Platform trials: demystifying the statistics

Kaspar Rufibach
Methods, Collaboration & Outreach Group, PD Data Sciences
Basel / Welwyn Oncology forum
February 2023

What is happening? A paradigm shift!

Traditional approach to (early-phase cancer) trials:

- **Narrow** focus to one cancer type, e.g. 1st line follicular lymphoma.
- Better response / survival than standard therapy?
- Designed to enroll enough patients to answer that question.
- Maybe: collect biomarker data and analyze **retrospectively** $\Rightarrow$ discover relationship years later.

"One indication at a time" not always sustainable.

- **Targeted** therapy: Hypothesized to "hit" molecular target.
- **Immunotherapy**: Unleashes patient's immune system against disease.

Organ-specific cancers $\Rightarrow$ molecularly-defined sub-cancers.

Why basket, umbrella, master, platform?

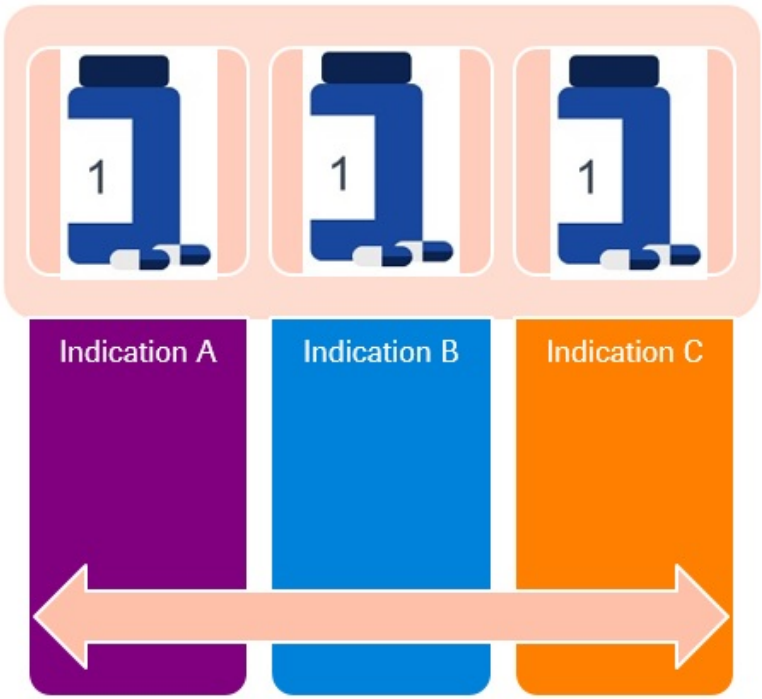
Answer multiple questions **faster and more efficient** than with single trials (single-arm or randomized).

Shared infrastructure, central molecular screening.

Potential for **borrowing**.

Potential for **shared control arm**.

