Estimand in Formulation Studies - Insight from IMscin trial

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Due to time constraint only IMscin001 trial is covered in this presentation

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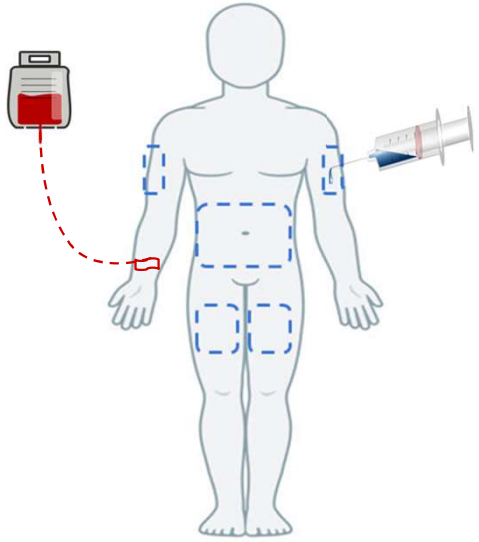
5. Summary

Formulation Studies: Bioequivalence (BE)

- Two test formulations are bioequivalent if their relative bioavailability falls within limits defined by regulatory guidances.
  - Examples: Clinical studies material (Ph2 vs Ph3) to Market formulation, **Change in formulation in late stage,** New formulation for pediatrics.

Intravenous (IV)

- Requires IV access by trained healthcare professionals
- Requires reconstitution or dilution of the IV vial
- Longer administration time
- More burdensome and cost to healthcare centres

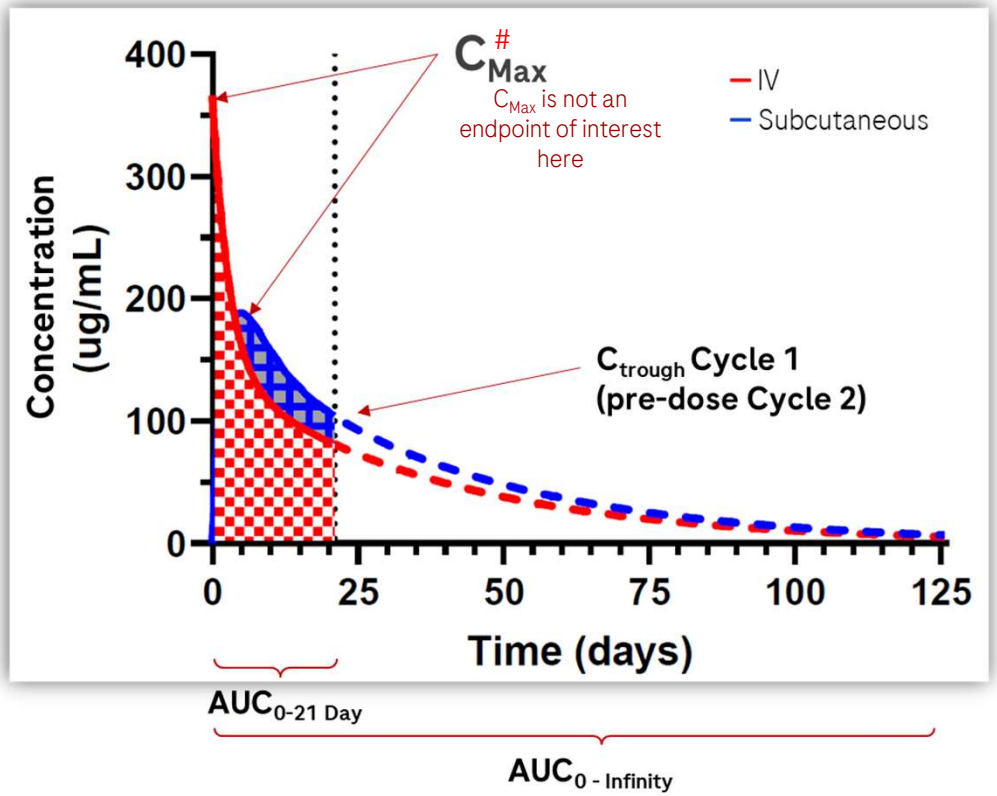


Subcutaneous (SC)

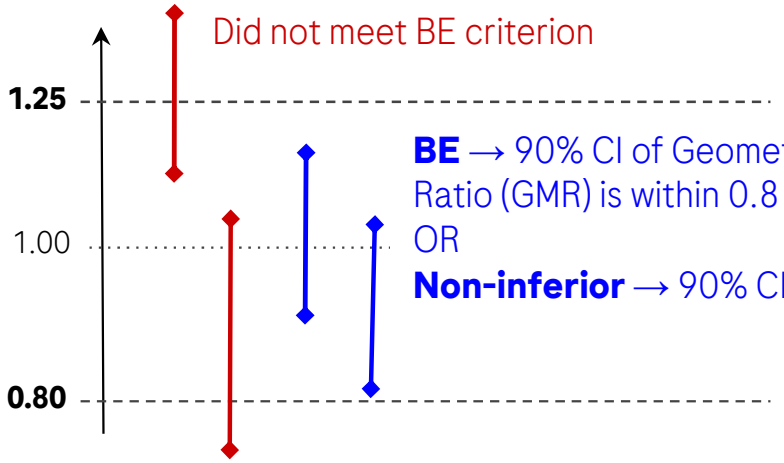
- Easier, greater flexibility, home or self administration
- Reduced pain and discomfort
- "Ready-to-use" SC vial
- Shorter administration time
- Reduced cost & time in clinic and burden on healthcare centres

Formulation Studies: Bioequivalence (BE)

Endpoints: Pharmacokinetics (PK)



BE Criteria*



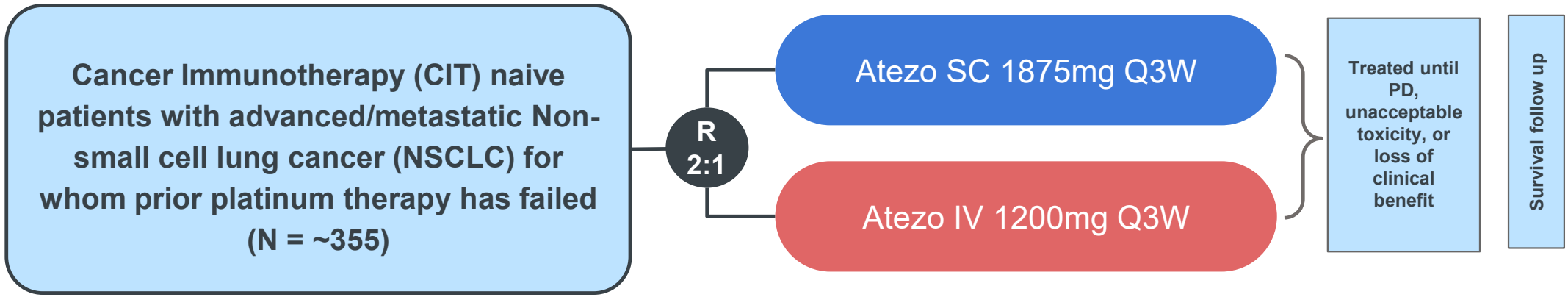
Example: Hypothesis for Non-Inferior scenario

H_0: *SC dose is inferior to the IV dose with a non-inferiority margin less than 0.8 (i.e., the GMR* $C_{trough,SC}/C_{trough,IV} < 0.8$*),*

H_1: *The SC dose is non-inferior to the IV dose (i.e., the GMR* $C_{trough,SC}/C_{trough,IV}$ *is ≥ 0.8*).*

* FDA Draft Guidance: Statistical Approaches to Establishing Bioequivalence, Dec 2022

Introduction - IMscin001 Study (part-2#) [NCT03735121]



Primary Objectives	To demonstrate non-inferiority of exposure to atezolizumab SC compared with atezolizumab IV on the basis of the co-primary endpoints: • **Observed serum C_{trough} at Cycle 1 (predose Cycle 2)** • **Model-predicted AUC from 0 to 21 days at Cycle 1**
Secondary Objectives	**PK* (Model predicted:- $C_{trough, C1}$, $C_{trough, ss}$, and AUC_{ss})**, Progression Free Survival*, Overall Survival*, Objective Response Rate*, Duration of Response, Safety, Immunogenicity and PROs.

