Design and Analysis of Umbrella and Basket Trials

Axel Benner and Christina Beisel

Division of Biostatistics, German Cancer Research Center (DKFZ)
Heidelberg, Germany

October 20, 2016

Individualized/Personalized/Precision Medicine

Personalized Medicine

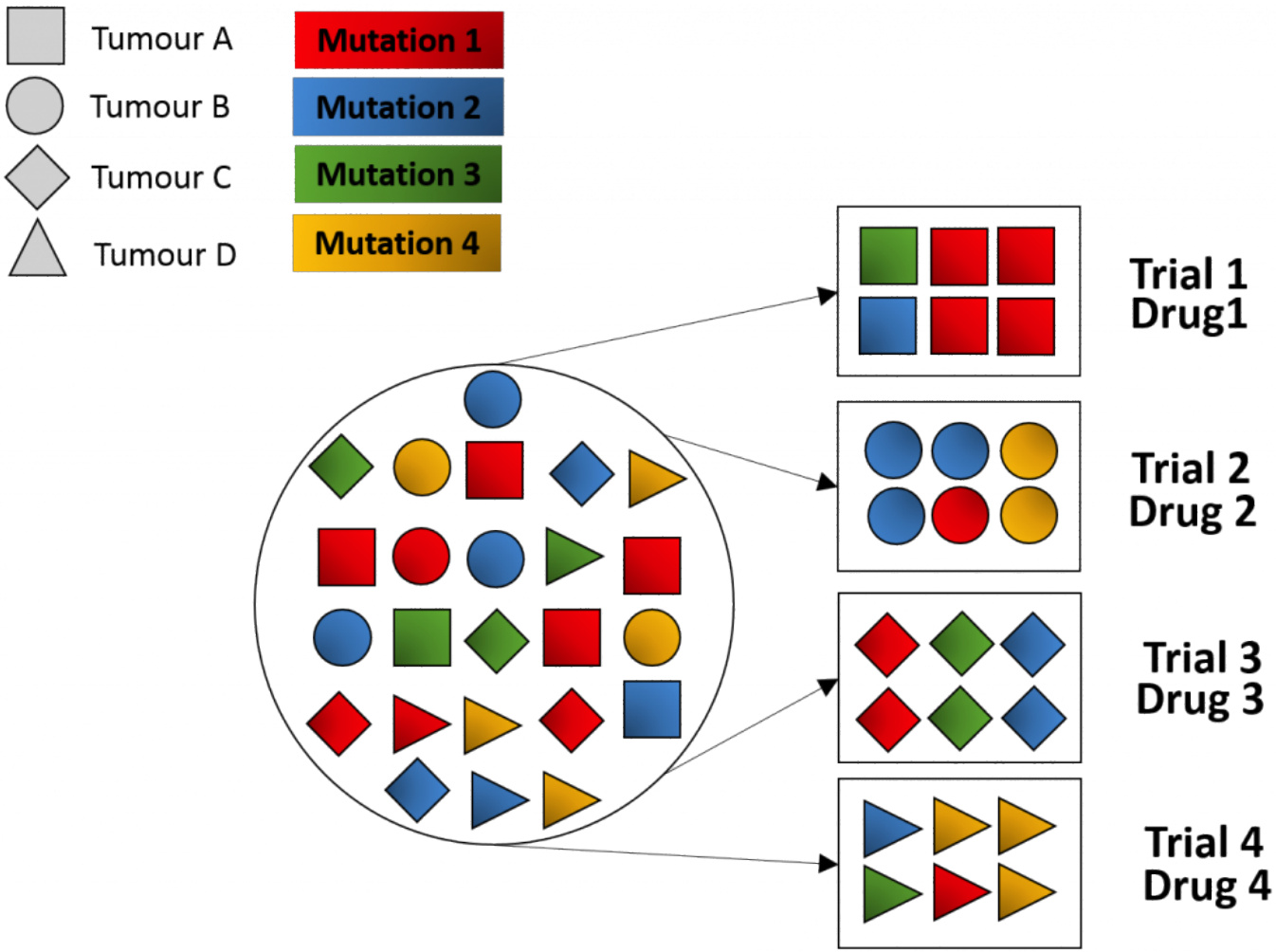
(Providing) the right drug for the right patient at the right dose and time.

Sadée & Dai, 2005

A form of medicine that uses information about a person's genes, proteins and environment to prevent, diagnose and treat disease.

National Cancer Institute

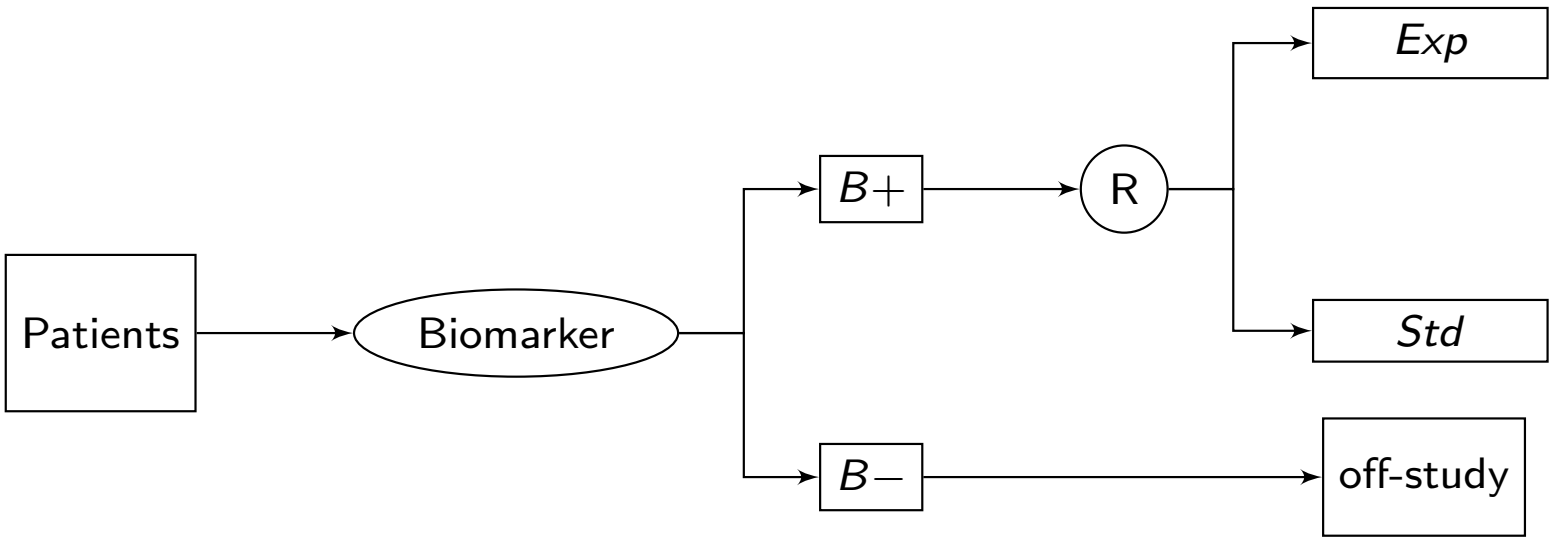
Traditionally, tumor histology determines (cytotoxic) treatment



https://www.bhdsyndrome.org/forum/bhd-research-blog/genetic-sequencing-approaches-to-cancer-clinical-trials/

Design of Clinical Trials

- Biomarkers gain more importance for selection of treatment strategies, e.g. by enrichment trials