Basket trial



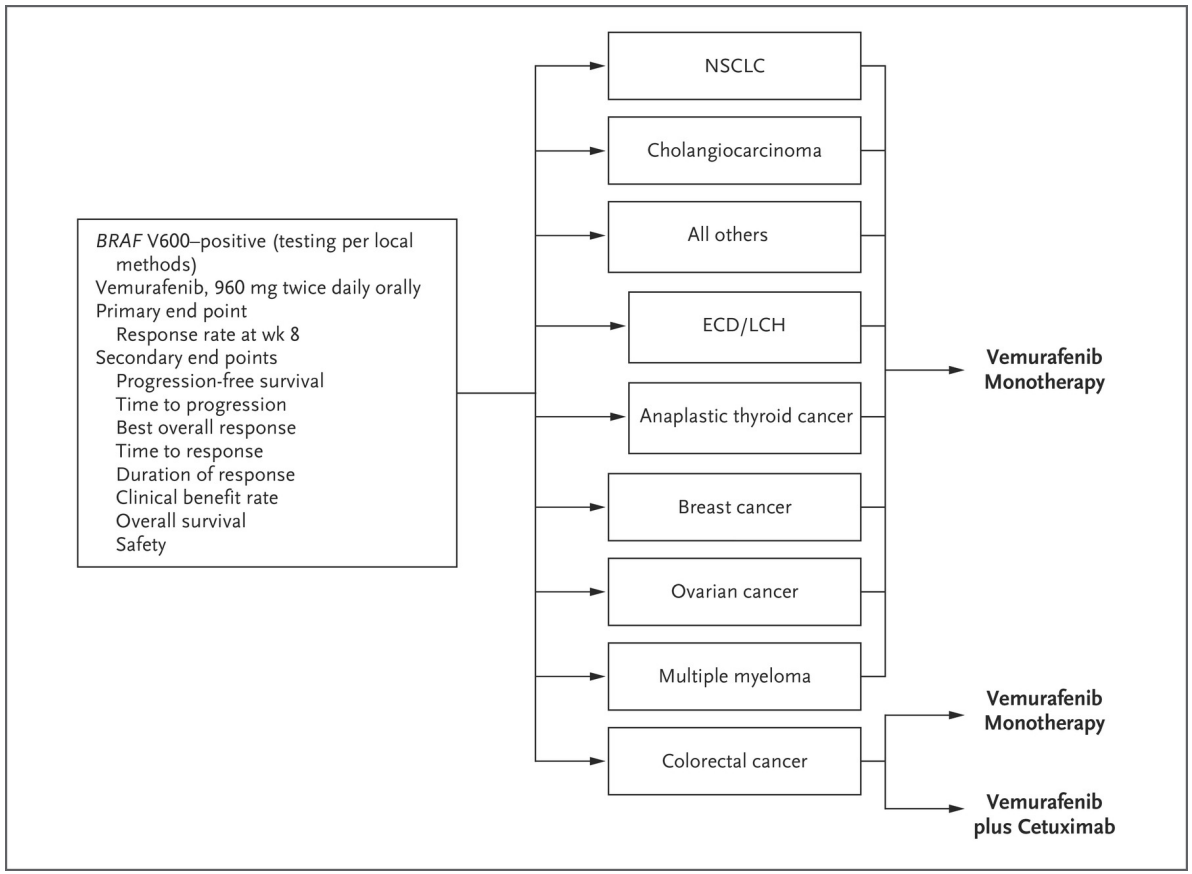
- **Multiple diseases** or histologic features.
- **Single targeted therapy**.
- **Target-positive** patients enter trial.
- Randomization rare.

Objective:

- Identify **large signal** of activity specific to basket's molecular feature.
- Establish **mode-of-action** across indications.

VE-BASKET

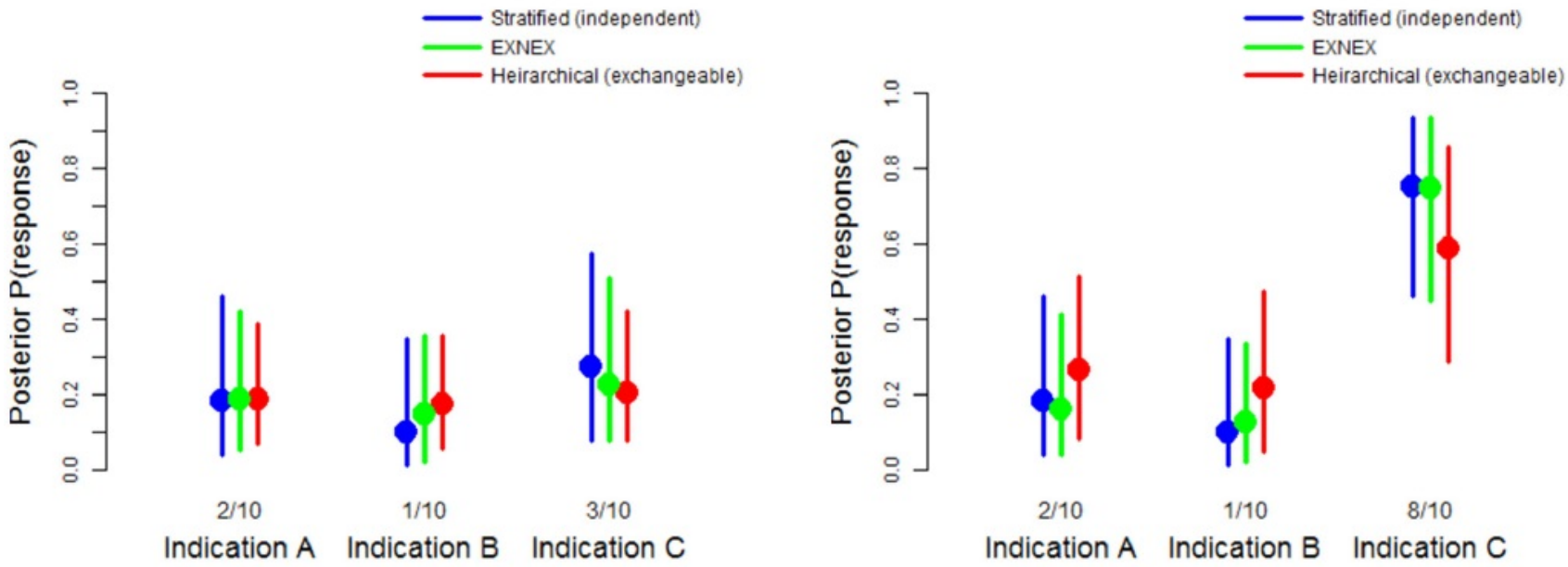
Vemurafenib in nonmelanoma with BRAF V600 mutations



- **Histology-independent** Phase 2 basket.
- Hyman *et al.* (2015); Hobbs and Landin (2018).
- https://clinicaltrials.gov/ct2/show/NCT01524978clinicaltrials.gov.

What is borrowing?

Borrowing in basket trials

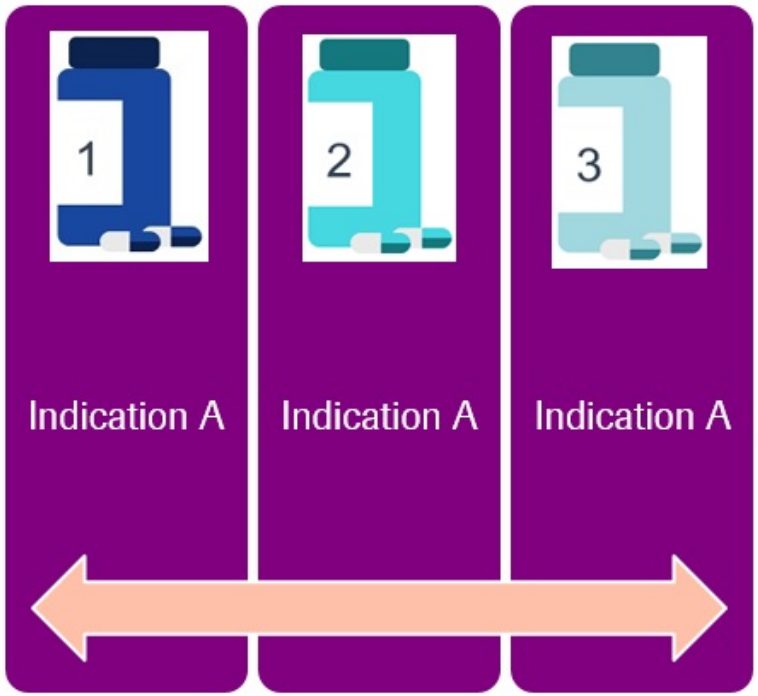


Source of image

- Assume indications are **dependent**.
- **Reduce variability** if results consistent.
- Pull estimates to overall mean if inconsistent, no variability reduction.

Collignon *et al.* (2020): "Pooling across substudies requires rationale supporting intended indication and should be preplanned."

