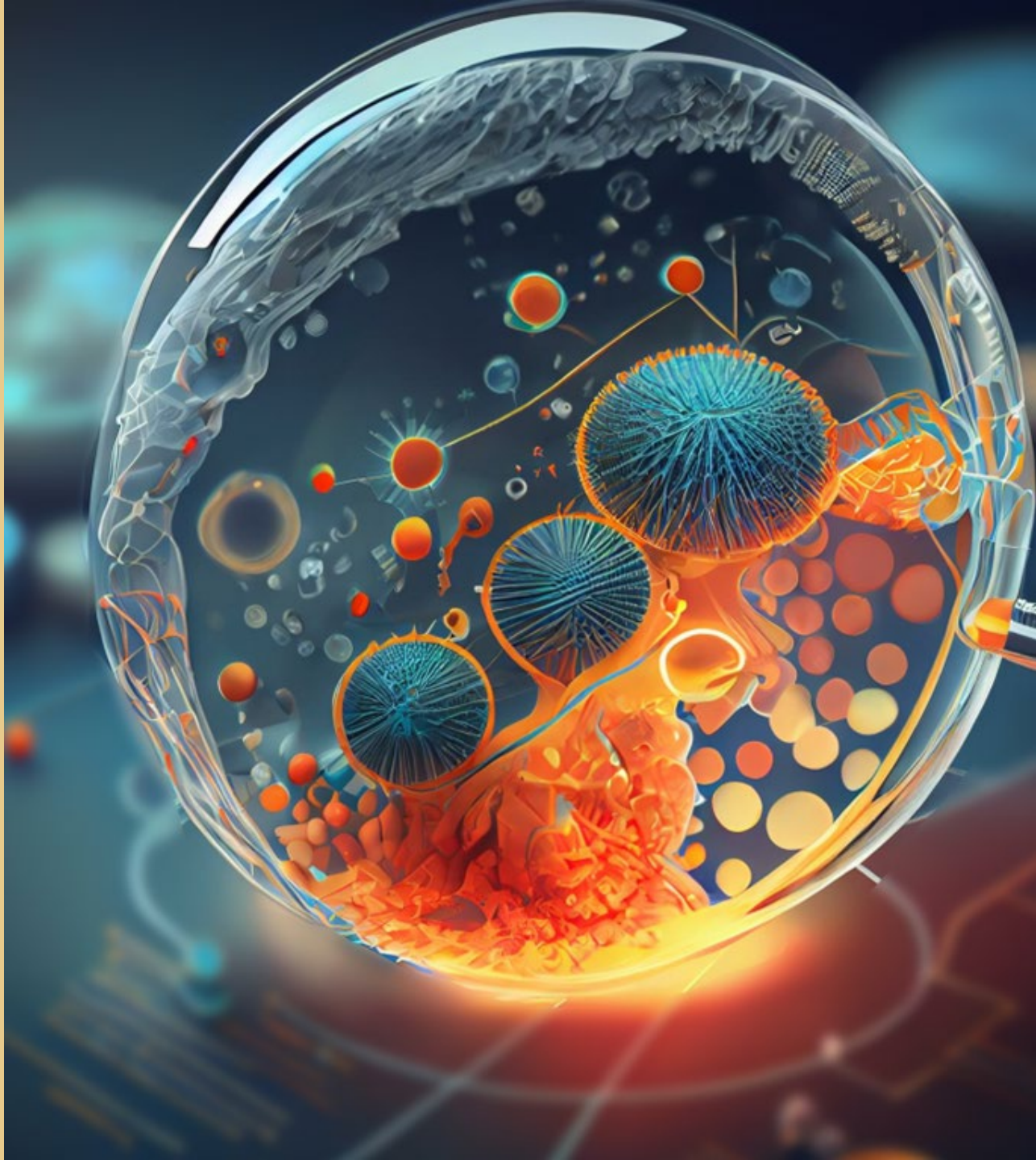
eha Sf(PM)

Trial design of precision medicine studies

N-of-1 and others



September 25 2024 Philipp Staber

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for the right patient

at the right time

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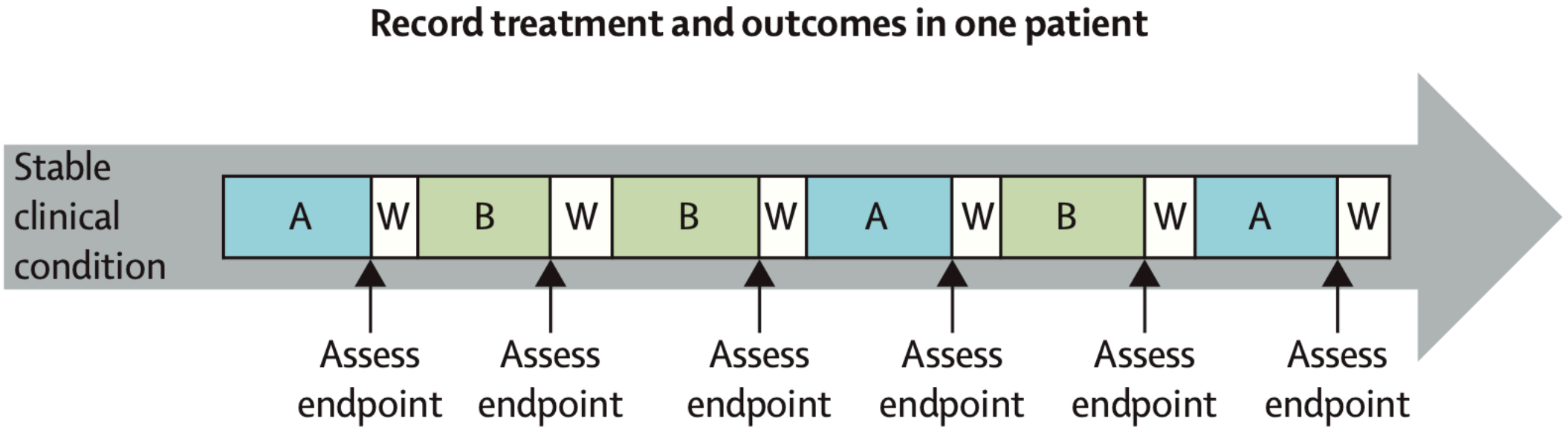
N of one study design

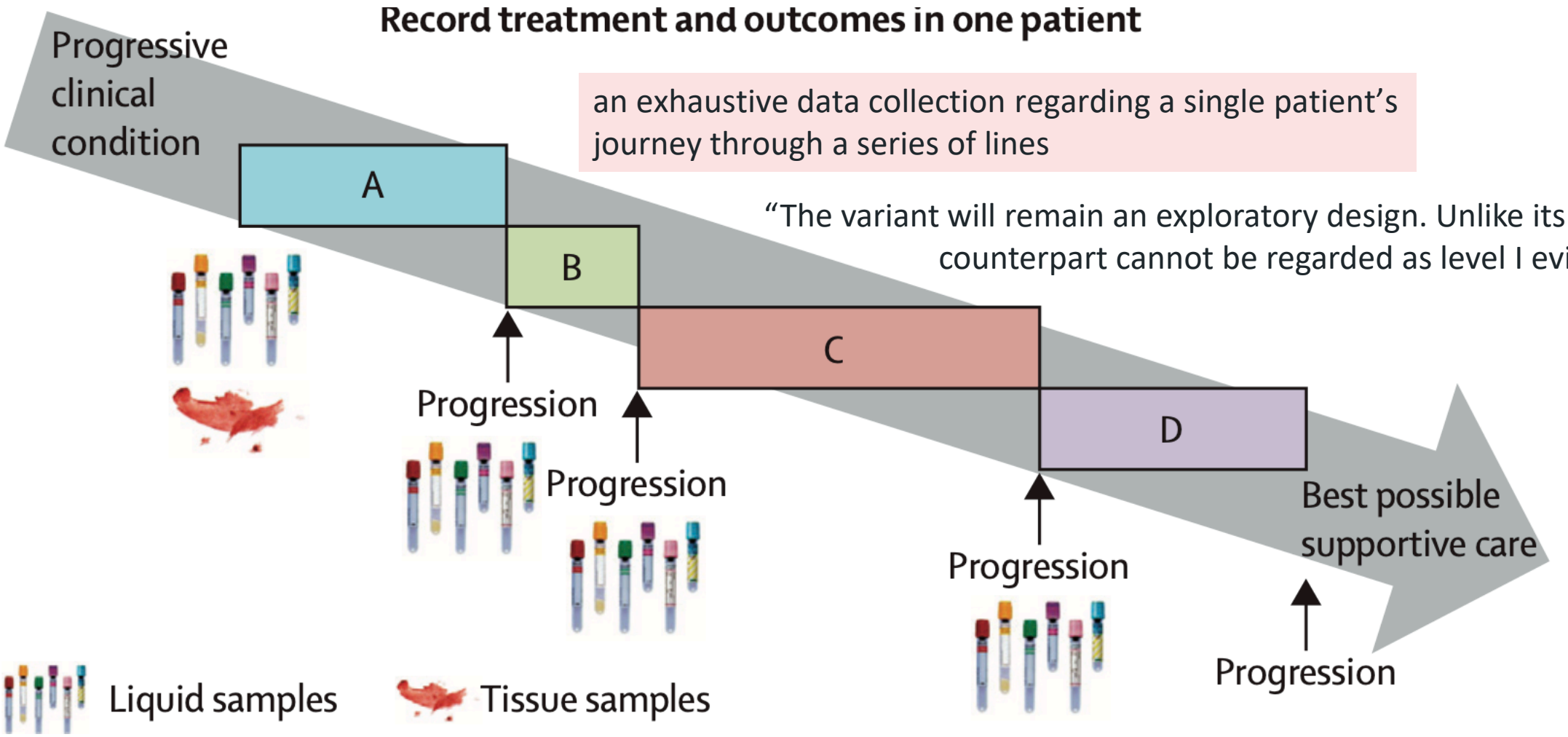


- repeated cycles of treatments challenge (eg, A-B-A-B) in a single participant
- A is the test drug and B is the comparison drug
- ie, a single patient, multi-cycle crossover trial

In oncology, clinicians are not willing to re-challenge a patient with a drug that did not work

Collette L, Tombal B. Lancet Oncol. 2015

N of one study design in oncology

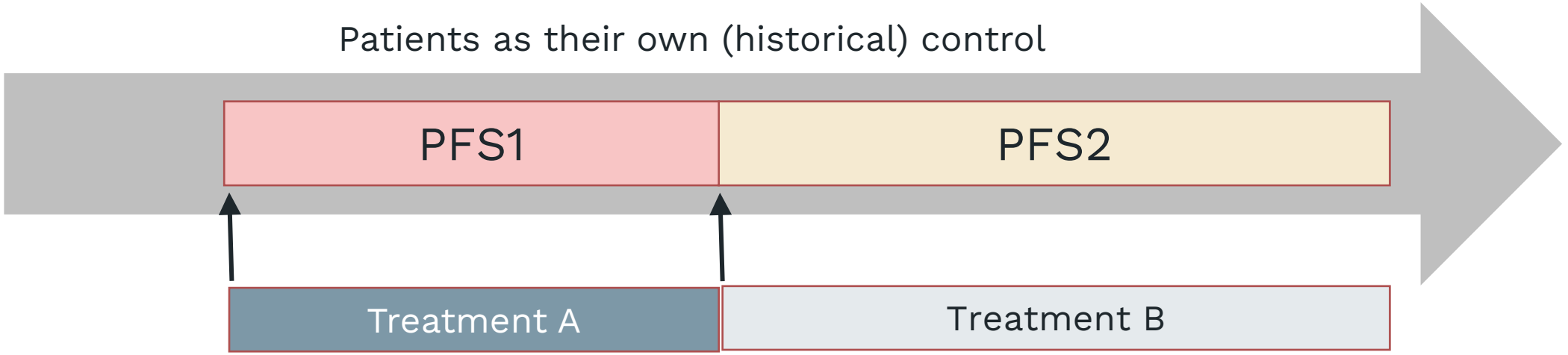


an exhaustive data collection regarding a single patient's journey through a series of lines

"The variant will remain an exploratory design. Unlike its original counterpart cannot be regarded as level I evidence."

Collette L, Tombal B. Lancet Oncol. 2015

N of one study design in oncology variant: progression-free survival ratio



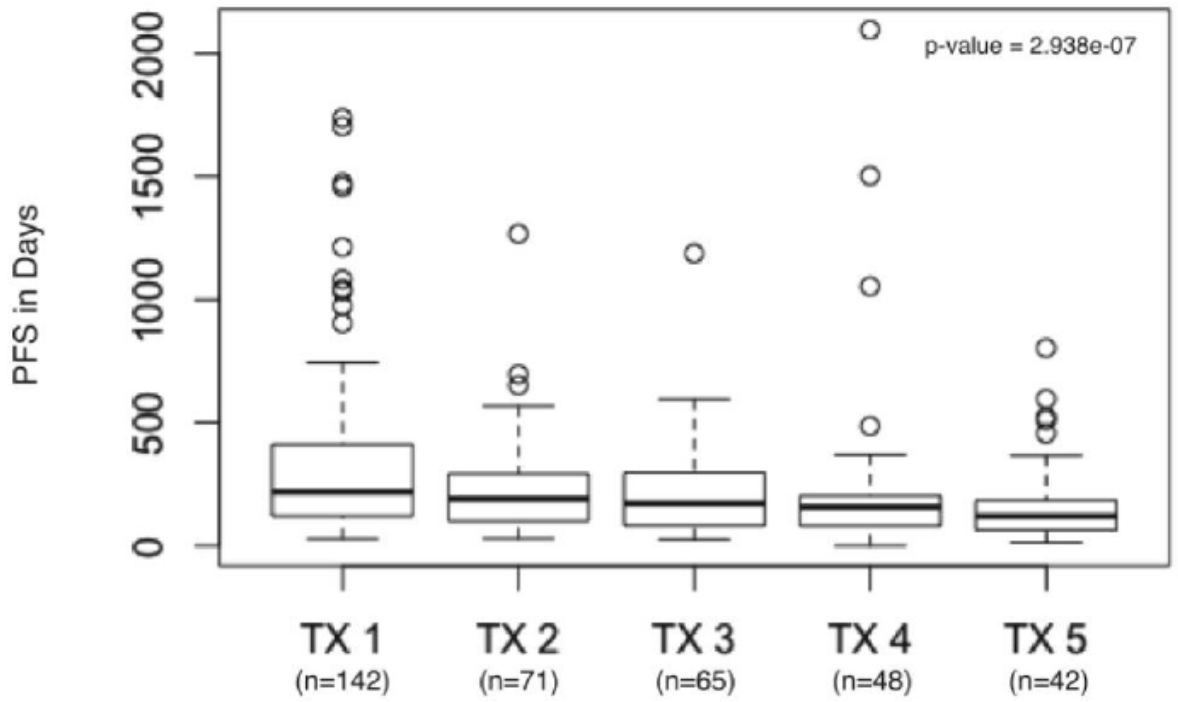
- Compares the PFS by a new treatment (PFS2) to the antecedent treatment (PFS1)
- Clinical benefit is defined as a **PFS2/PFS1 >1.3,** **H_0 hypothesis of 15%**
- This paired analysis within individual patients should compensate for heterogeneity

- 1.3 threshold and 15% assumption have only been weakly substantiated
- Selection bias on participants with short PFS1

- H_0 assumption needs disease stage specific determination or a randomized comparison

Van Hoff et al JCO 1998

Progression-free Survival decreases with each subsequent therapy in p1 trials



- H_0 assumption needs disease stage specific determination or a randomized comparison

