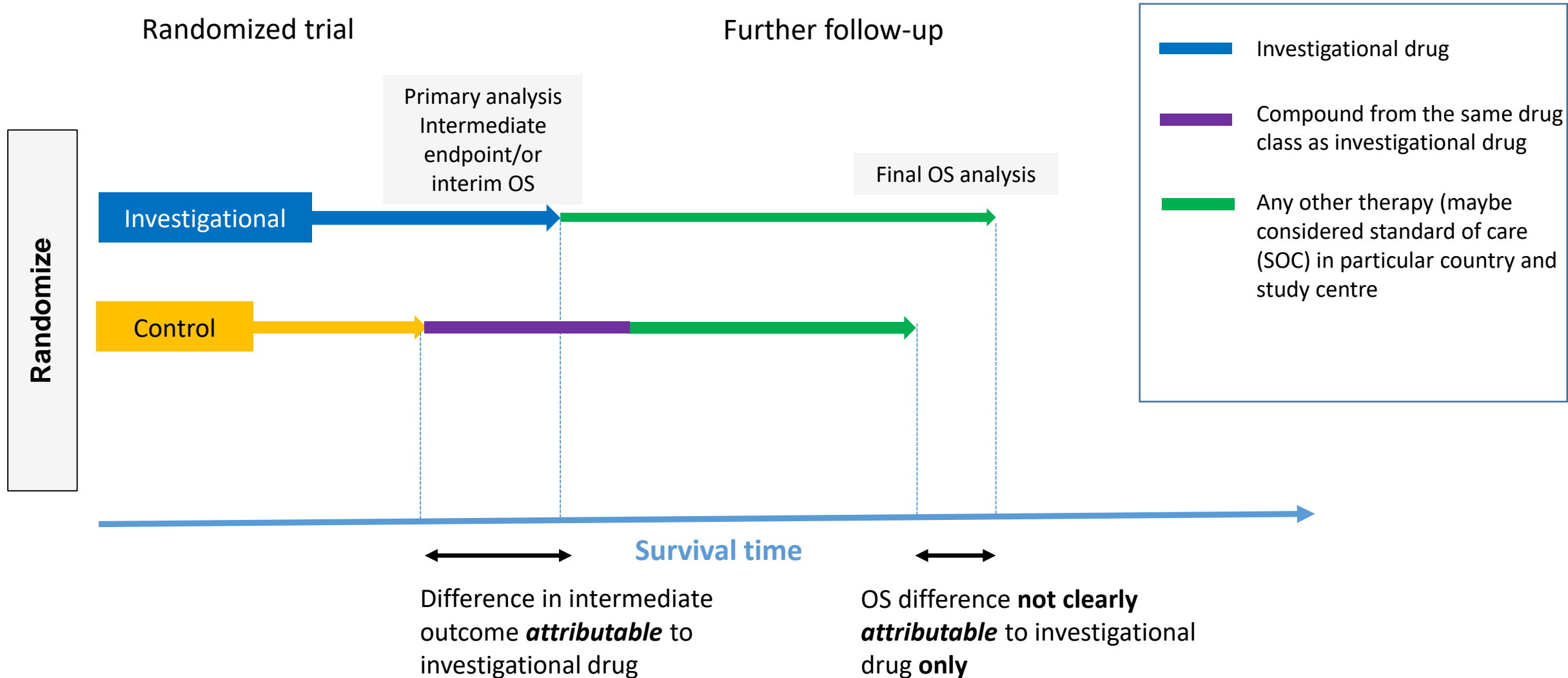| Description of Treatment Switching	Type of Treatment Switching
From control arm to investigational arm	Cross-over
From control arm to same drug class as investigational arm	Treatment Switching, can be analyzed using cross-over methods
From control or investigational arm to drug (class) of interest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

A 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

Randomized trial

Further follow-up

Randomize

Investigational

Control

Primary analysis
Intermediate
endpoint/or
interim OS

Final OS analysis

Survival time

Difference in intermediate outcome *attributable* to investigational drug

OS difference **not clearly** *attributable* to investigational drug **only**

Investigational drug

Compound from the same drug class as investigational drug

Any other therapy (maybe considered standard of care (SOC) in particular country and study centre

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

Randomized trial

Further follow-up

Randomize

Investigational

Control

Primary analysis
Intermediate
endpoint/or
interim OS

Final OS analysis

Survival time

Difference in intermediate outcome *attributable* to investigational drug

OS difference **not clearly** *attributable* to investigational drug **only**

Investigational drug

Compound from the same drug class as investigational drug

Compound from a drug class of interest

Any other therapy (maybe considered standard of care (SOC) in particular country and study centre

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

Now let us switch to the different presenter ...

Change in treatment landscape: a lung cancer example

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

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).

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

Further interesting examples

Example 1:

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.

Example 2:

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

Herrlinger U, Schaefer N, Stainbach JP et al. Bevacizumab Plus Irinotecan Versus Temozolomide in Newly Diagnosed O 6-Methylguanine-DNA Methyltransferase Nonmethylated Glioblastoma: The Randomized GLARIUS Trial. Journal of Clinical Oncology. 2016; 34 (14): 1611-1619. doi: 10.1200/JCO.2015.63.4691

Estimands in clinical trials with treatment switching

OBJECTIVE
ESTIMAND
Population
Variable / Endpoint
Treatment condition of interest
Handling of intercurrent events (IEs)
IE: Start of subsequent therapy at any time
IE: Crossover to investigational drug at ana time
IE: Crossover to investigational drug at disease – related time point
Population - level Summary
ESTIMATION

29.06.2020

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

Conclusions & Summary

- Treatment switching is a reality and should 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

- This 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: