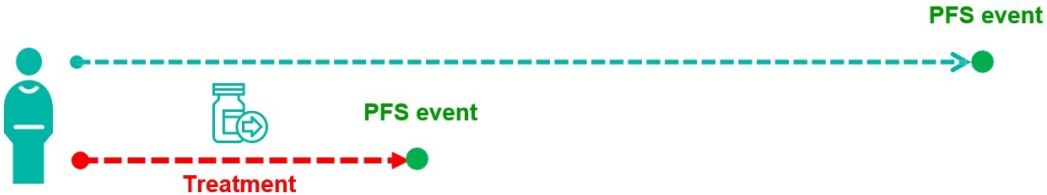
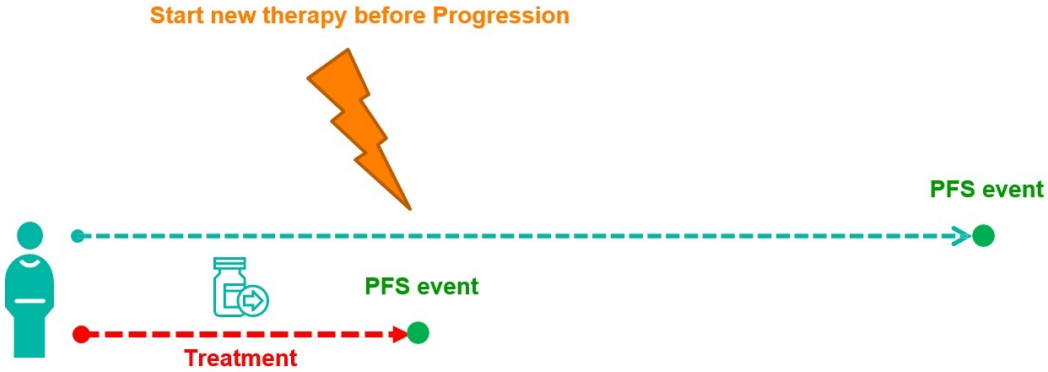
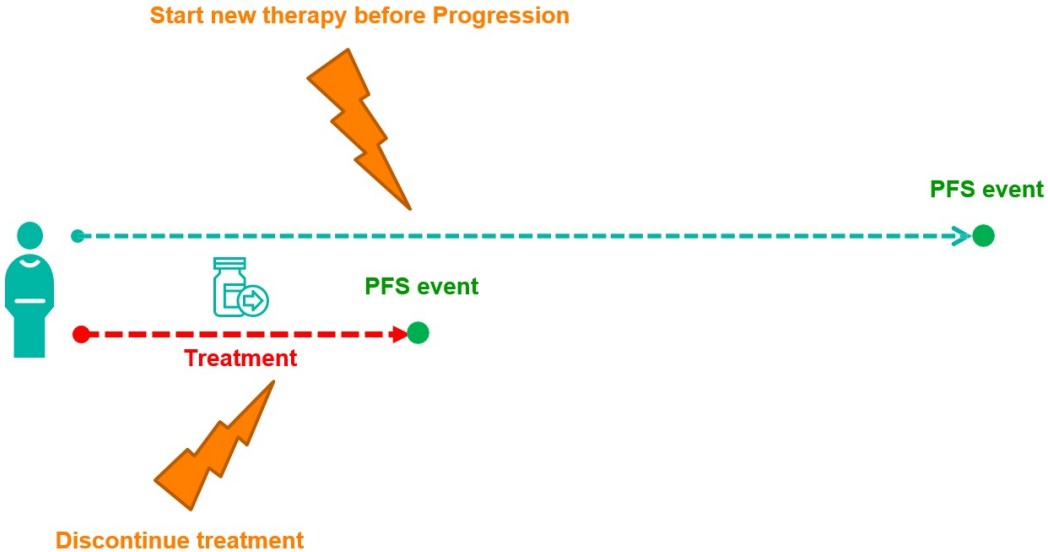
Good outcome:

This is something I need to look into,
as it will help me in my work!


PFS event
Treatment


PFS event
PFS event
Treatment


Start new therapy before Progression
PFS event
PFS event
Treatment


Start new therapy before Progression
PFS event
PFS event
Treatment
Discontinue treatment

Do these clinical events affect your interpretation of the treatment effect?

Is the treatment effect clearly defined?

What data would you collect?

If you do not know how to ask the right question, you discover nothing.

W.E. Deming, American Statistician

Past: too sloppy in translating clinical trial objectives to clear statistical quantities.

1) Stakeholders not aligned.

2) Analysis method not aligned to scientific question.

3) Data collection requirements unclear.

4) Heterogeneity between trials.

Present and future:

ICH E9(R1) estimands addendum.

Clear upfront definition of treatment effect of interest.

Have discussions upfront.

Get clarity early on.

Shorten filing timelines.

Polarix Oncologic Drugs Advisory Committee (ODAC).

2-arm RCT in DLBCL.
R-CHOP vs. R-CH-Polatuzumab-P.
Primary endpoint: "PFS".