Bailey CH et al J.o.Cancer 2012

Precision medicine

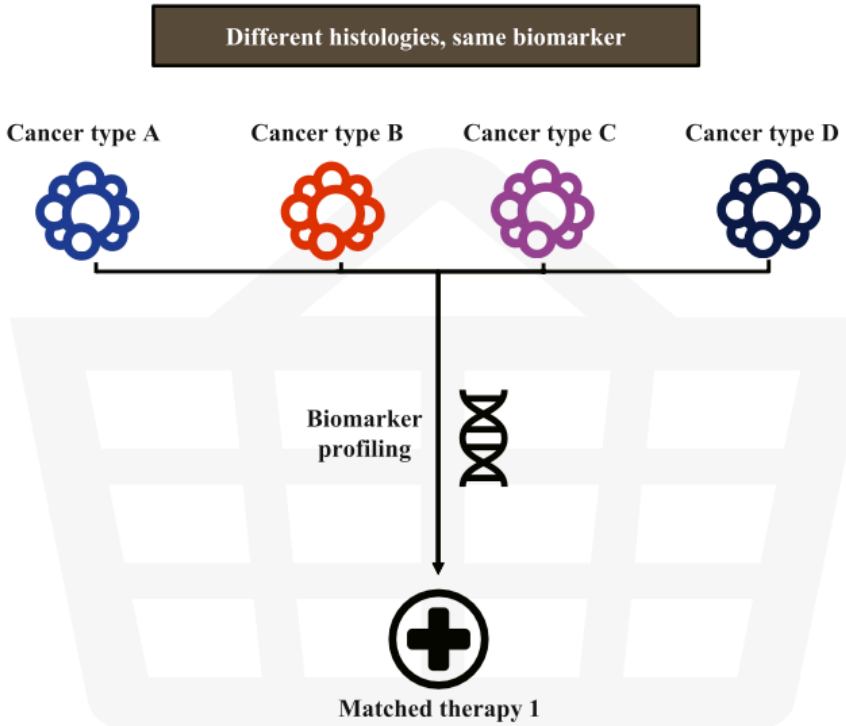
The right drug

for the right patient

at the right time

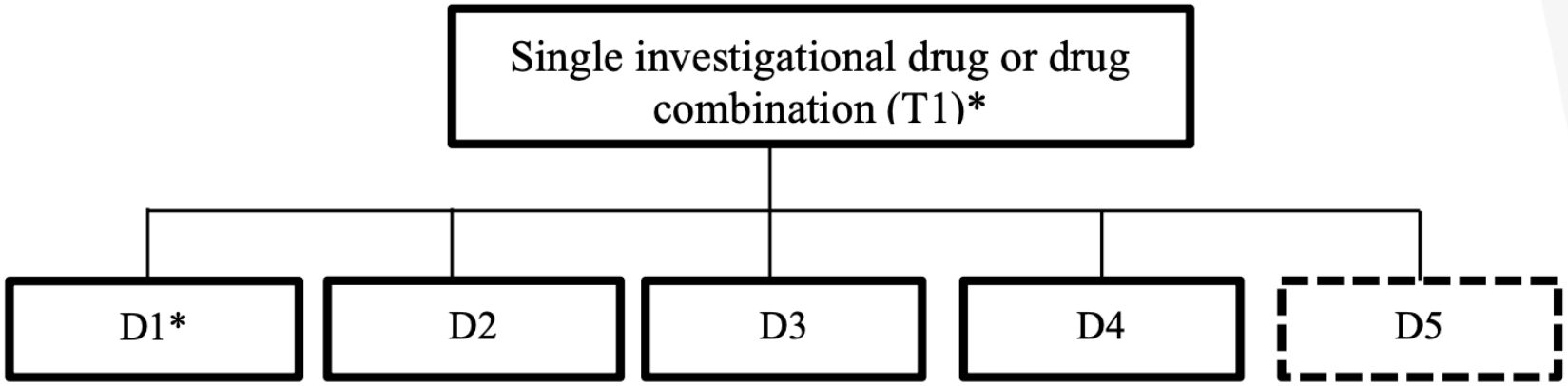
How to put this into a clinical study?

Precision medicine



basket design

The right drug



* T = investigational drug; D = protocol-defined subpopulation in multiple disease subtypes; D5 = dashed lines indicate potential amendments to include additional subpopulations.

U.S. Department of Health and Human Services Food and Drug Administration
March 2022 procedural
Le Tourneau C. et al. European Journal of Cancer 2023

Precision medicine

The right drug

for the right patient

at the right time

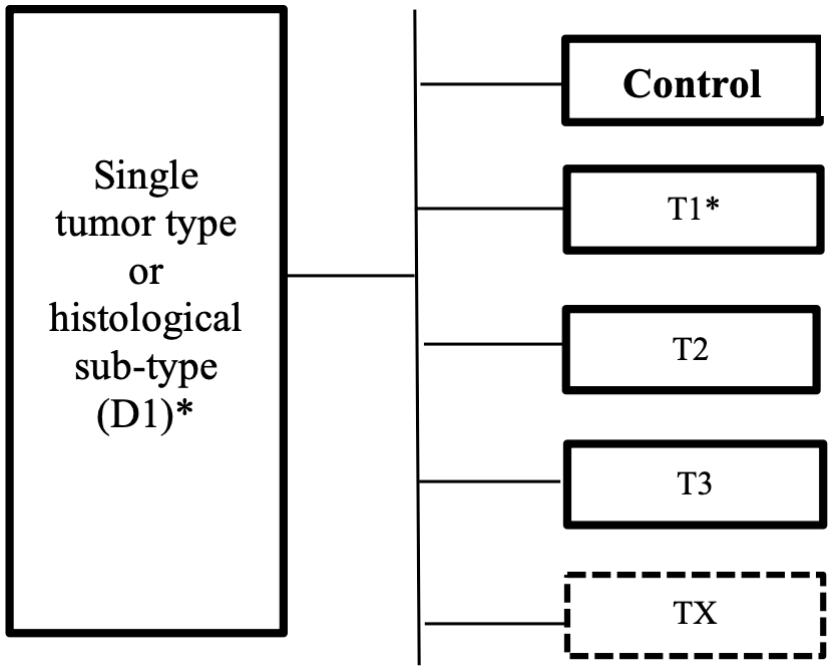
How to put this into a clinical study?