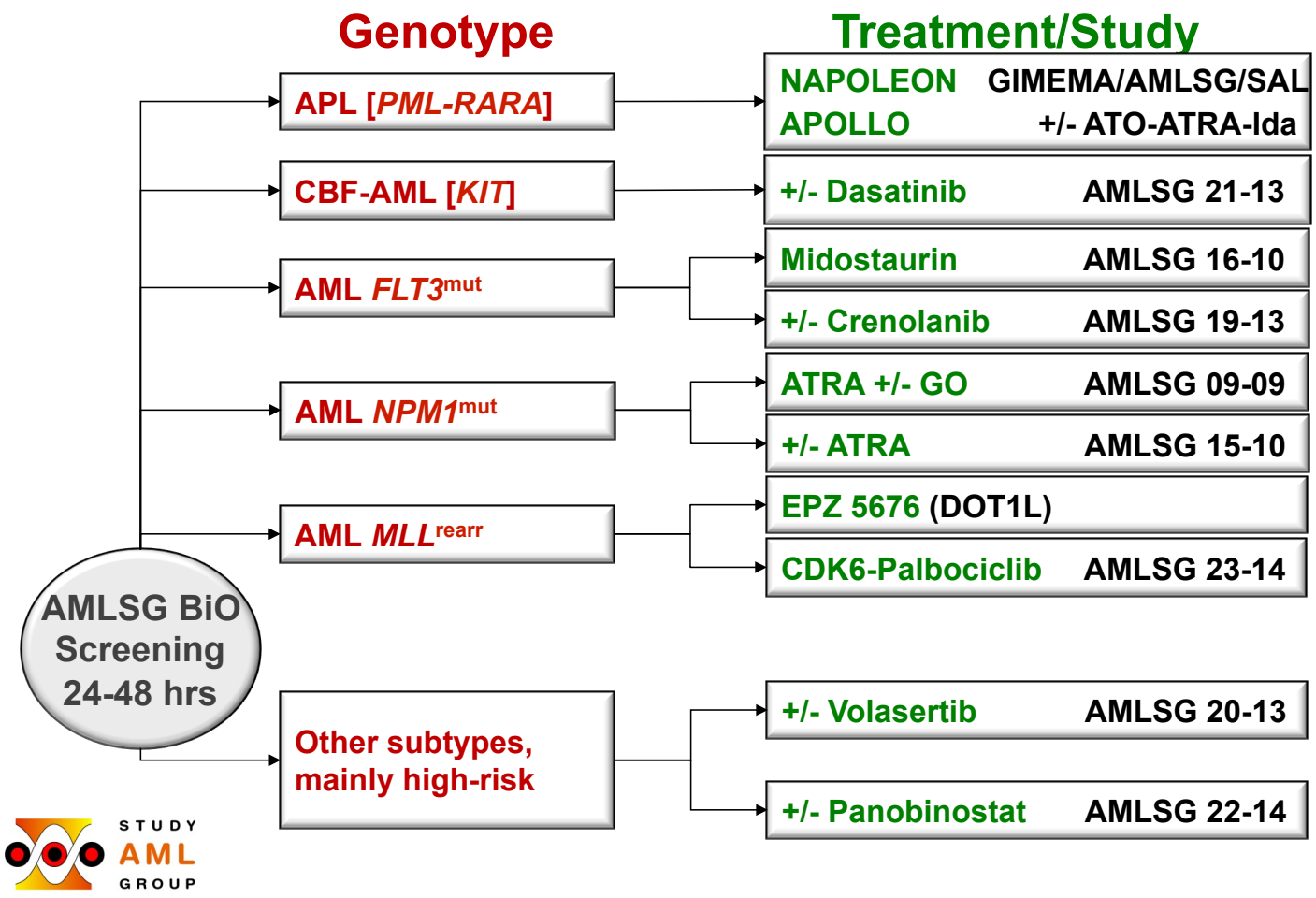


- Challenge: With multiple targets based on multiple markers we are often close to the situation that we are faced with in rare diseases.

Biomarker-driven Clinical Trials

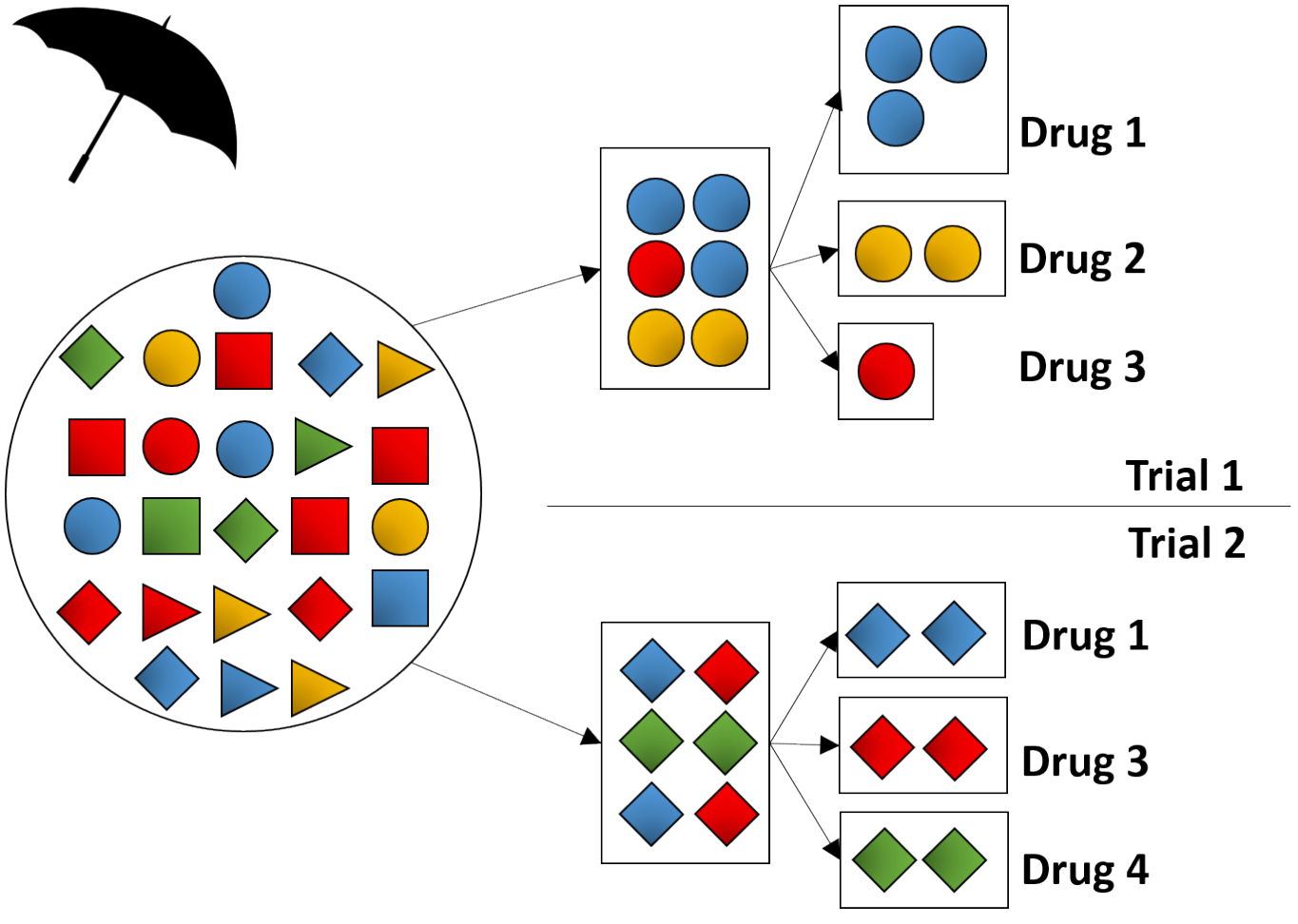
Example: Acute Myeloid Leukemia (AML)

Genotype-adapted clinical intervention trials of the German-Austrian AML study group (AMLSG)



Umbrella Trials

Enroll marker-defined cohorts in parallel under the "umbrella" of a specific histology or tumor type



Umbrella Trials

The umbrella design focuses on a single tumor type or histology

The reason and rationale for the umbrella trial design first and foremost is to facilitate screening and accrual of patients

Primary features of the umbrella design

- It involves a group of two or more enrichment designs within the same protocol
- It allows for randomized comparisons
- It can have flexible biomarker cohorts
- It allows to add/drop biomarker subgroups