Umbrella trial

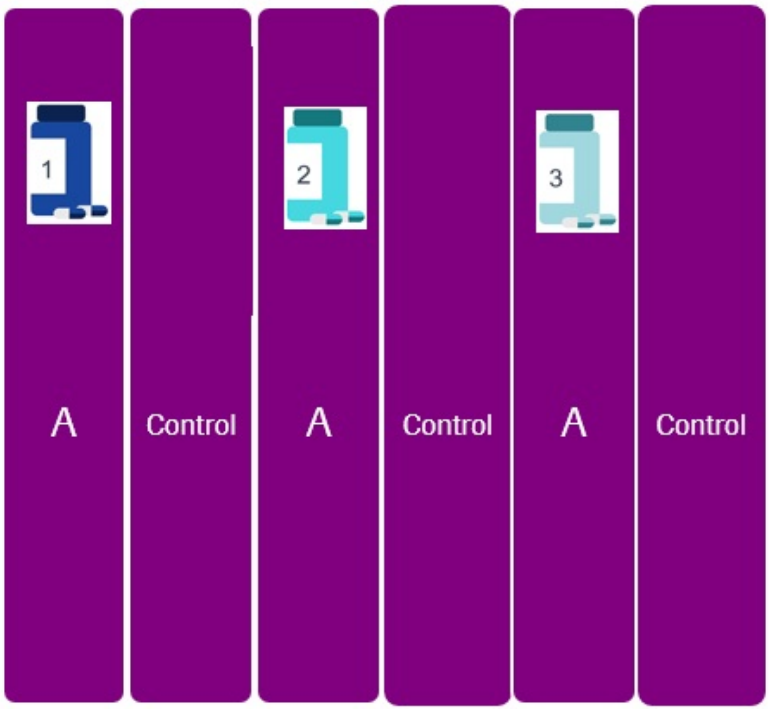


- Patients (and sub-trials) share **common disease** (= "umbrella").
- **Multiple targeted** treatments.

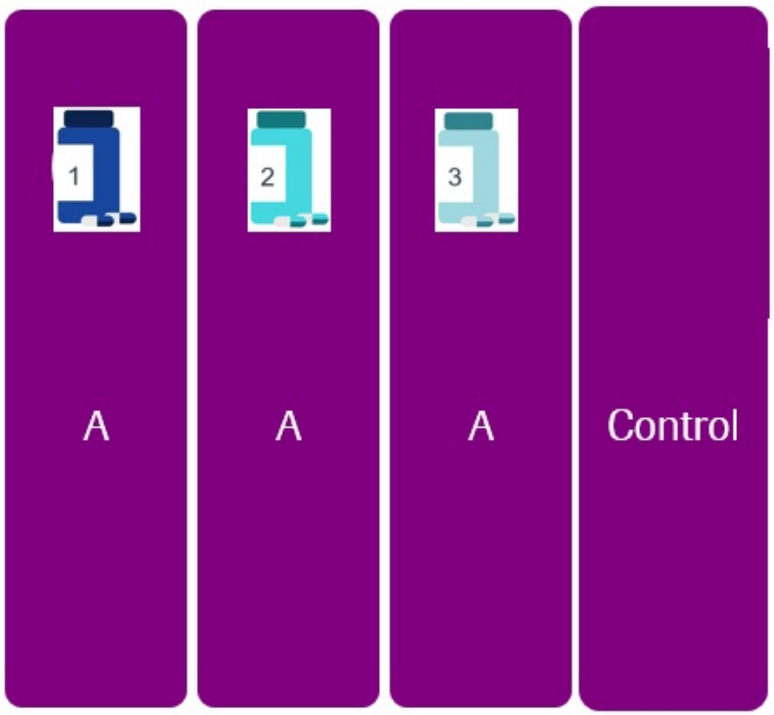
Objective: identify **large signal** of activity that is likely driven by molecular features.

Randomized arm possible.