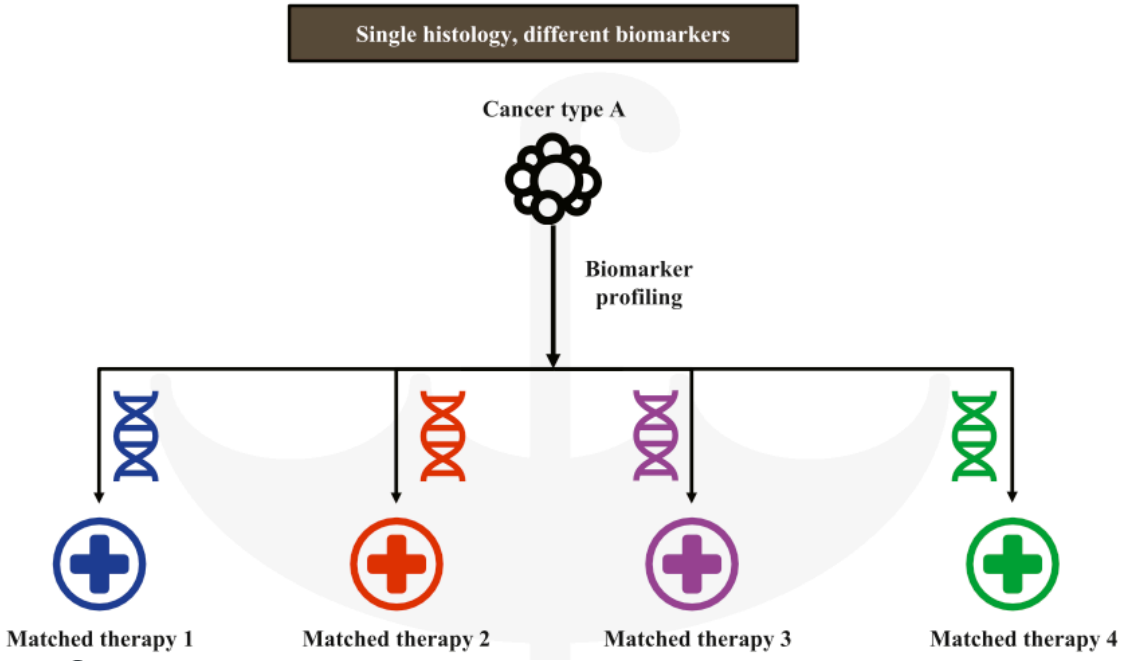
Precision medicine

umbrella design

The right drug

for the right patient



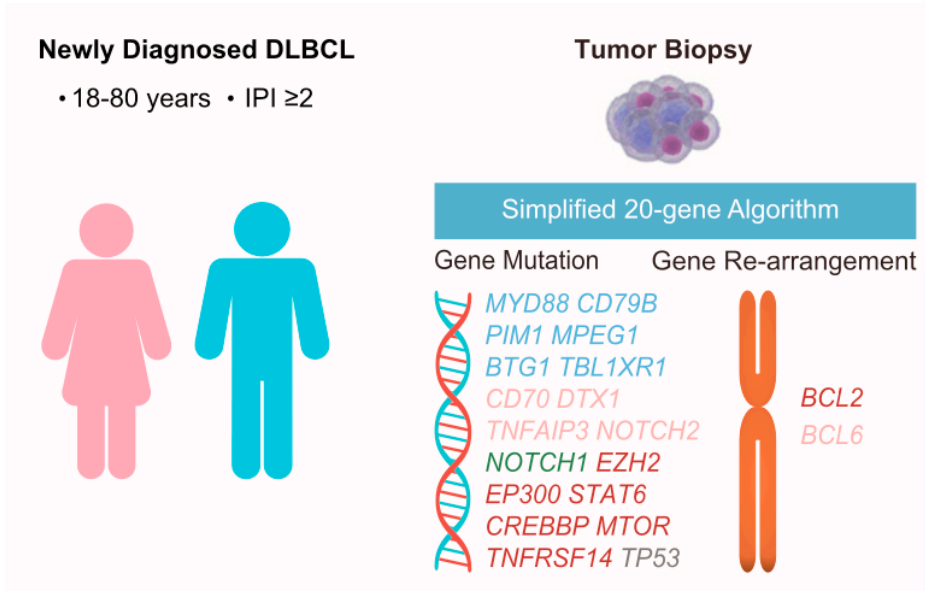


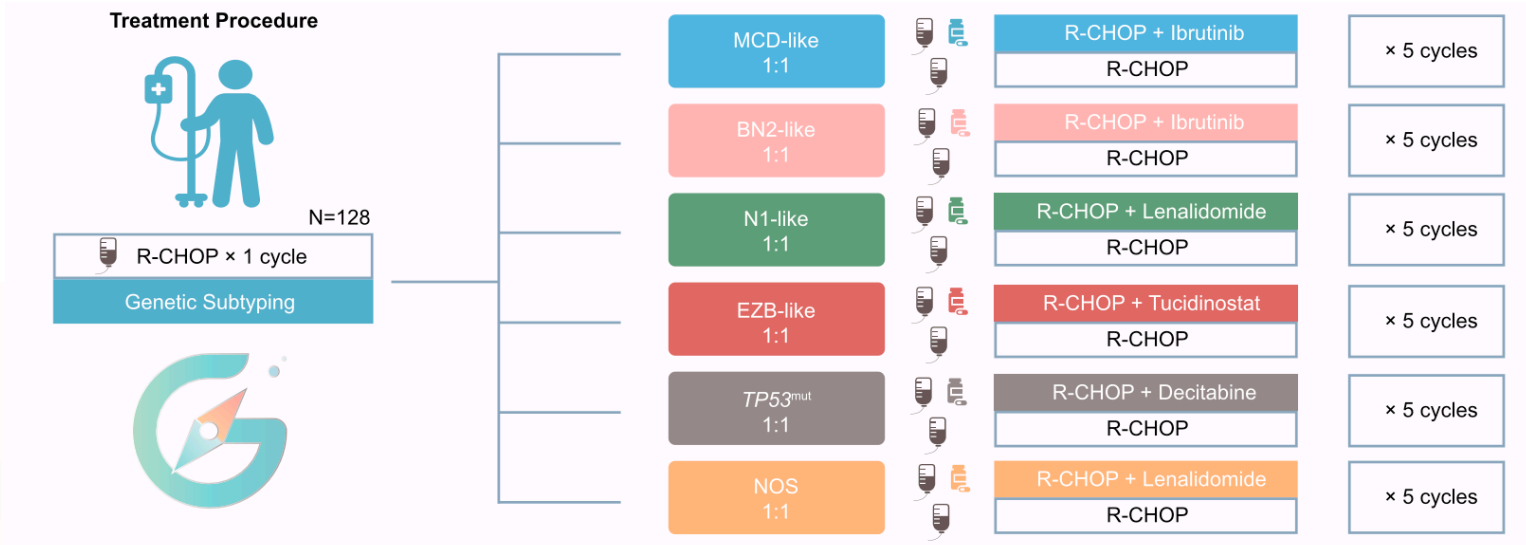
* T = investigational drug or investigational drug combination; D = protocol defined subpopulation