Example: FOCUS4 Trial (Kaplan et al. JCO 2013) for Colorectal Cancer

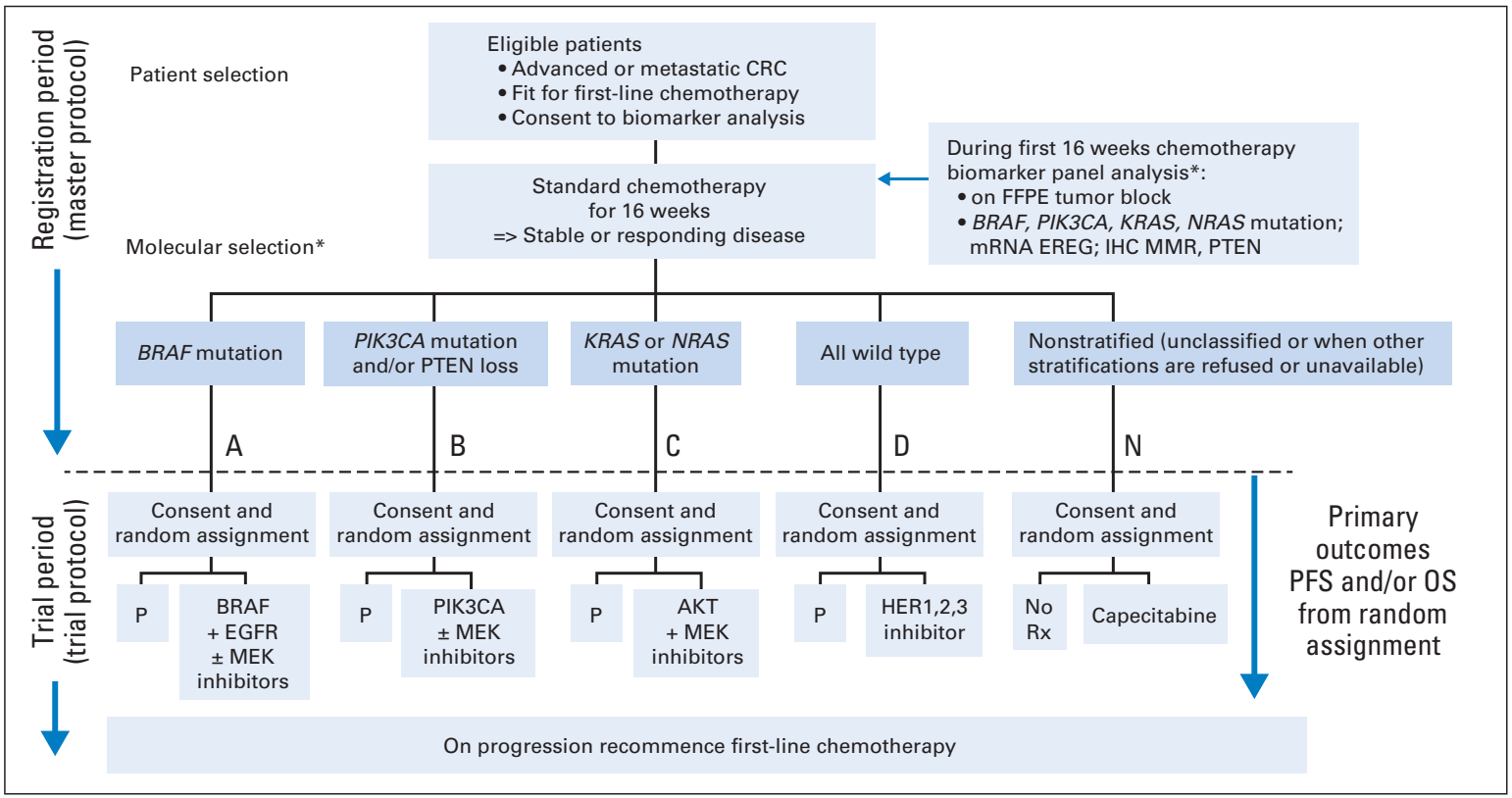
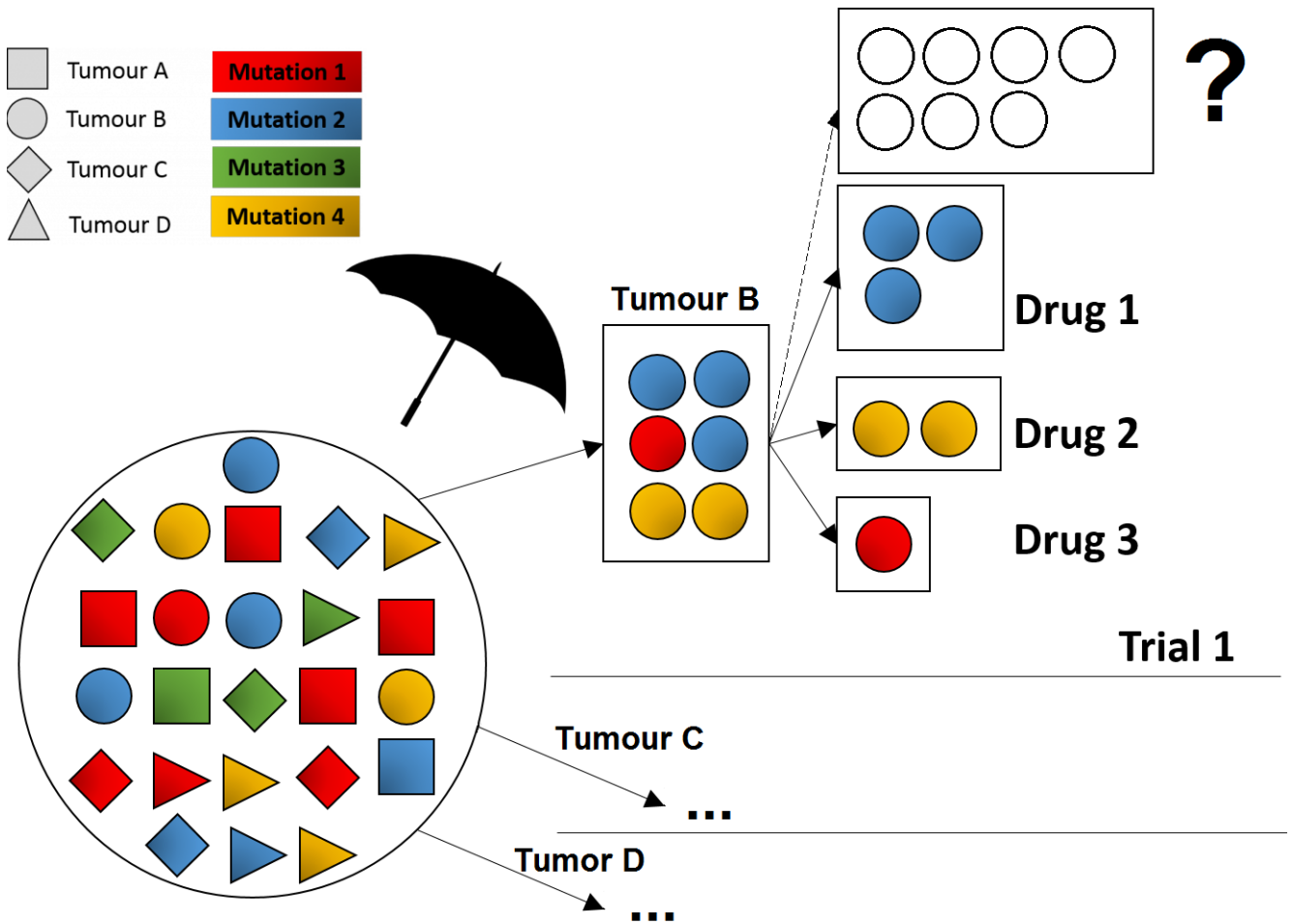
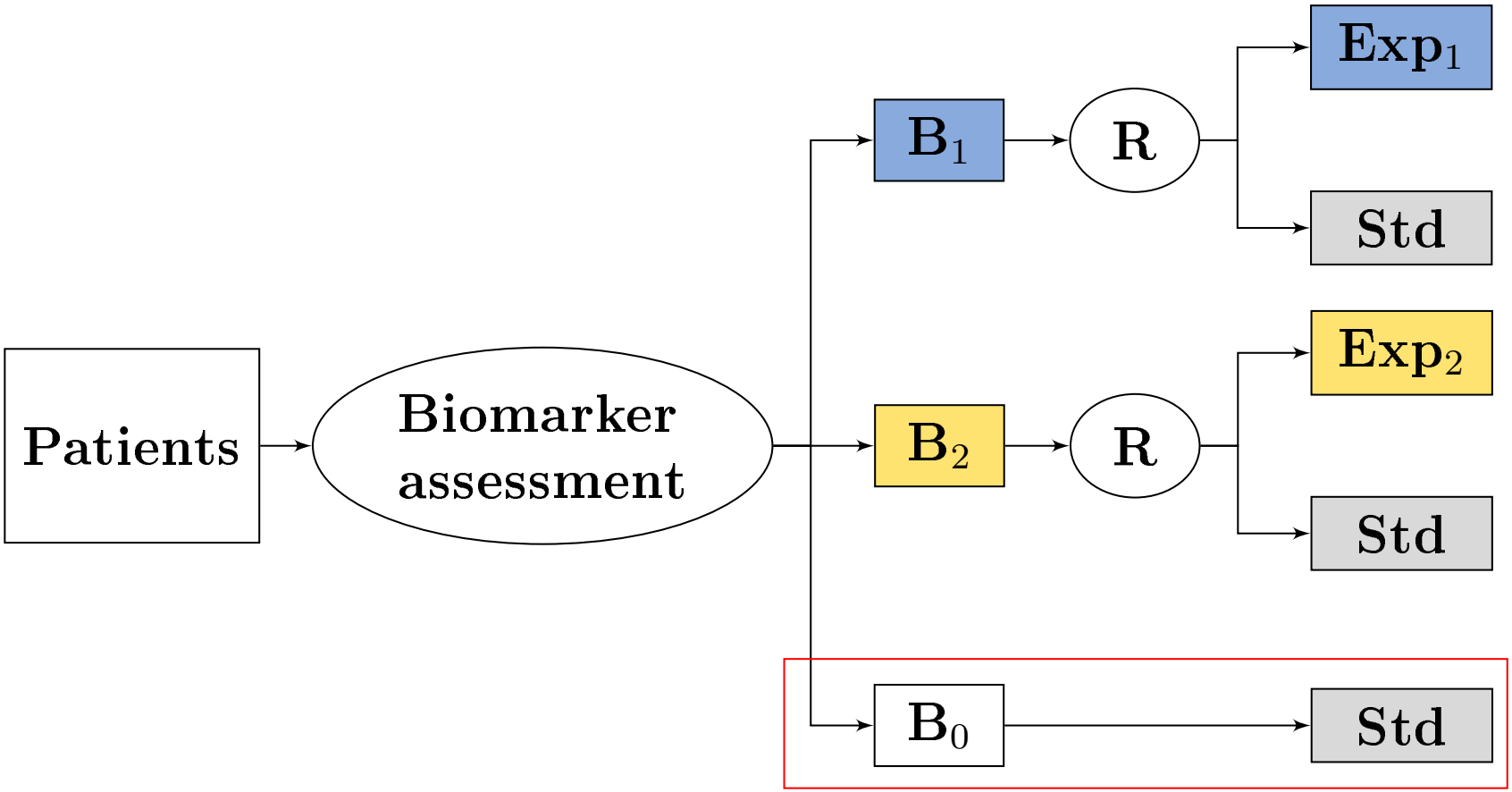