 # IMscin001 study was 2 part design. Part 1 focused on dose finding and part 2 on dose confirmation.

** Key Secondary Endpoints*

Bioequivalence (BE) Studies - Pre Estimand!

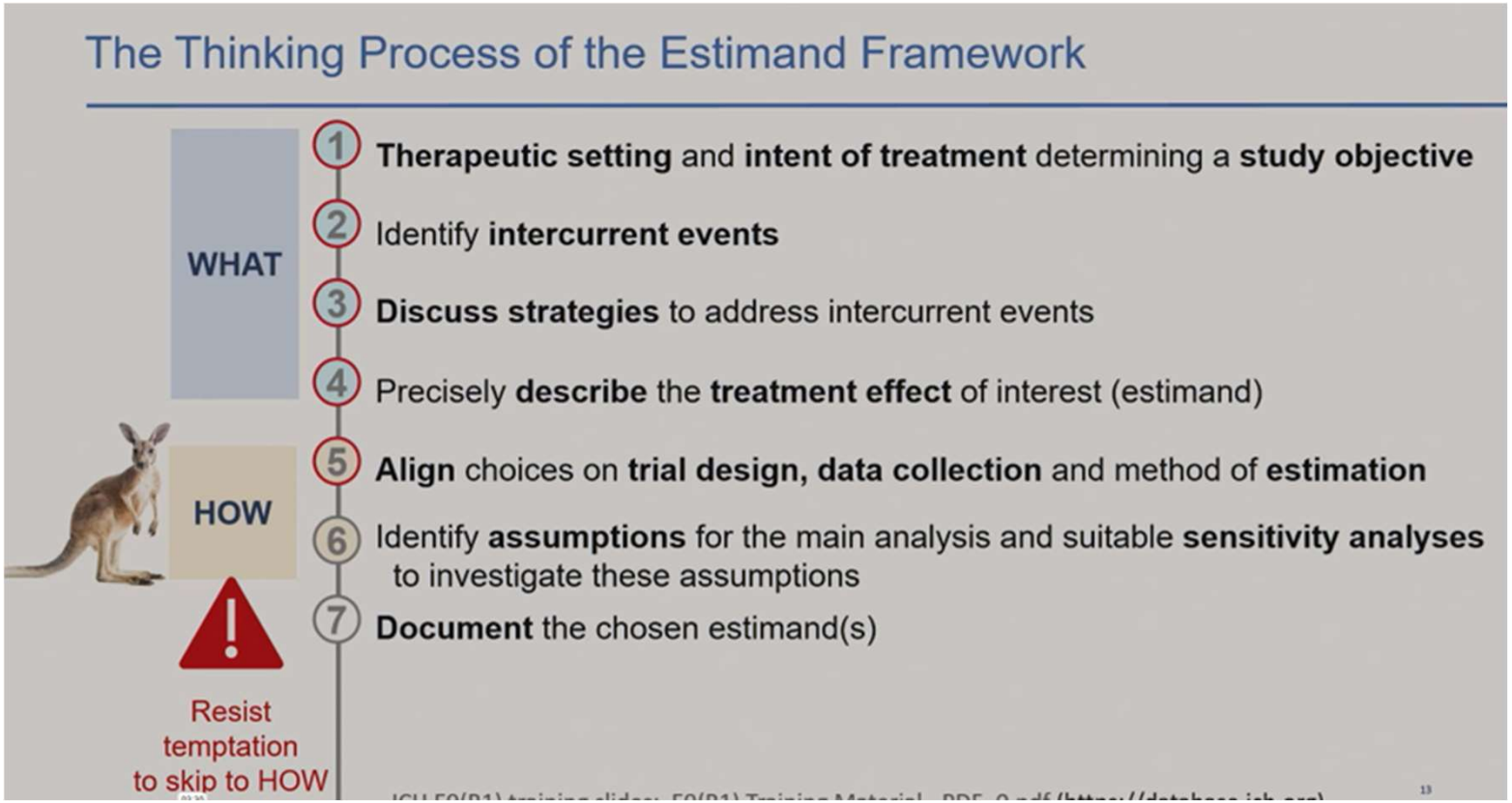
- Pre-Estimand implementation: Example (FeDeriCa study -Primary Analysis 2019)
  - **Per protocol PK evaluable population with exclusion criteria specified in SAP**