in single disease subtypes; TX = dashed lines indicate potential amendments to include future treatment arms.

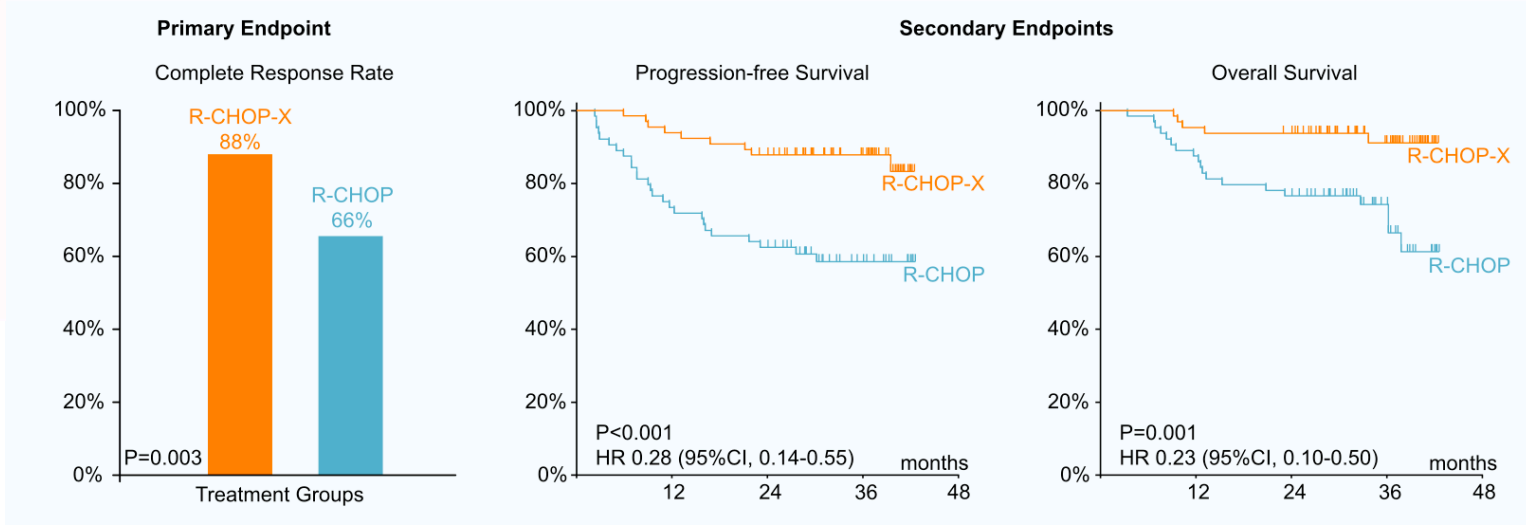
U.S. Department of Health and Human Services Food and Drug Administration March 2022 procedural
Le Tourneau C. et al. European Journal of Cancer 2023