Fig 1. Trial schema for FOCUS4. (*) The molecular cohorts are arranged in a hierarchy from left to right. For example, a patient with both a *PIK3CA* mutation and a *KRAS* mutation will be classified into the *PIK3CA* mutation cohort. CRC, colorectal cancer; EGFR, epidermal growth factor receptor; EREG, epiregulin; FFPE, formalin fixed, paraffin embedded; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; MMR, mismatch repair; OS, overall survival; P, placebo; PFS, progression-free survival; Rx, treatment.

What about biomarker-negative patients?



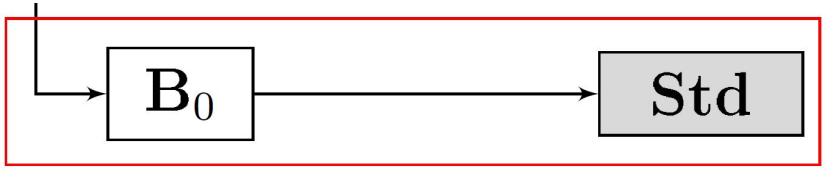
Multi-biomarker hybrid design



Analysis

Potential benefit from inclusion of marker-negative patients:

- Collect data for retrospective biomarker identification
- Investigate prognostic properties of biomarkers
- Non-prognostic markers: Pool of standard-of-care arms
- Prognostic markers: Include biomarker-status as factor variable B_i in Cox model



Comparison of models in different populations

- **Approach 1:** Separate models for biomarker 1 and biomarker 2

$$\lambda_1 = \lambda_{0_1} \exp(\beta_1 \times treat_1) \qquad \text{(sample size: } n_1\text{)}$$

$$\lambda_2 = \lambda_{0_2} \exp(\beta_2 \times treat_2) \qquad \text{(sample size: } n_2\text{)}$$

- **Approach 2:** Exclude biomarker negative patients

$$\lambda = \lambda_0 \exp(\gamma_2 \times B_2 + \beta_1 \times treat_1 + \beta_2 \times treat_2)$$

$$\text{(sample size: } n_1 + n_2\text{)}$$

- **Approach 3:** Include biomarker-negative patients

$$\lambda = \lambda_0 \exp(\gamma_1 \times B_1 + \gamma_2 \times B_2 + \beta_1 \times treat_1 + \beta_2 \times treat_2)$$

$$\text{(sample size: } n\text{)}$$

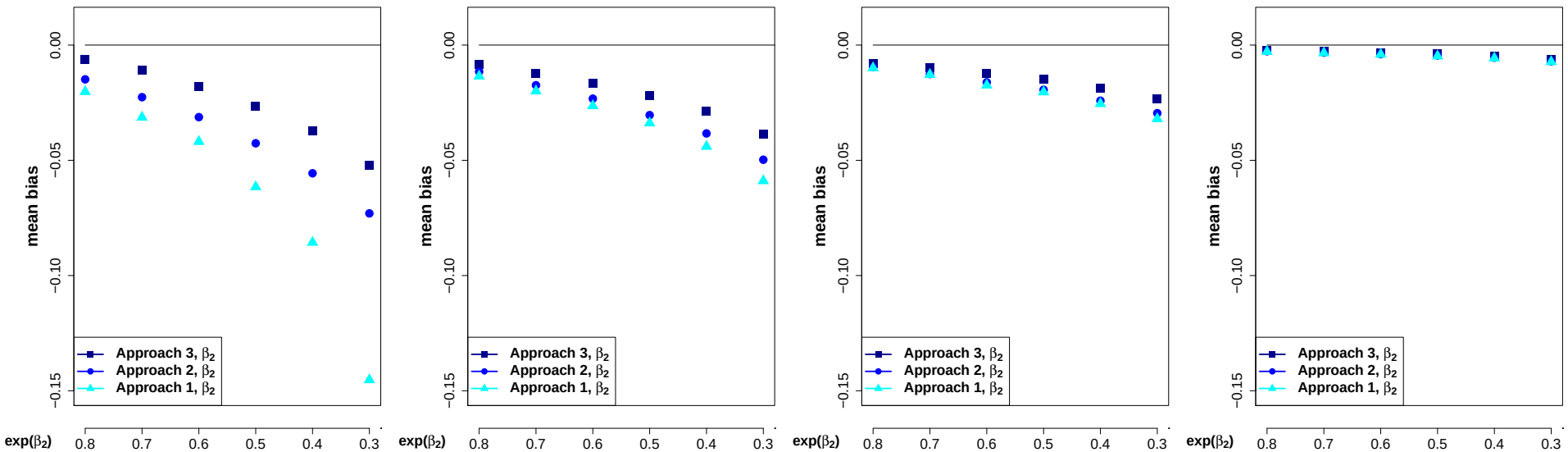
where $n = n_1 + n_2 + n_0$

Comparison: bias for β_2

Approach 1: $\lambda_2 = \lambda_{0_2} \exp(\beta_2 \times treat_2)$

Approach 2: $\lambda = \lambda_0 \exp(\gamma_2 \times B_2 + \beta_1 \times treat_1 + \beta_2 \times treat_2)$

Approach 3: $\lambda = \lambda_0 \exp(\gamma_1 \times B_1 + \gamma_2 \times B_2 + \beta_1 \times treat_1 + \beta_2 \times treat_2)$



$\lambda_0 = 0.05$, $\gamma_1 = \ln(0.5)$, $\gamma_2 = \ln(2)$

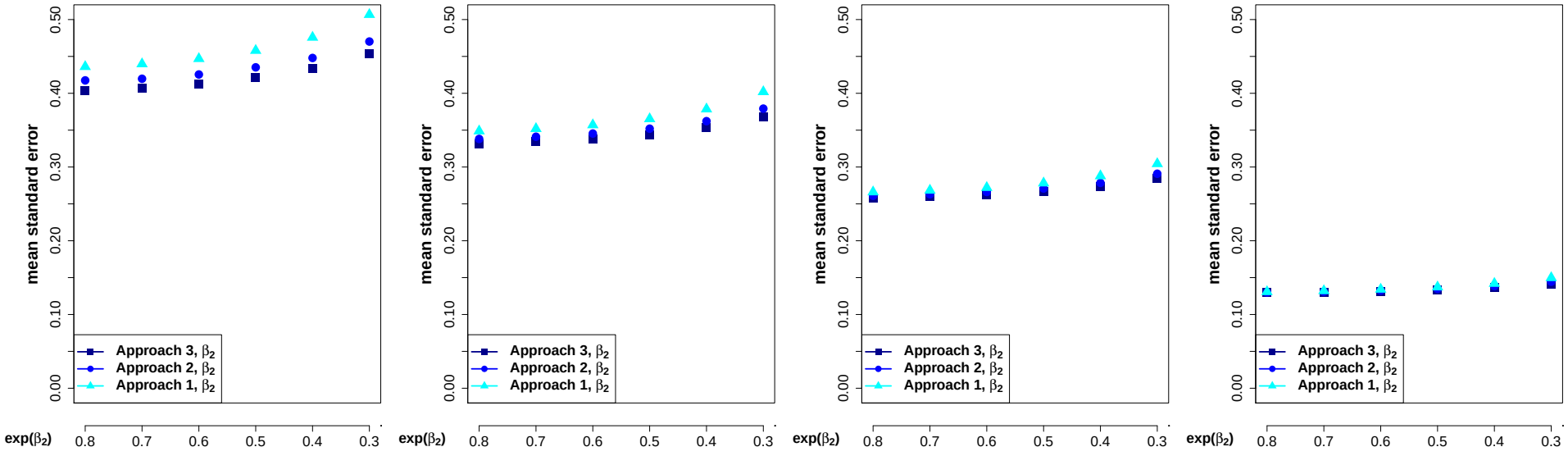
Population proportions: (B_0,B_1,B_2): 2:1:1, (10,000 Simulations)

