ADAPTIVE 2-IN-1 DESIGN, EXPANSION DECISION AND EXTENSIONS

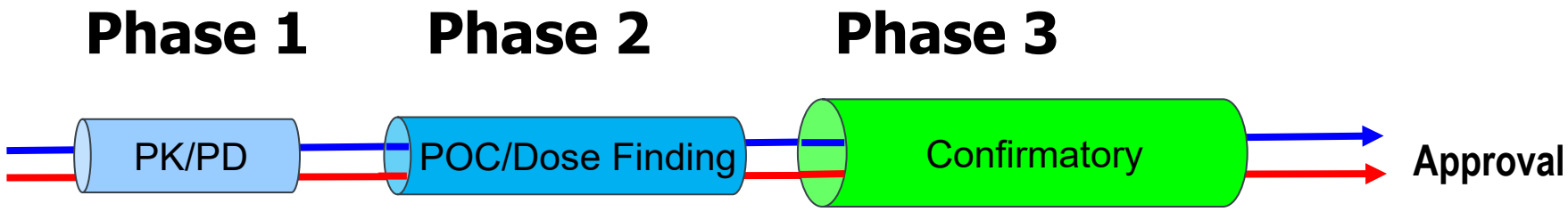
Cong Chen

Executive Director and Head of Early Oncology Statistics, BARDS
Merck & Co., Inc., Kenilworth, NJ, USA

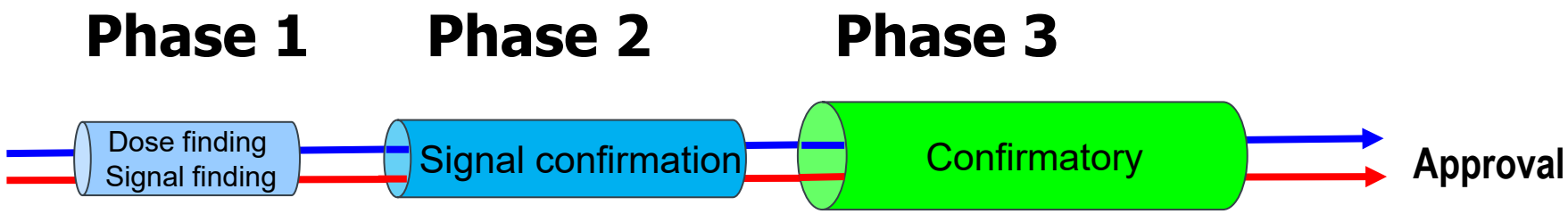
ASA San Diego Chapter Meeting, Oct 22, 2021