Example of umbrella design

GUIDANCE-01 trial



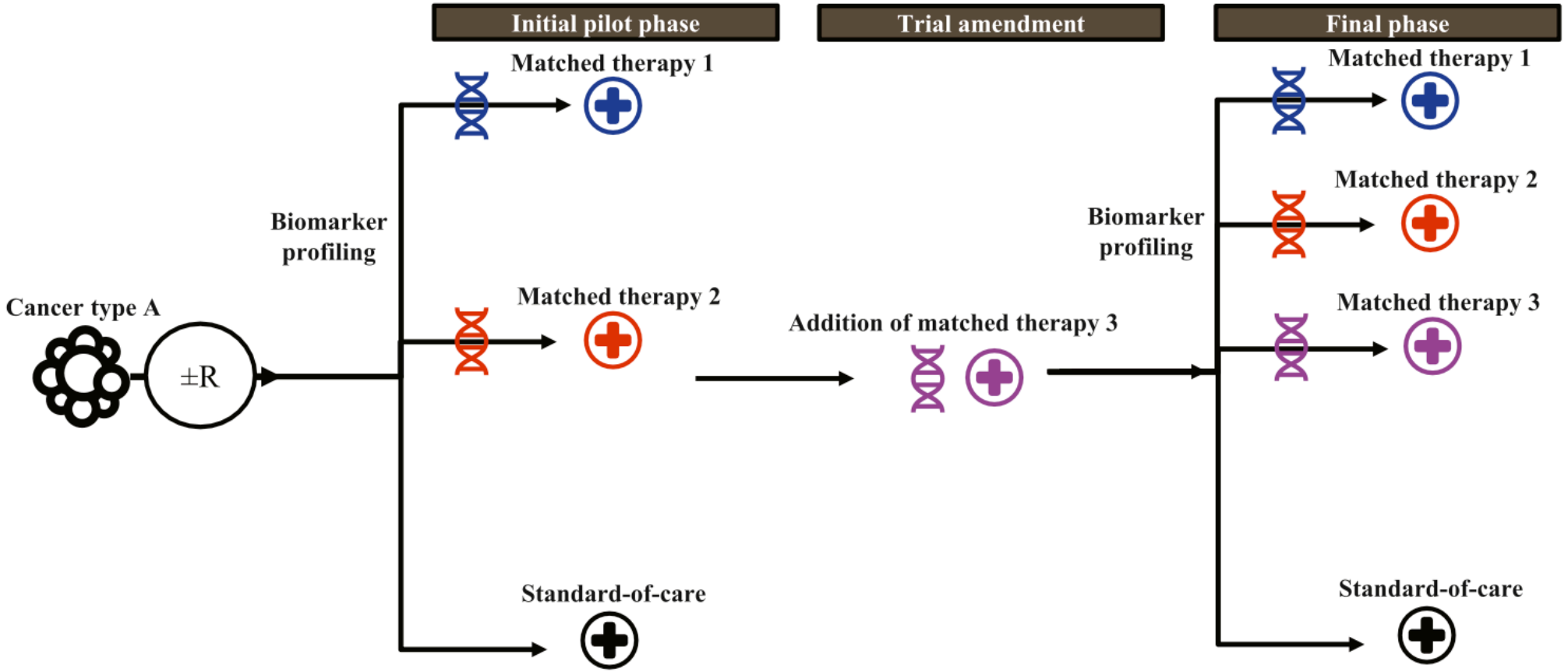




Zhang M-C et al. Cancer Cell 2023

Adaptive umbrella design

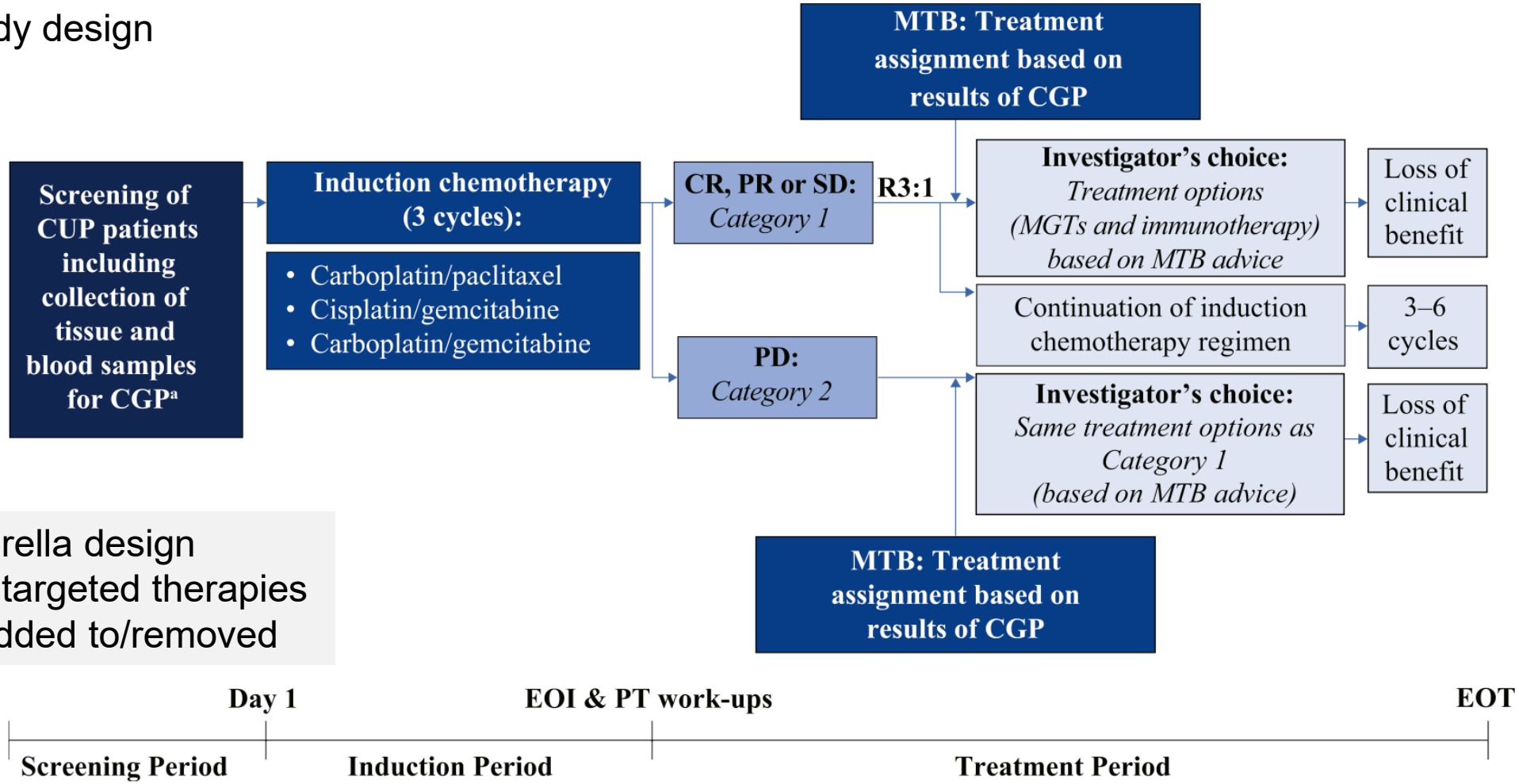
platform trial methodology



Le Tourneau C. et al. European Journal of Cancer 2023

Example of adaptive umbrella design

CUPISCO study design



adaptive umbrella design
(e.g. multiple targeted therapies that can be added to/removed

Le Tourneau C. et al. European Journal of Cancer 2023

If PM studies aim to assess the effect of assay guided treatments

1. Clinical effect: Overall response rate (ORR), PFS, PFS2/PFS1, …
2. One or more defined assays (in vitro diagnostics, IVD)

3. Not clearly defined non-recurrent (individual) treatments

Treatments: - not the investigational part of the study
- well known (e.g. approved), dosing, AE profile

Treatment allocation:

Uncertain relationship of assay to implemented treatment

- Solved via Molecular Tumor Board and post hoc analysis

Trial design of precision medicine studies

If PM studies aim to assess the effect of assay guided treatments

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- Associated regulatory challenges:
  - clinical trial regulation (CTR): structure and rules of clinical trial
  - In vitro diagnostics regulation (IVDR): performance study

If PM studies aim to assess the effect of assay guided treatments