Comparison: standard error for β_2

Approach 1: $\lambda_2 = \lambda_{0_2} \exp(\beta_2 \times treat_2)$

Approach 2: $\lambda = \lambda_0 \exp(\gamma_2 \times B_2 + \beta_1 \times treat_1 + \beta_2 \times treat_2)$

Approach 3: $\lambda = \lambda_0 \exp(\gamma_1 \times B_1 + \gamma_2 \times B_2 + \beta_1 \times treat_1 + \beta_2 \times treat_2)$



$n = 100$ $n = 150$ $n = 250$ $n = 1000$

$\lambda_0 = 0.05$, $\gamma_1 = \ln(0.5)$, $\gamma_2 = \ln(2)$

Population proportions: (B_0,B_1,B_2): 2:1:1, (10,000 Simulations)

Small sample size bias and Firth correction

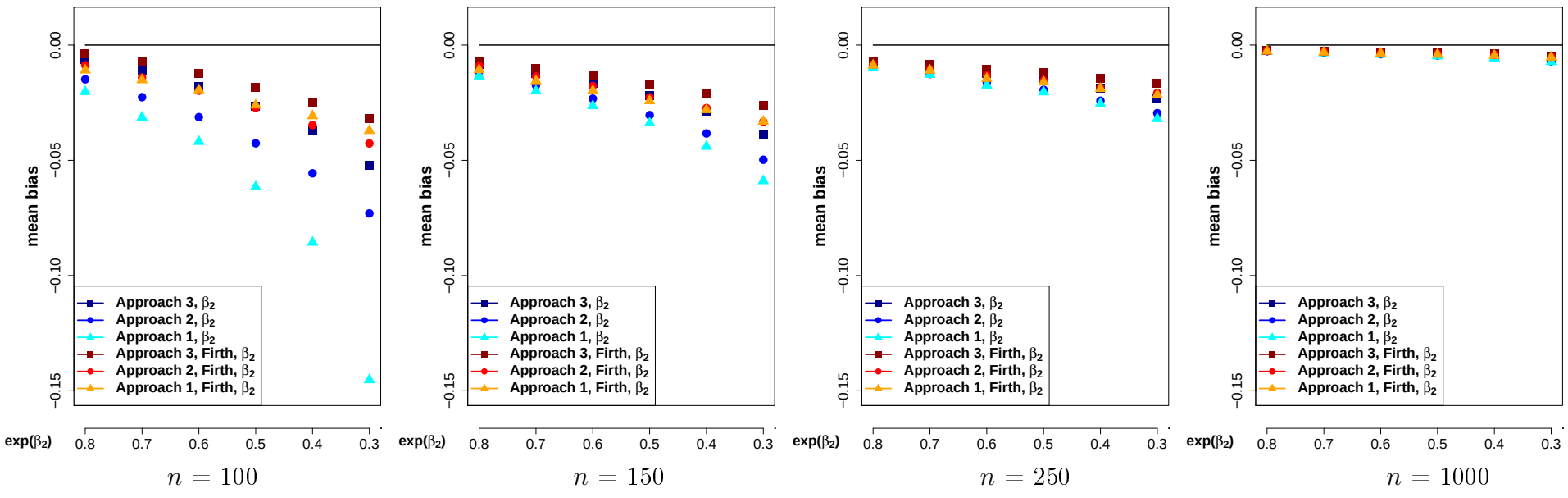
- Maximum-likelihood methods not necessarily unbiased for finite samples
- Langner et al. (2003) investigated behavior of bias in relation to sample size for Cox regression
  - Bias depends on sample size, but also on baseline risk and treatment hazard rate
- Small sample size bias in simulation study
- Use Firth (1993) correction to reduce bias

Comparison: bias for β_2 with Firth correction

Approach 1: $\lambda_2 = \lambda_{0_2} \exp(\beta_2 \times treat_2)$

Approach 2: $\lambda \ = \lambda_0 \exp(\gamma_2 \times B_2 + \beta_1 \times treat_1 + \beta_2 \times treat_2)$

Approach 3: $\lambda \ = \lambda_0 \exp(\gamma_1 \times B_1 + \gamma_2 \times B_2 + \beta_1 \times treat_1 + \beta_2 \times treat_2)$



$\lambda_0 = 0.05$, $\gamma_1 = \ln(0.5)$, $\gamma_2 = \ln(2)$

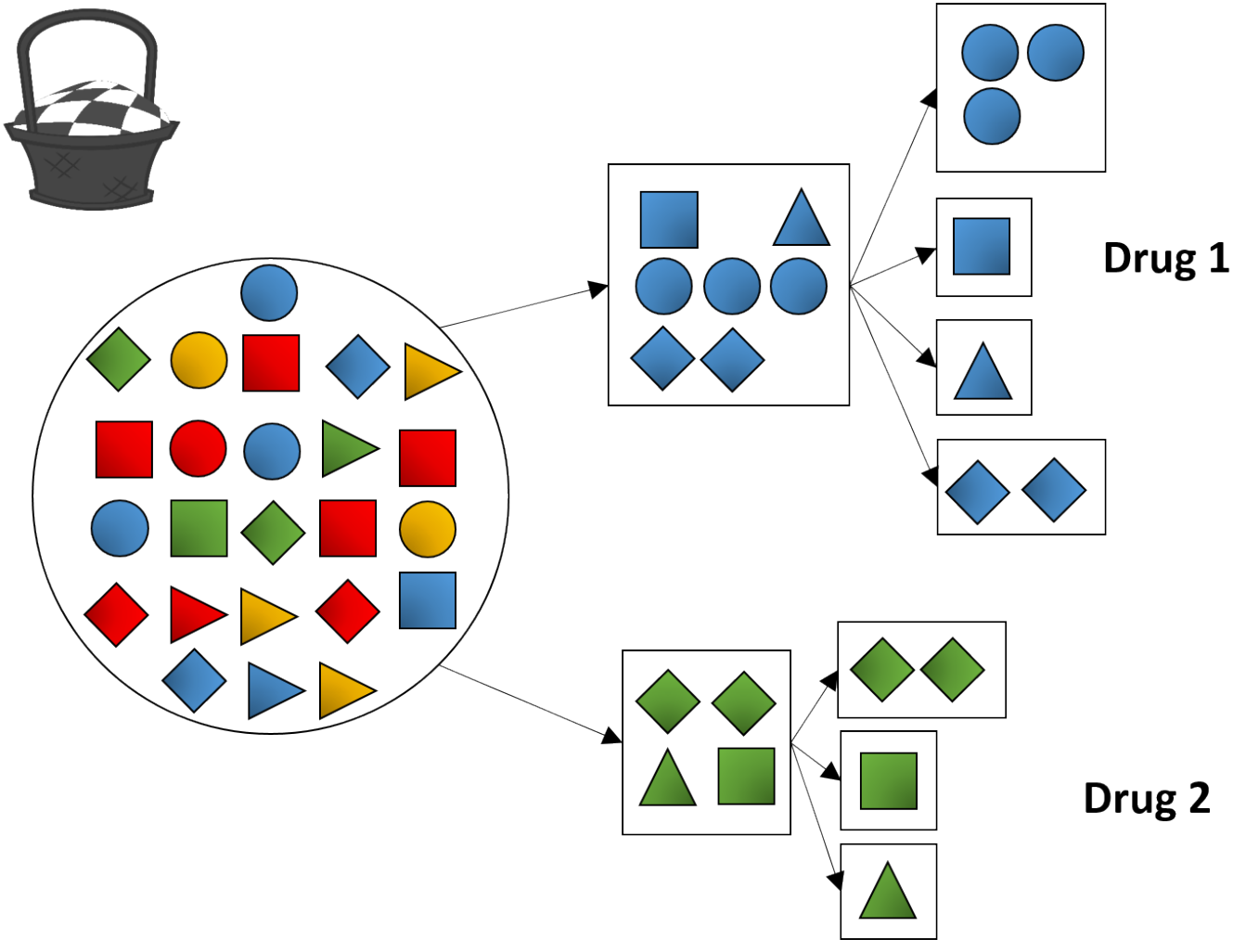
Population proportions: (B_0,B_1,B_2): 2:1:1, (10,000 Simulations)

Summary of results

- For smaller sample sizes:
  - Reduction of bias by using combined analysis (Approach 2)
  - Even further reduction of bias by including of biomarker-negative patients (Approach 3)
  - Additionally small improvements for standard errors
- Approaches perform similar for larger sample sizes
- Differences smaller when Firth correction is used

Basket Trials

Histology-agnostic enrollment of marker-defined cohorts ("baskets")



Basket Trials

Basket trials allow the study of multiple molecular subpopulations of different tumor or histologic types within one study.