Is it clear what ”PFS” is?

Estimand attribute	Analysis 1 (pre-specified in SAP): PFS as per protocol	Analysis 2 (requested by FDA): PFS with censoring at NALT
Population	As per protocol	
Endpoint	PFS: time to PD or death	
Summary measure	Hazard ratio	
Treatment conditions	As per protocol	

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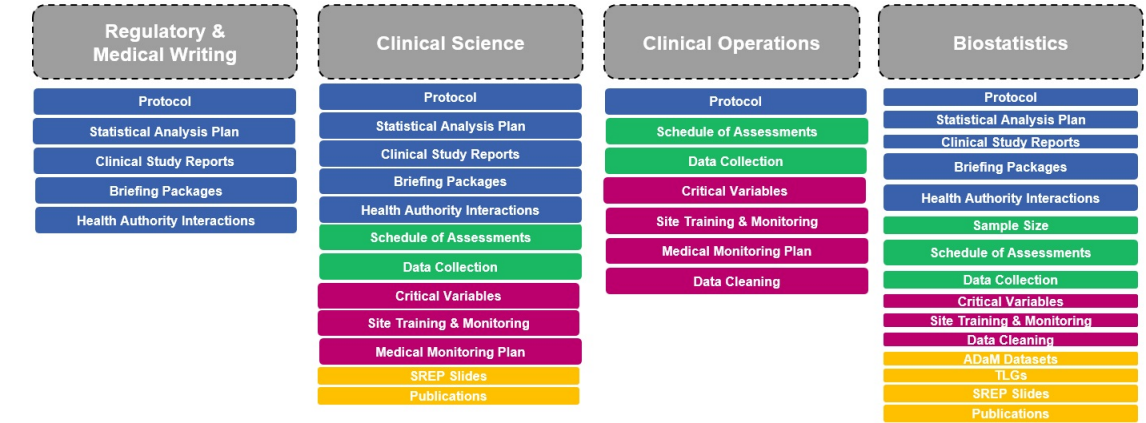
Treatment conditions	As per protocol	
Intercurrent events and handling strategy	NALT Treatment policy	NALT “censoring”?
P-value	0.0177	0.0567
Implied scientific question	What is the time to PD / death irrespective of taking NALT?	What is the time to PD / death assuming NALT would not exist?

Do I need to care?

Yes!


Regulatory & Medical Writing
Protocol
Statistical Analysis Plan
Clinical Study Reports
Briefing Packages
Health Authority Interactions
Clinical Science
Protocol
Statistical Analysis Plan
Clinical Study Reports
Briefing Packages
Health Authority Interactions
Schedule of Assessments
Data Collection
Critical Variables
Site Training & Monitoring
Medical Monitoring Plan
SREP Slides
Publications
Clinical Operations
Protocol
Schedule of Assessments
Data Collection
Critical Variables
Site Training & Monitoring
Medical Monitoring Plan
Data Cleaning
Biostatistics
Protocol
Statistical Analysis Plan
Clinical Study Reports
Briefing Packages
Health Authority Interactions
Sample Size
Schedule of Assessments
Data Collection
Critical Variables
Site Training & Monitoring
Data Cleaning
ADaM Datasets
TLGs
SREP Slides
Publications
Regulatory Documentation
Trial Design
Study Conduct
Analysis & Reporting

Covid.

Ukraine war.

Patients!

Physicians. Investigators.

Trial developers.

Regulators.

HTA bodies.

Precise formulation of clinical question of interest: not a stats thing!

How about regulators?

Ionan et al. (2023+) (paper written jointly by FDA and industry authors):

- "Statistical and clinical colleagues typically collaborate closely during the FDA review of regulatory submissions. **Use of the estimand framework can improve the efficiency and quality of this collaboration.** Collaborative discussions are sometimes especially challenging due to multiple complex trial design and analysis issues. **The estimand framework provides a structure to facilitate such discussions.**"
- "This framework has already proved very useful, not only in tackling new questions but also in **understanding better "old" problems**. Our subjective experience has been that **estimand thinking has been well-accepted so far and that uptake is good.**"

Shanti Gomatam (FDA statistician) in BBS seminar on 12th April 2023:

- "My appreciation of the estimand framework has increased over time."
- "The estimand framework is useful even in cases where we do not officially implement it. It helps me to get points across more precisely."

It is not innovative if it does not work.

Mark Baillie, Statistician at Novartis in Basel

Thank you for your attention.

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Slides can be downloaded on
www.kasparrufibach.ch

References I

Ionan, A. C., Paterniti, M., Mehrotra, D. V., Scott, J., Ratitch, B., Collins, S., Gomatam, S., Nie, L., Rufibach, K. and Bretz, F. (2023+). Clinical and statistical perspectives on the ICH E9(R1) estimand framework implementation **15** 554–559. https://doi.org/10.1080/19466315.2022.2081601

Doing now what patients need next

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R version: R version 4.2.3 (2023-03-15 ucrt)
Base packages: stats / graphics / grDevices / utils / datasets / methods / base
Other packages:

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