Traditional Drug Development Paradigm

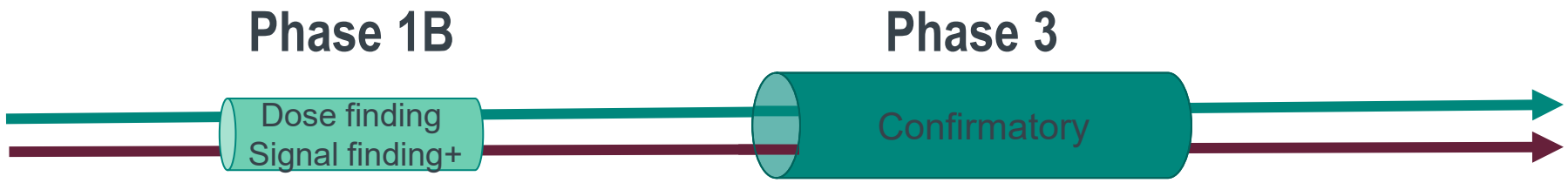
Typical non-oncology

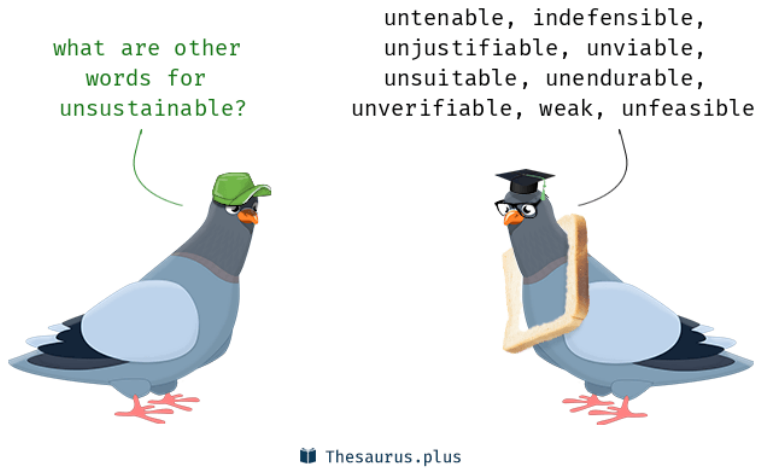


Oncology



Contemporary Oncology Drug Development





Epacadostat (IDO1) in Melanoma

- The most advanced new MOA right after PD-1/PD-L1
- ECHO-202: Phase 1B in combo with Keytruda
  - ORR=**56%*** (100 mg) vs **~37%** for Keytruda alone based on historical data
- ECHO-301 (April 6, 2018)

BIOTECH

Incyte's cancer drug fails trial, marking major blow for immunotherapy combination treatment