Primary features of basket trials

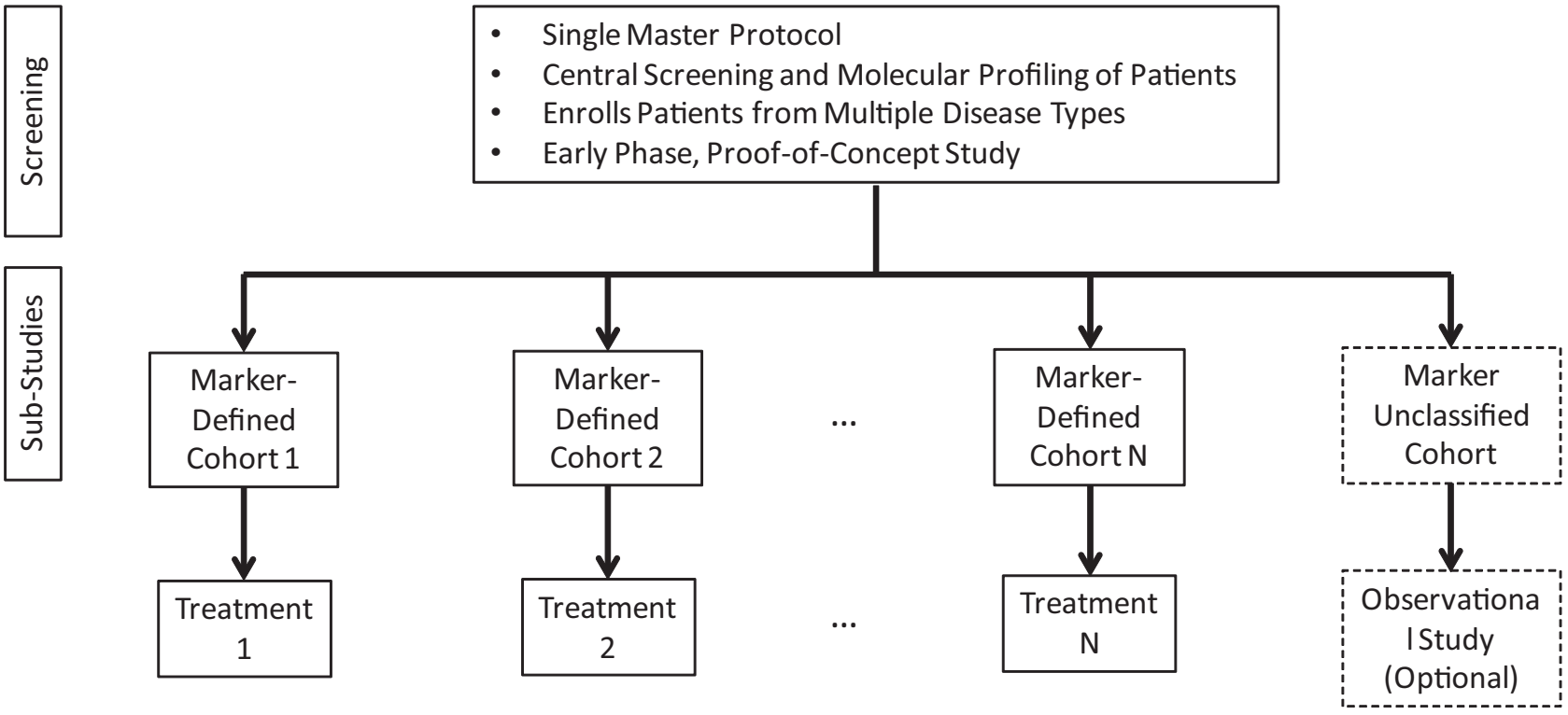
- The design affords the flexibility to continually open and close arms of the study
- They can include highly rare cancers that would be difficult to study in randomized controlled trials
- Countless possibilities exist in designing and analysis of basket trials, such as writing protocols for each cohort and creating a screening and treatment infrastructure.

Basket Trials

Characteristics

- Marker-defined cohorts
- Typically non-randomized
- Primary purpose: treatment

Challenge Multiple targets $\rightarrow$ close to rare diseases trials



Basket Trials

Example: CUSTOM Trial (Lopez-Chavez et al. JCO 2015)

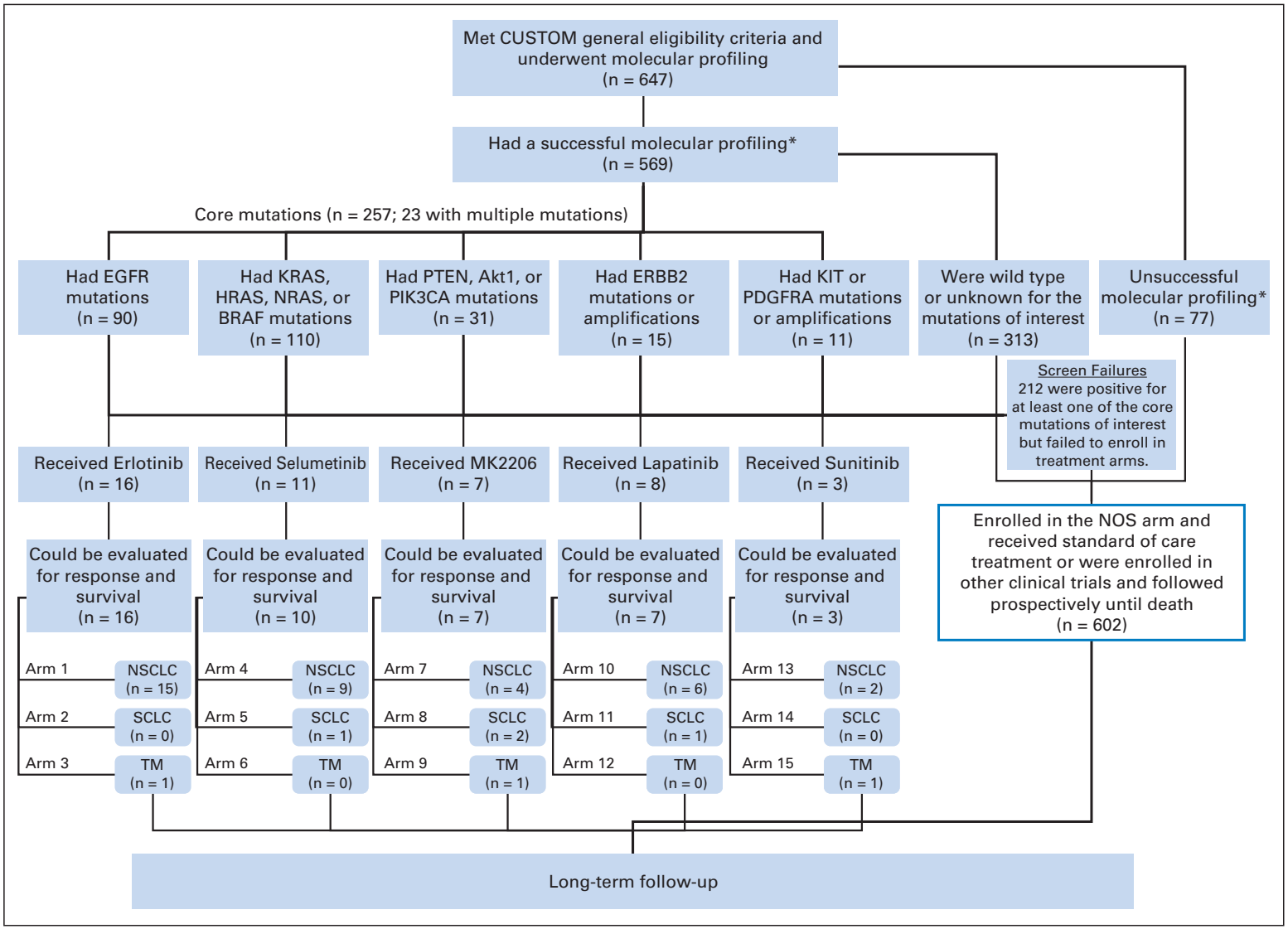


Fig 1. Flow diagram of patient population and treatment assignments. EGFR, epidermal growth factor receptor; NOS, not otherwise specified; NSCLC, non–small-cell lung cancer; PDGFRA, platelet-derived growth factor receptor alpha; SCLC, small-cell lung cancer; TM, thymic malignancy. (*) Successful molecular profiling was defined as having at least one core molecular analysis successfully performed.