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Combined study (informal definition): clinical trial of a medicinal product together with a performance study of an IVD or a clinical investigation of a medical device.

The topic was identified as a priority during the ACT EU multistakeholder platform workshop held on 22-23 June 2023.

‘COMBINE’ project- on the regulatory landscape for combined studies on the IVDR/MDR/CTR interface

2023: Aug | Sep | Oct | Nov | Dec

2024: Jan | Feb

PHASE 1

1. Issue list ✓
2. Mapping of IVDR/MDR/CTR EU landscape
3. Mapping of relevant activities
4. Proposals for solutions

Deliverable: document describing 3 analysis elements & proposed solutions

PHASE 2

Possible development of solutions

E. Macintyre

P. Staber

EHA EUROPEAN HEMATOLOGY ASSOCIATION

European Commission

If PM studies aim to assess the effect of assay guided treatments

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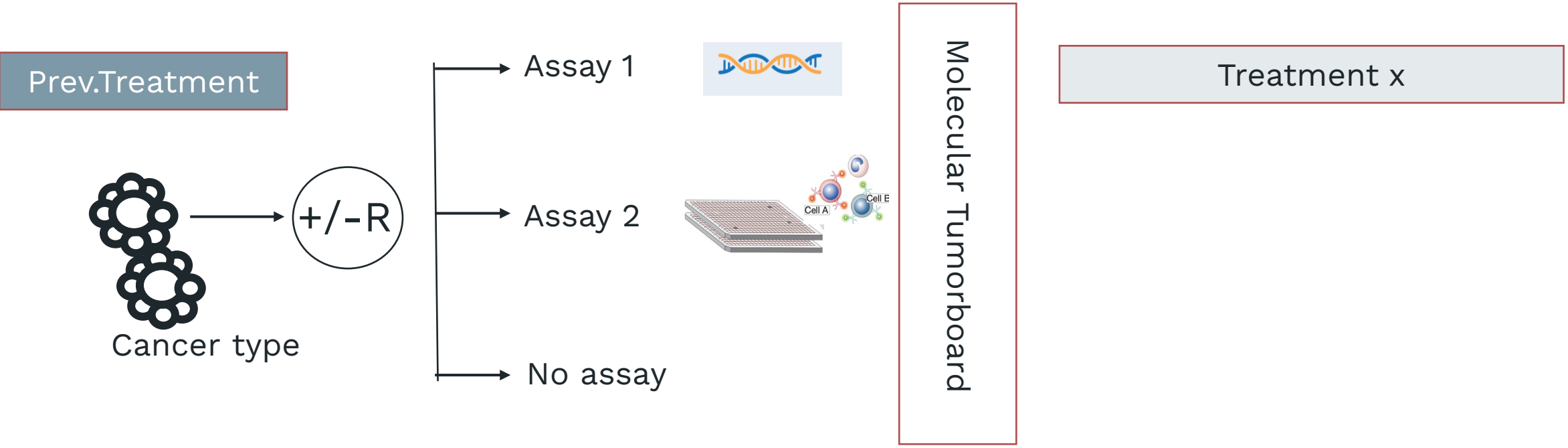
Trial design of precision medicine studies

Suggested design for assay guided studies:
Adaptive umbrella with N-of-1 variant (PFS-ratio)



List of additional challenges

EHASWG
SCIENTIFIC WORKING GROUPS
Precision Hematology

- Availability of n-of-1 drugs (approved, who should pay?)
- Assay certification?
- … tbd

- regulatory approvals (FDA,EMA):
  extension of drug indications based on assays

- Or alternative design models?

eha Sf(PM)