Umbrella trial - potential for shared control arm



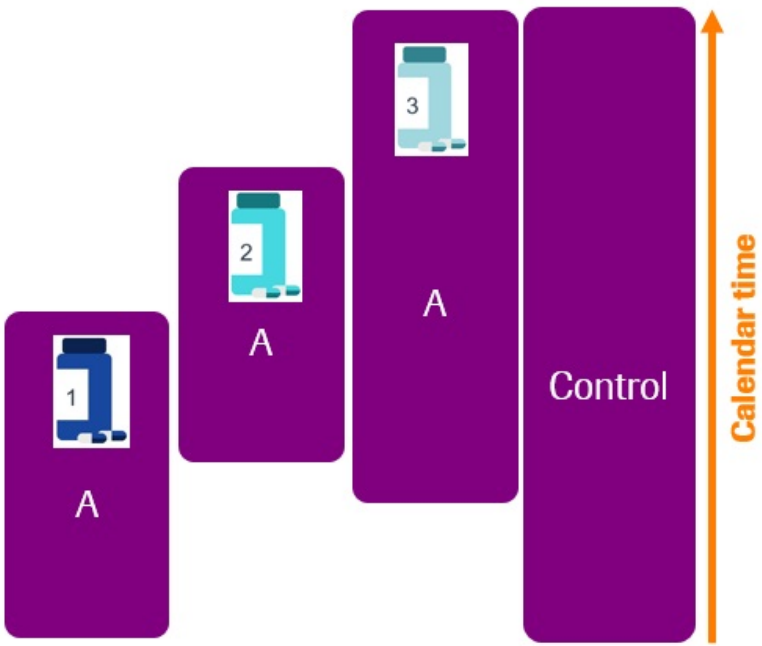
Umbrella trial - potential for shared control arm



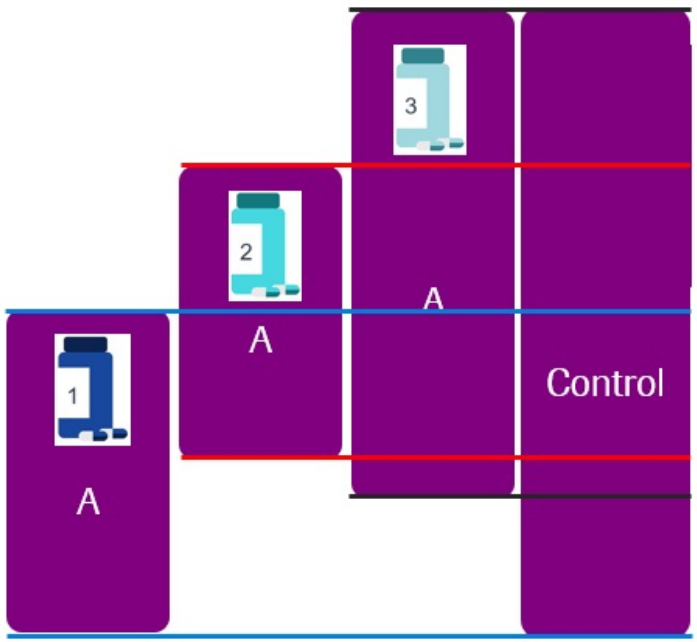
Shared control arm:

- Possible at all? Must be **biomarker-independent**!
  - External?
  - Internal?
  - Randomized?
- **Efficiency gain**.

Until you hit reality!



Until you hit reality!



Challenge familiar to **external controls** for single-arm trials.