Reasons for exclusion from the Per Protocol PK-evaluable may include, but may not be limited to:

- lack of the Cycle 1 C_{trough} (predose Cycle 2) PK sample,
- a C_{trough} sample collected outside the pre-specified window (day 21 +/- 2 days),
- administration of a dose amount that deviates from the planned dose by >20% at Cycle 1,
- use of an injection site other than the thigh at Cycle 1,
- duplicate times of collection for the Cycle 1 C_{trough} sample.

  - Exclusion criteria heavily scrutinised by various regulatory authorities
  - Analysis with different exclusion/inclusion criteria requested by health authorities to assess the robustness of response.
  - Queries from health authorities to check unblinding process and to assess integrity of trial.

Introduction - Estimand



Source: PSI Bioequivalence Publication Team. How Estimands can be applied to Bioequivalence and Other Clinical Pharmacology Trials (PSI Conference 2023) H. Lynggard, S. McKendrick, M. Baird, E. Kerwash, V. Lanius, F. Lash, D. Wright

Implementing Estimand Framework
- Challenges Faced & Resolution

- **Awareness and Adoption of Estimand framework - Journey continues!**
  - Training for Statistician and other stakeholders (Science, Safety, Clinical Pharmacology, etc) is key!
  - Guidance and templates for adoption and standardisation (*e.g. see TransCelerate CPT, SAP and CSR templates (link)*)
  - Continuous training, knowledge sharing to continuously improve the implementation
  - Support from other stakeholders and management in adoption and change in culture

- **Retrospective implementation of estimand in SAP**
  - Recommendation to adopt estimand framework when designing protocol and choice of statistical analysis should not drive estimand
  - Resolution:
    - Discussion with the SME and study team to list any hurdles (e.g. missing data) in adoption
    - Growing examples from Roche, availability of templates, support from SME and study team

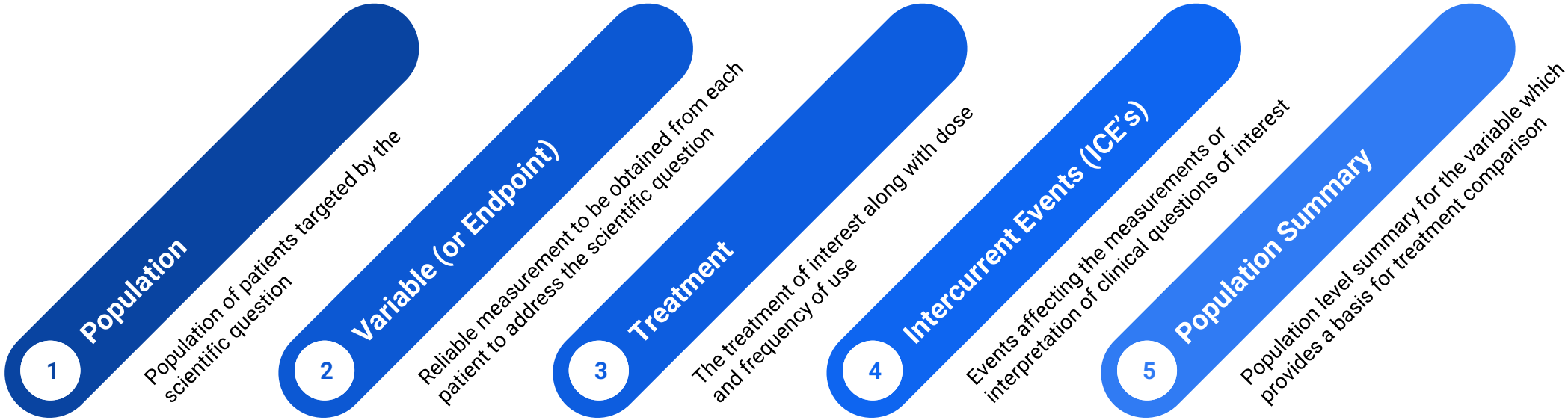
Implementing Estimand Framework
- Challenges Faced & Resolution