By ADAM FEUERSTEIN @adamfeuerstein / APRIL 6, 2018

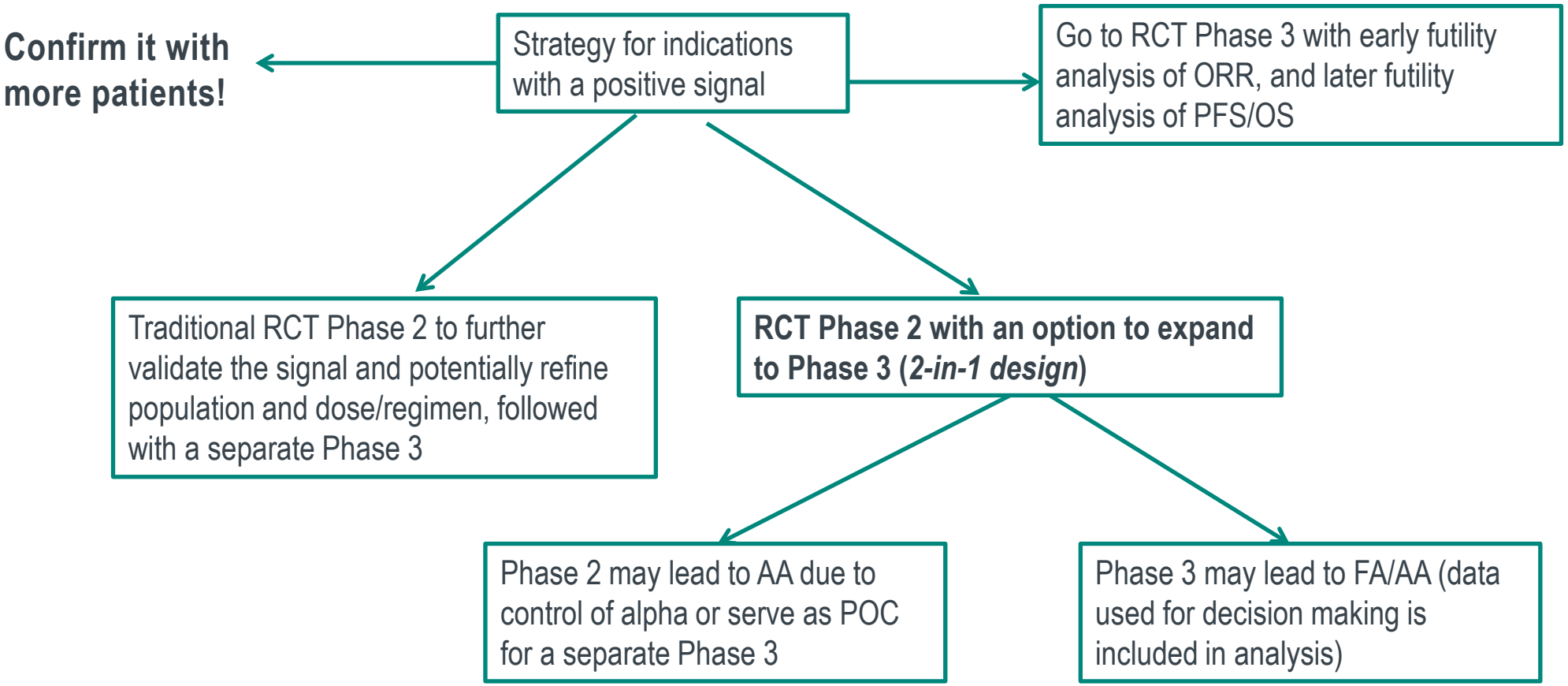
Keytruda+Axitinib in 1L RCC

- Both Keytruda and axitinib were known to have monotherapy activity in RCC prior to combination study
- Phase 1B: 38/52 (**73%**; 95% CI 59·0-84·4) patients achieved an objective response (vs **31%** for sunitinib)
  - The median PFS was 21 months (vs 11 months for historical sunitinib)
- KN-426 (Oct 18, 2018)

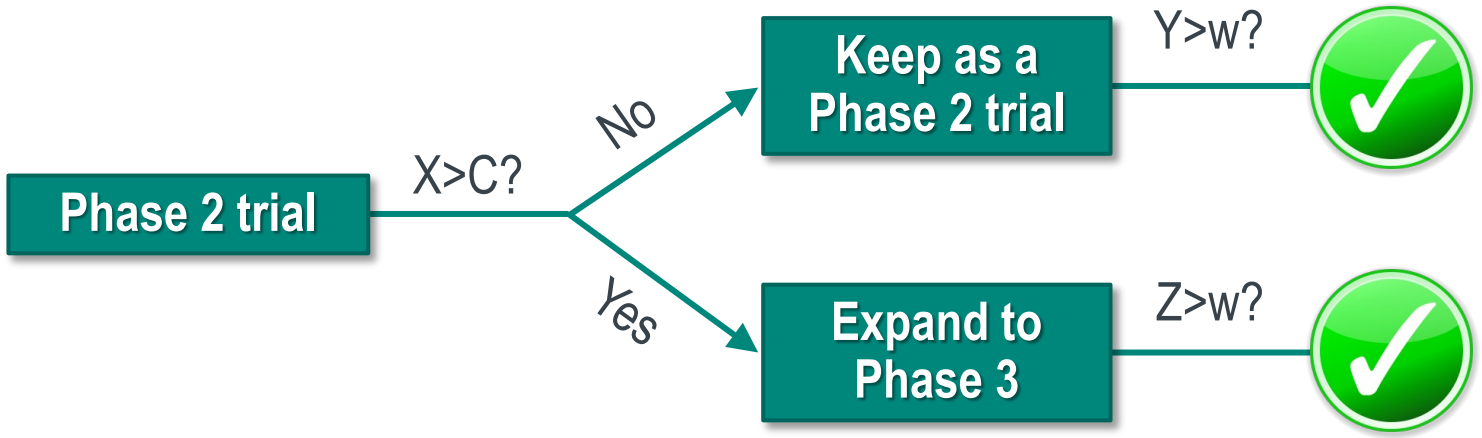
Merck (MRK) Reports Significant Improved OS & PFS Data from Pivotal Phase 3 KEYNOTE-426 Trial Investigating KEYTRUDA (pembrolizumab) in Combination with Pfizer's (PFE) Inlyta (axitinib)