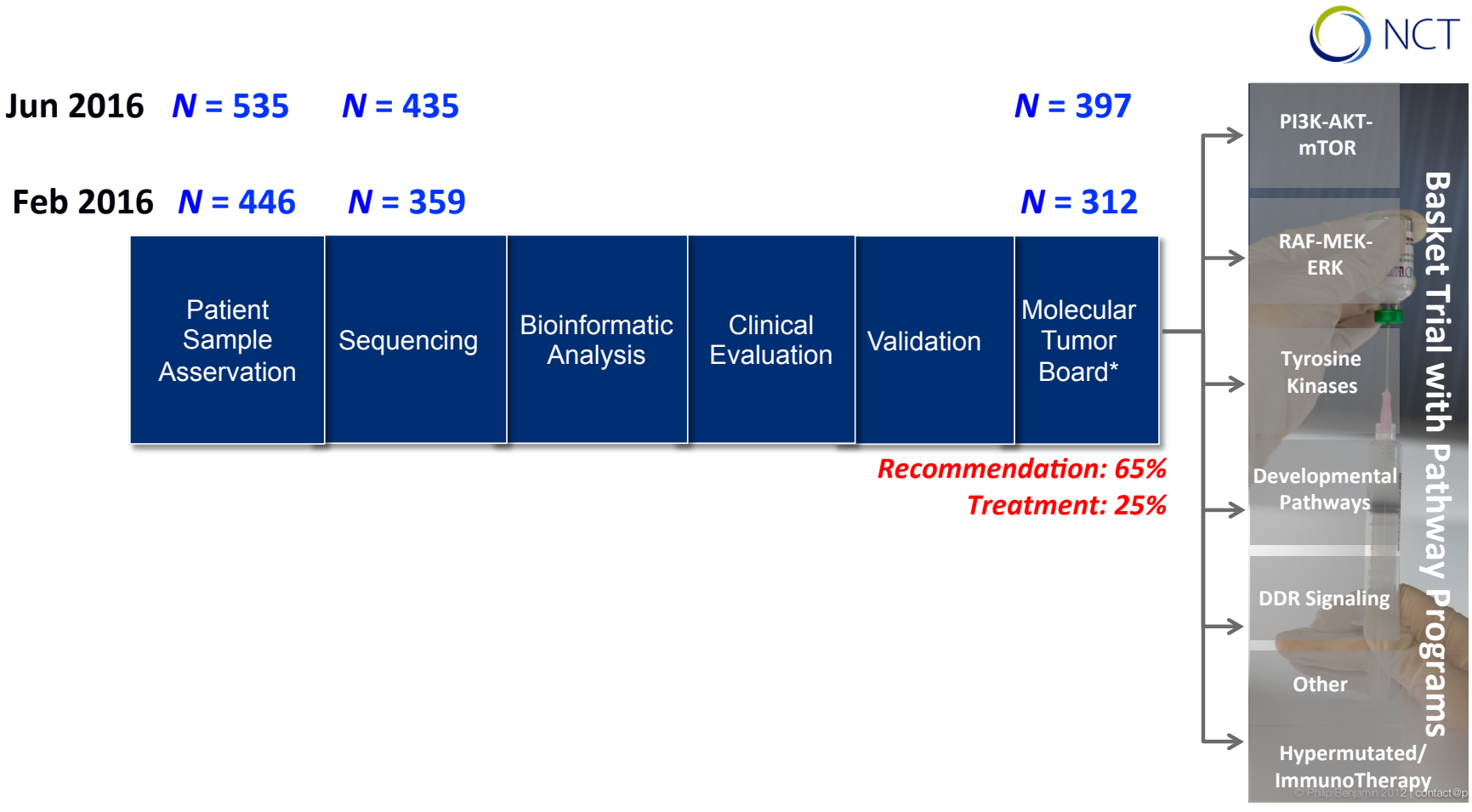
Statistical Evaluation of the NCT MASTER basket trial

NCT MASTER

The MASTER (Molecularly Aided Stratification for Tumor Eradication Research) program:

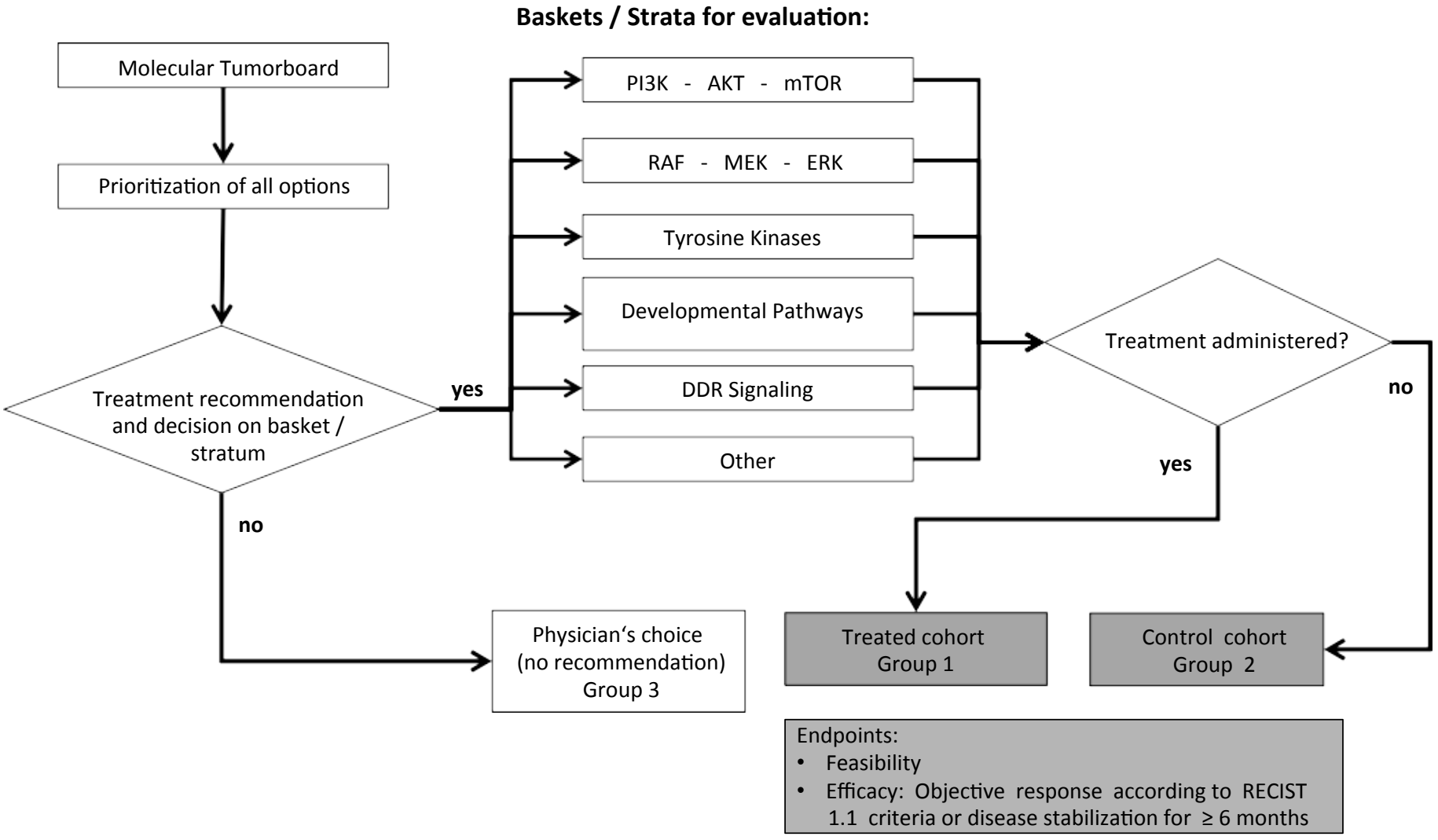
Analysis of high-throughput diagnostics and histopathological evaluations to generate hypotheses for new targeted tumor therapies.

NCT MASTER - Flow Chart



NCT Heidelberg: Stefan Fröhling, Christoph Heining, Hanno Glimm, Stefan Gröschel, Peter Horak
Claudia Scholl (Functional Genomics)
DKTK (German Cancer Consortium) – München, Frankfurt/Mainz, Dresden, Essen/Düsseldorf, Freiburg, Berlin, Tübingen

Actual Study Design



Causal effect of treatment

- Randomized controlled trials are the gold standard for causal inference.
- Unfortunately they are not always feasible for a variety of reasons, including ethical concerns.
- Consequently, in such situations **assessment of causal effects must be derived from non-randomized studies**.

NCT MASTER Basket Trial

- Individual recommendation of treatment
- May be associated with confounding

Possible methods against bias

1. Direct adjustment for confounding in regression models
   - Logistic regression
2. Propensity score methods
   - Propensity score: Conditional probability of treatment assignment given baseline characteristics (Rosenbaum & Rubin, 1983)
   - Optimal matching
3. Use of Instrumental variables

Causal Inference - DAG

Directed Acyclic Graph (DAG)

A graph where all edges are directed (doesnt contain bidirected dashed arcs denoting unobs. common causes/confounders) and which contains no cycles

We use DAGs to identify the causal structure of the data.