- **Relevant data collected in eCRF for estimand implementation**
  - *PK sample collection date and time, injection sites*
  - *details on missing samples &/or reasons for discontinuation.*
  - *further details on participant withdrawal*
  - Resolution:
    - eCRF were detailed and updated due to Roche early adoption hence relevant data were available

- Other stakeholders aware of estimand framework, but some saw it as another statistics jargon and others as an issue for mainly data science!
  - Resolution:
    - **Biostatistics leadership in study is the key to implement estimand framework**

Estimand - Implementation in IMscin001 study

A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared.[1-3]

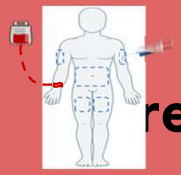
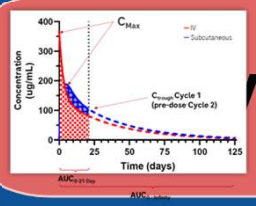


Reference of interest:

1. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. 2020.
2. Estimands in hematologic oncology trials. Sun S, Weber HJ, Butler E, Rufibach K, Roychoudhury S. Pharm Stat. 2021 Jul;20(4):793-805. doi: 10.1002/pst.2108. Epub 2021 Mar 8. PMID: 33686762.
3. Estimands: bringing clarity and focus to research questions in clinical trials. Clark TP, Kahan BC, Phillips A, White I, Carpenter JR. BMJ Open. 2022 Jan 3;12(1)

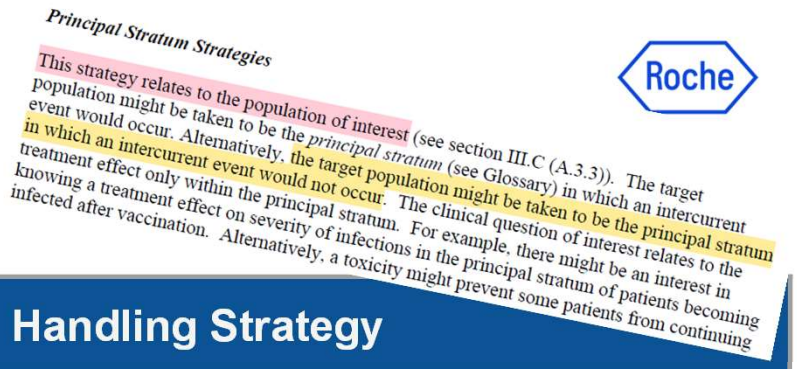
Objectives and Estimand Attributes

To demonstrate non-inferiority of observed drug exposure following treatment with atezolizumab IV compared with atezolizumab SC in patients with locally advanced or metastatic NSCLC who have not been exposed to cancer immunotherapy and for whom prior platinum- based therapy has failed.

Population	**Patients with locally advanced or metastatic NSCLC who are CIT-naive & for whom prior platinum therapy has failed**
 **reatment**	**Atezolizumab SC or IV (at the determined dose at baseline)**
 **/ariable**	**(i) Observed serum C_{trough} at Cycle 1 (predose Cycle 2)** **(ii) Model-predicted AUC from 0 to 21 days at Cycle 1**

Other key secondary endpoints such as PFS, OS not covered here

Intercurrent Events (ICE) and Handling Strategy



Principal Stratum Strategies

This strategy relates to the population of interest (see section III.C (A.3.3)). The target population might be taken to be the *principal stratum* (see Glossary) 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. For example, there might be an interest in knowing a treatment effect on severity of infections in the principal stratum of patients becoming infected after vaccination. Alternatively, a toxicity might prevent some patients from continuing

Intercurrent Events (ICEs)		Handling Strategy					
		Treatment Policy	Hypothetical	Composite Variable	While on Treatment	Principal Stratum	Other ?
Observed Cycle 1 C_{trough}	Premature discontinuation before cycle 2 from treatment/study			Missing data and not ICE			
	Wrong injection site					✓	
	Inaccurate or outside of window PK samples					✓	
Modelled Cycle 1 $AUC_{0-21\ d}$	Premature discontinuation before cycle 2 from treatment/study			Missing data and not ICE			
	Absence of post-treatment PK blood sample					✓	
	Inaccurate time/date for administration or PK blood samples					✓	

Is Principal Stratum the correct handling strategy?