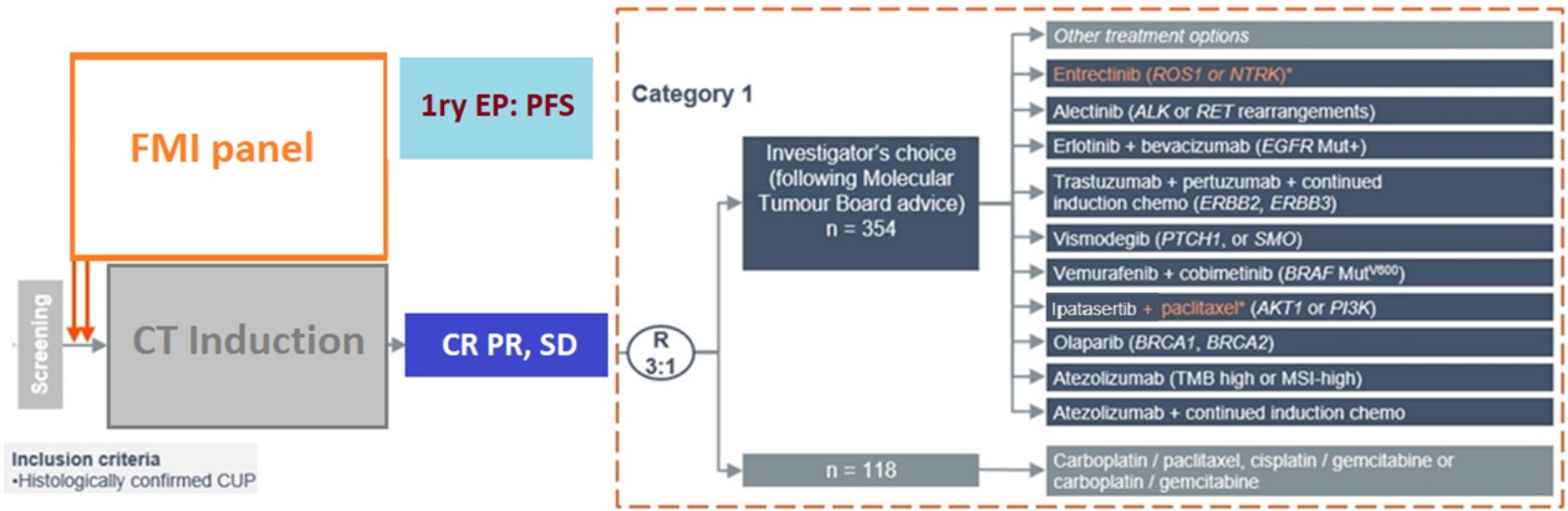
Upfront evaluation of **operating characteristics** virtually impossible.

CUPISCO

Cancer of unknown primary origin (CUP)

- CUP: $> 5\%$ of cancer patients.
- EU: Roche to commercialize FMI.
- Get approval for test $\Rightarrow$ only possible as companion diagnostic. Unrealistic for FMI panel!
- Phase 4 trial: show benefit of strategy, involving tumor board advice. Reimbursement!
- Link to more info, clinicaltrials.gov

Cancer of unknown primary origin (CUP)



Master and platform

Master:

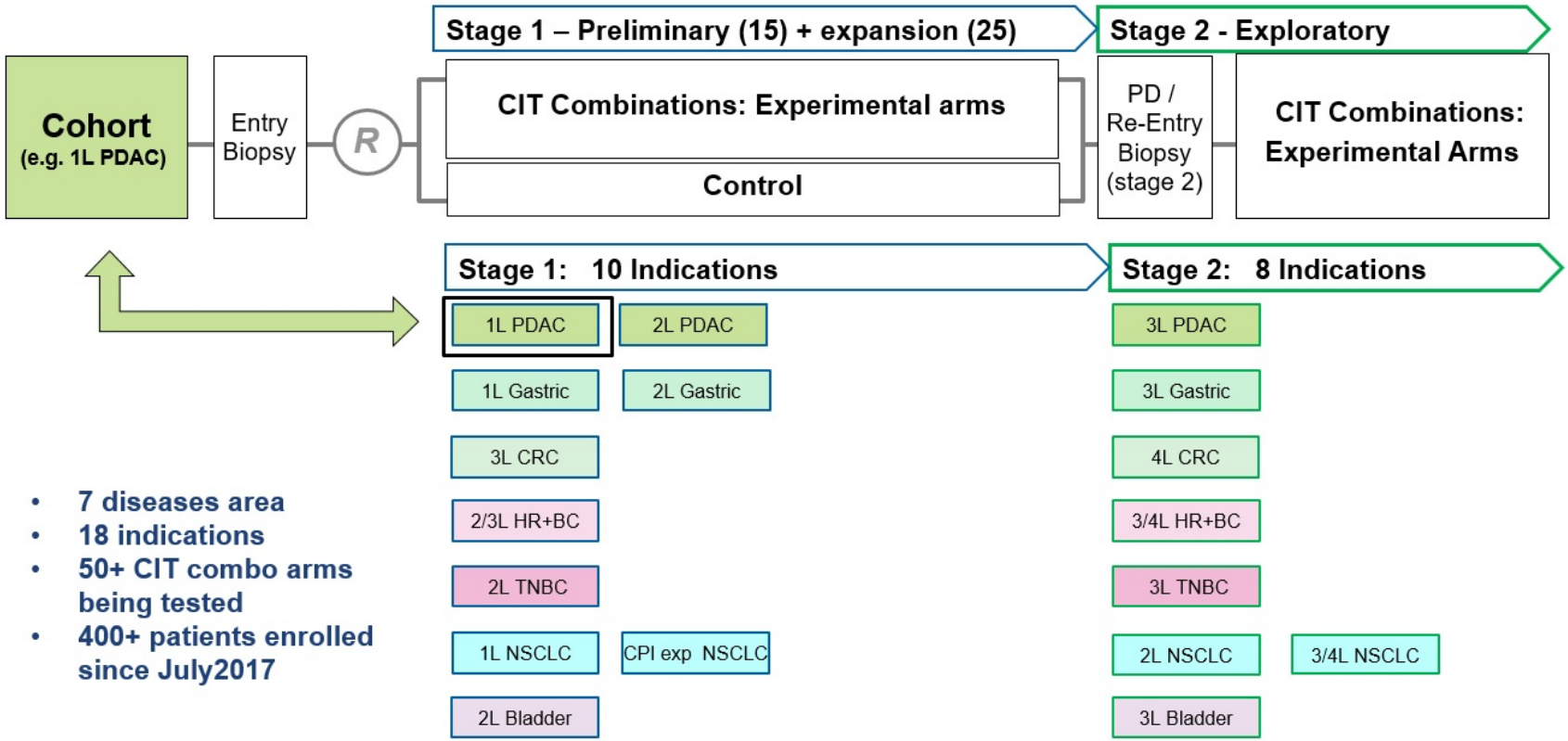
- Evaluate >1 treatments in >1 patient types or diseases within same **overall trial structure**.
- Substudies share **key design components** + **operational aspects** $\Rightarrow$ better coordination than in independently run single trials.

Platform: master protocols in which

- paired marker-treatment cohorts
- continually enter and exit the trial
- under the same protocol.
- May be basket, umbrella, or neither.

Woodcock and LaVange (2017); Renfro (2019); Collignon *et al.* (2020)

MORPHEUS



- Platform of **umbrella** trials within many indications ($\Rightarrow$ basket).
- Every subtrial has clinicaltrials.gov entry.

Advantages

Basket: multiple diseases, single therapy:

- Shared infrastructure.
- Accommodates study of **rare** tumor types.
- Enroll patients with molecular feature across tumor types.
- Multiple pathways for regulatory approval.
- **Borrowing**.

Umbrella: single disease, multiple therapies:

- **Central** molecular screening: No need to re-screen to enroll into multiple separate trials.
- Potentially **shared (randomized) control arm**.
- Improved prognostic **homogeneity** (same tumor type).

Challenges

Basket: multiple diseases, single therapy:

- **Prognostic heterogeneity** inevitable across tumor types, even with same marker.
- **Distribution of cancer types** unknown up front $\Rightarrow$ too-rare baskets.
- Challenging if not impossible to define controls (internal, external, randomized) across diseases.
- Risk of type I error.
- Treatment heterogeneity.

Umbrella: single disease, multiple therapies:

- Difficult to enroll for markers that are rare.
- Risk of type I error.
- Use of controls.

Multiplicity in master protocols

Family-wise error rate (FWER): probability of declaring ≥ 1 false-positive.