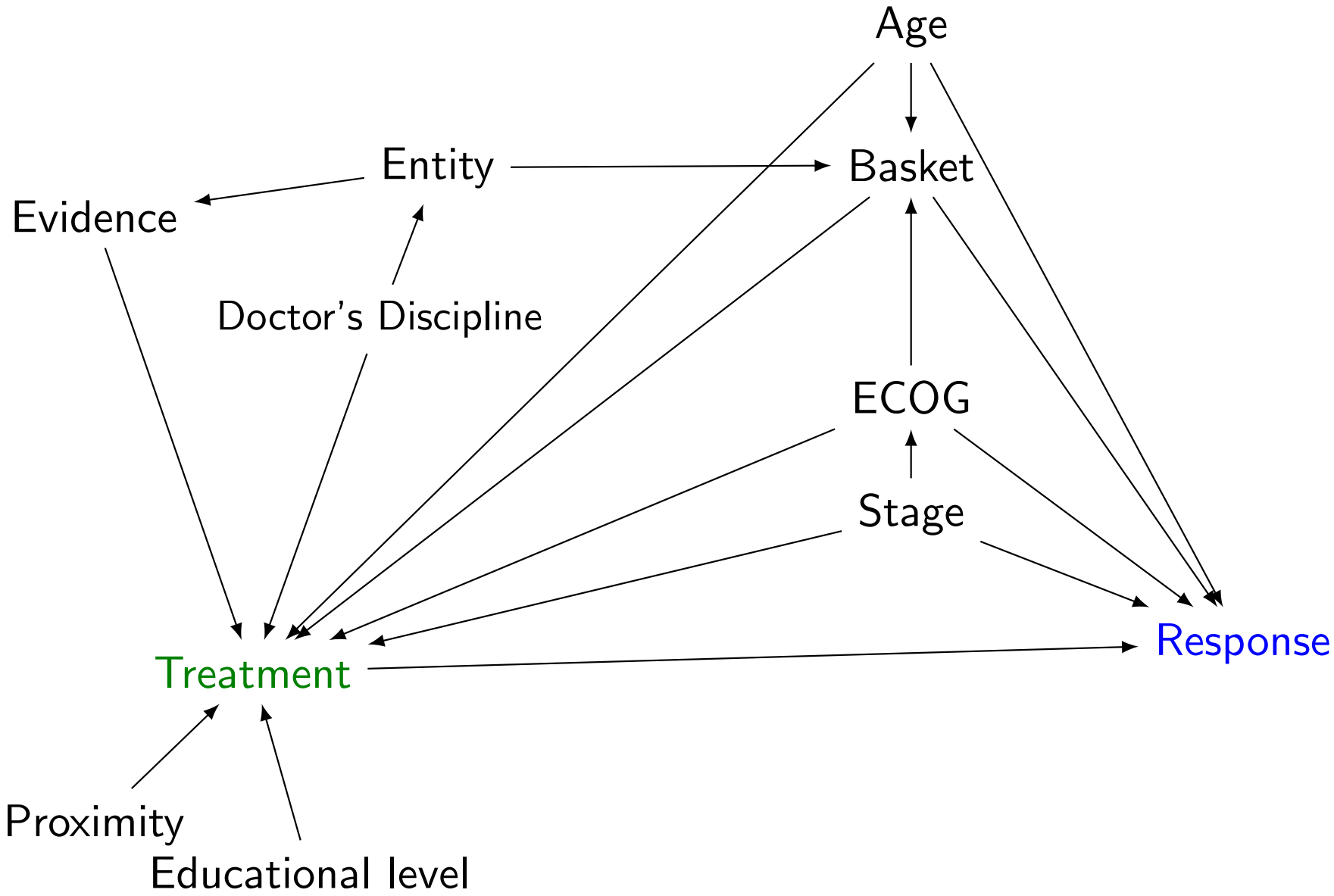
Y outcome of interest (Response); $D \in \{0, 1\}$ binary Treatment indicator

X observed characteristics; U unobserved characteristics

Interest: Causal effect $D \to Y$

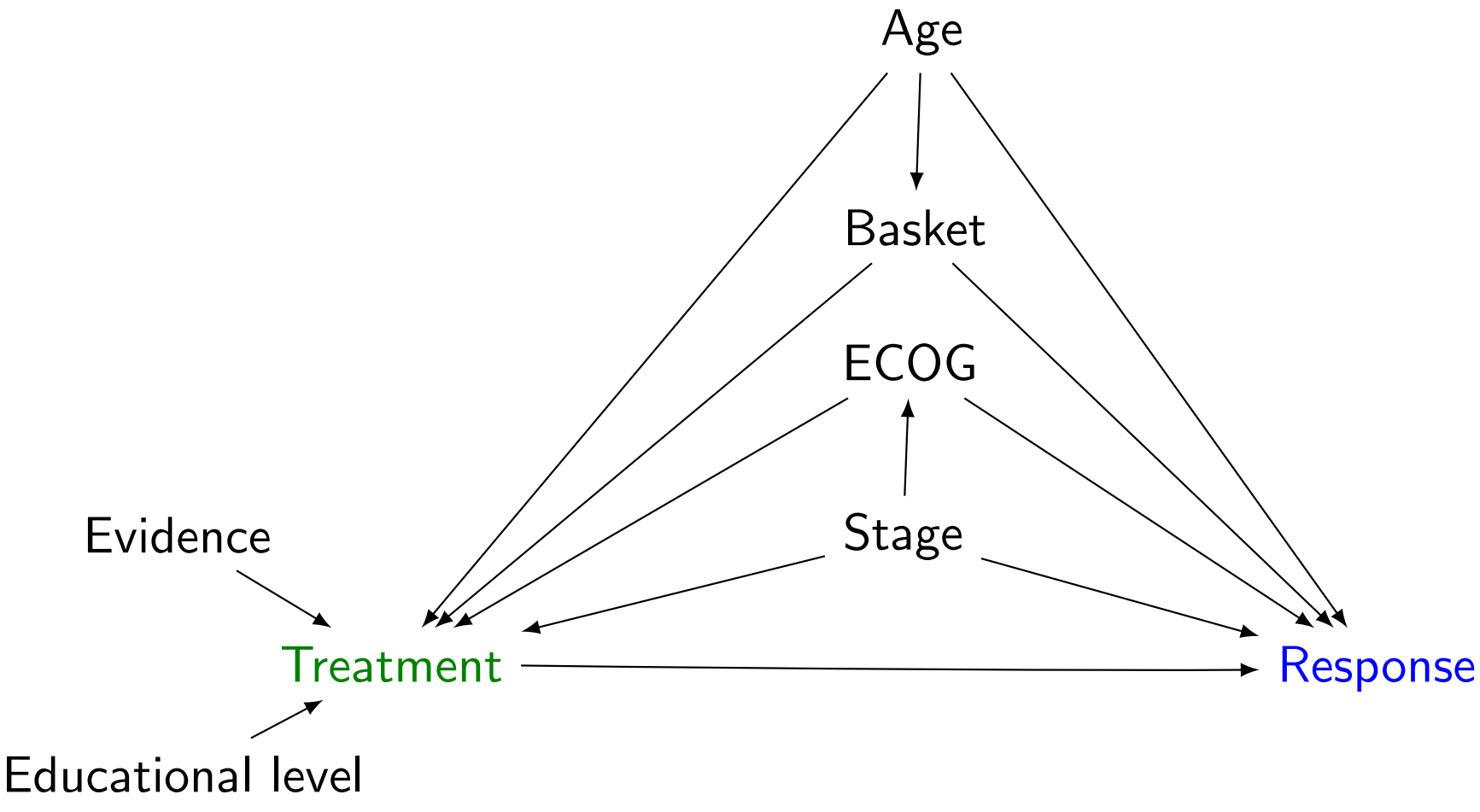
- What would happen to Y if D was changed externally (exogenously) from 0 to 1?
- NOT: Find the best fitting model for predicting Y

Causal Inference - DAG (NCT MASTER)



Causal Inference - DAG (NCT MASTER)

(Hypothesized) essential graph



Resources for NCT MASTER

Webpage:

www.nct-heidelberg.de/en/research/nct-master

Contact:

Study Office
Phone: +49 6221 5636253
E-mail: master@nct-heidelberg.de

Project Leader and coordinator of the program

Prof. Dr. med Hanno Glimm
Head Applied Stem Cell Biology, (Assistant) Medical Director Translational Oncology

Prof. Dr. Stefan Fröhling
Head Molecular and Cellular Oncology Translational Oncology

Dr. Daniela Richter
Scientific Coordinator NCT Precision Oncology Program

Finally: Points to Consider

Challenges:

- Strata of small size
- Strong heterogeneity

Study Design:

- Adaptation to refine, add and remove biomarker-treatment strategy combinations
  Allow to refine baskets, to add new baskets, to remove baskets.

Evaluation strategy:

- Success of trial vs. success of strata
  Use chain procedures starting with global null hypothesis of no effect
- Apply Firth correction