Principal Stratum (PS) or Subgroup?

Definition Principal Stratification (ICH E9R1, May-21):

*"Classification of subjects according to the **potential** occurrence of an ICE on all treatments. With two treatments, there are four principal strata with respect to a given intercurrent event. [...]"*

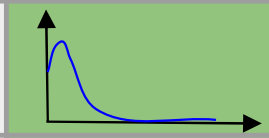
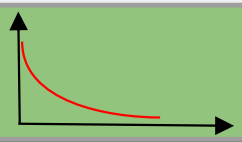
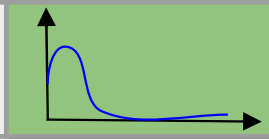
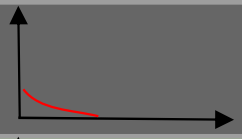
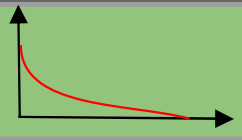
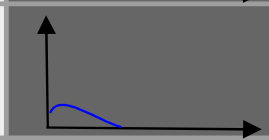
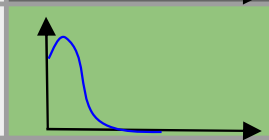
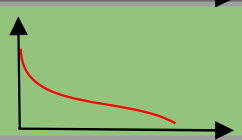
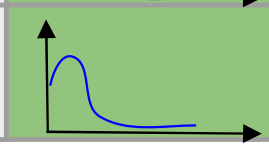
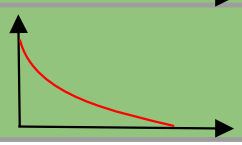
*"It is important to distinguish "principal stratification" [...], which is based on **potential** intercurrent events [...], from subsetting based on **actual** intercurrent events [...]"*

- The former leads to the use of causal analysis for its natural estimation framework, which requires a predictive model
- The latter leads to a subgroup analysis, which in general breaks down randomization for treatment comparison and should be avoided

→ Naming solely a strategy is not sufficient; precise definition of handling ICE is mandatory

Analysis Set

PS terminology replaced by “Subjects with ICE and missing data excluded from the analysis set”

Participant	SC Arm	Participant	IV Arm
1		A	
2		B	 Inaccurate or outside of window PK samples
3	 Missing data Premature discontinuation from treatment	C	
4	 Wrong injection site	D	 Missing data Absence of post-treatment PK blood sample
5		E	
6		F	

Overview of Primary Estimand in IMscin001 Study

Objective: To demonstrate non-inferiority of observed drug exposure following treatment with atezolizumab IV compared with atezolizumab SC in patients with locally advanced or metastatic NSCLC who have not been exposed to cancer immunotherapy and for whom prior platinum- based therapy has failed.

Estimand: Observed Cycle 1 C_{trough} in patients with correct PK samples

Main Estimator: General linear mode *(Missing, inaccurate or outside of window PK excluded from analysis set)*

Main Estimate: GMR & 90% CI of Atezo SC vs. IV of Cycle 1 C_{trough}

Estimand: Cycle 1 C_{trough} values derived from the popPK model

Supplementary Estimand 1: Model Cycle 1 C_{trough}

Main Estimate: GMR & 90% CI of Atezo SC vs. Atezo IV

Estimand: Modeled $AUC_{0\text{-}21d}$ in patients with at least one post-baseline PK sample

Main Estimator: General linear model *(missing or inaccurate samples excluded from analysis set)*

Main Estimate: GMR & 90% CI of Atezo SC vs. IV of Cycle 1 model predicted $AUC_{0\text{-}21d}$

Results all in agreement providing robust basis for treatment comparison

Summary

- Biostatistics leadership in study to advocate and implement estimand framework, and to educate stakeholders on the value of the framework
- Intricacies of PK trials remain underexplored in ICH E9(R1) and in FDA Bioequivalence guidance hence we need growing relevant examples and case studies from the Data Science and Clinical Pharmacology community.
- Naming solely a strategy is not sufficient; precise definition of handling intercurrent event is mandatory
- Health Authority scrutiny observed in FeDeriCa study was not seen with IMscin001 and relate to robust estimands.

Doing now what patients need next