Sources of multiplicity:

- subgroups,
- endpoints,
- multiple (interim) analyses,
- "data-dredging".

Regulatory context - two scenarios

Run platform of Phase 1b's - no upfront regulatory intent.

Preplan platform with confirmatory / regulatory intent.

- Basket: rarely preplanned for registration purposes.
- Pure platform trials (i.e. umbrella within basket or vice versa) not easy to get approved.
- Competitive enrollment: more arms may delay recruitment for a given arm.
- Adaptivity much more complex in pivotal trials b/c type I error control:
  - **Multistage-multiarm designs** (MAMS): generalizations of group-sequential designs.
  - **Flexible adaptive designs**: use adaptive elements as building blocks.

Conclusions platform trials

Basket	▪ Same treatment, multiple indications? ▪ Potential for borrowing?
Umbrella	▪ Common disease, multiple treatments? ▪ Potential for shared control arm? ▪ Central molecular screening.
Shared control arm	▪ External controls, internal controls, randomization? ▪ Which control patients to compare to?
Future platform trials	▪ T1E control needed? Confirmatory adaptive design? ▪ Consider treatment candidates from competitors?

Can make drug development - not only oncology! - **operationally and statistically more efficient**.

Can make drug development possible at all - **rare diseases**. Different considerations may apply.

Statistical methods well understood.

References

Collignon, O., Gartner, C., Haidich, A.-B., James Hemmings, R., Hofner, B., Pétavy, F., Posch, M., Rantell, K., Roes, K., and Schiel, A. (2020). Current statistical considerations and regulatory perspectives on the planning of confirmatory basket, umbrella, and platform trials. *Clinical pharmacology and therapeutics*, **107**, 1059–1067.

Hobbs, B. P. and Landin, R. (2018). Bayesian basket trial design with exchangeability monitoring. *Statistics in medicine*, **37**, 3557–3572.

Hofner, B. and Pétavy, F. (2019). European regulators' view on platform trials - lessons recently learned. In *Talk at 4th EFSPI Regulatory Statisticis Workshop*.

Hyman, D. M., Puzanov, I., Subbiah, V., Faris, J. E., Chau, I., Blay, J.-Y., Wolf, J., Raje, N. S., Diamond, E. L., Hollebecque, A., Gervais, R., Elez-Fernandez, M. E., Italiano, A., Hofheinz, R.-D., Hidalgo, M., Chan, E., Schuler, M., Lasserre, S. F., Makrutzki, M., Sirzen, F., Veronese, M. L., Tabernero, J., and Baselga, J. (2015). Vemurafenib in multiple nonmelanoma cancers with braf v600 mutations. *The New England journal of medicine*, **373**, 726–736.

Renfro, L. and Sargent, D. (2017). Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples. *Annals of Oncology*, **28**(1), 34–43.

Renfro, L. A. (2019). Master protocols, basket trials, and umbrella trials: Overviews, features, challenges, and examples. In *Talk given within Bay area Biotech-pharma Statistics Workshop*.

West, H. J. (2017). Novel precision medicine trial designs: Umbrellas and baskets. *JAMA oncology*, **3**, 423.

Woodcock, J. and LaVange, L. M. (2017). Master protocols to study multiple therapies, multiple diseases, or both. *The New England journal of medicine*, **377**, 62–70.

Thank you for your attention.

kaspar.rufibach@roche.com

http://go.roche.com/dss-mco

http://www.kasparrufibach.ch

numbersman77

numbersman77

Doing now what patients need next

R version and packages used to generate these slides:

R version: R version 4.1.1 (2021-08-10)

Base packages: grid / stats / graphics / grDevices / utils / datasets / methods / base

Other packages: biostatKR / mvtnorm / bpcp / ggplot2 / SurvRegCensCov / flexsurv / fitdistrplus / muhaz / TrialSize / survival / animation / forestplot / checkmate / magrittr / rpact / MASS / reporttools / xtable

This document was generated on 2022-10-30 at 22:05:55.