STREETINSIDER.COM

Options Post Phase 1B Efficacy Screening



A Generic Statistically Seamless 2-in-1 Design



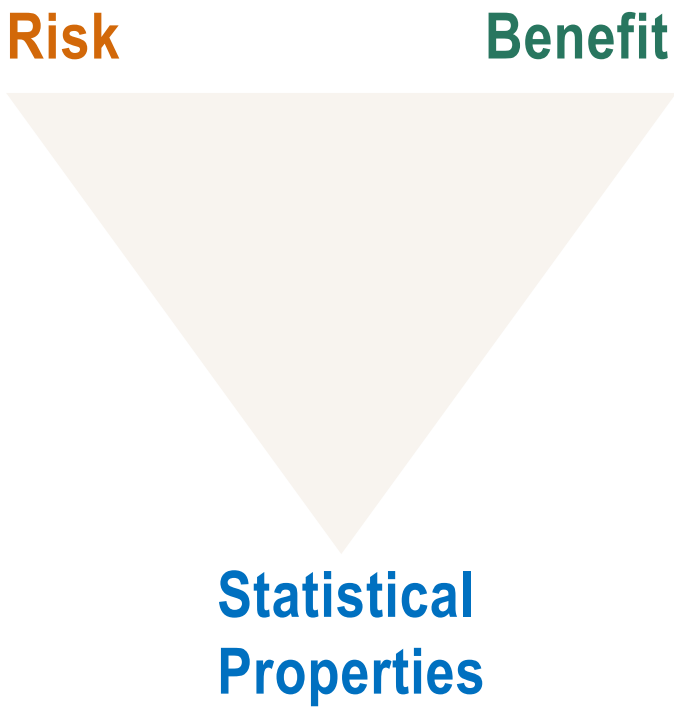
- The 3 endpoints that the standardized test statistics are based upon can be different
  - The expansion bar C is prespecified and should be binding
- No penalty for multiplicity control as long as $\rho_{XY} \geq \rho_{XZ}$ (automatically holds when the same Phase 2 endpoint is used for expansion decision-making due to nested populations)
  - w=1.96 to keep alpha controlled at 2.5% (step-down to higher level for Phase 2 as appropriate if it is not used for registration)

Key Questions to Ask Before a 2-in-1 Design is Considered

- Realistically, should you consider a randomized Phase 2 instead of a straight Phase 3 based on the preliminary Phase 1B single arm data?
- Is the program ready for a registration enabling study?
  - Any mid-trial change in endpoint/dose/population/CMC is subject to heavy scrutiny
- Is logistics worked out to enable timely expansion of enrollment?

Expansion Bar

- Expansion decision can be made at any time of the Phase 2
  - Earlier with smaller sample size when the intermediate endpoint is sensitive to intervention
  - Relative effect size between intermediate endpoint and clinical endpoint holds the key
- When deciding on expansion bar, same consideration as for GNG decision after a conventional Phase 2 POC applies
  - Lower bar if prior data is strong, additional cost is low and program value is high
- In addition to the expansion bar, a lower bar may be added to stop the trial for futility and a higher bar may be added for potential filing for AA



Background of a Real Example

- A small Phase 1B trial of a combination therapy with SOC has demonstrated exciting ORR in a biomarker-enriched 1st line gastric cancer
  - More patients are being added but uncertainty of signal remains due to lack of control
- A seamless Phase 2/3 trial based on 2-in-1 design with Phase 2 oversized for AA
  - Faster development and fewer patients compared to separate Phase 2 and Phase 3
  - Less risky than straight Phase 3 by skipping Phase 2

Given large number of similar programs and limited and uncertain commercial value of the indication, the expansion bar is determined by explicitly maximizing a benefit cost ratio (or return divided by investment).

The same benefit cost ratio analyses suggest to conduct more under-powered (but well-powered for 1.5Δ) small (but not too small) POC trials in oncology drug development (Chen and Beckman CCR 2014) and various other strategies that not only take traditional Type I/II errors but also ***Type III error*** (risk of lost opportunities) into consideration.

Application of The 2-in-1 Design

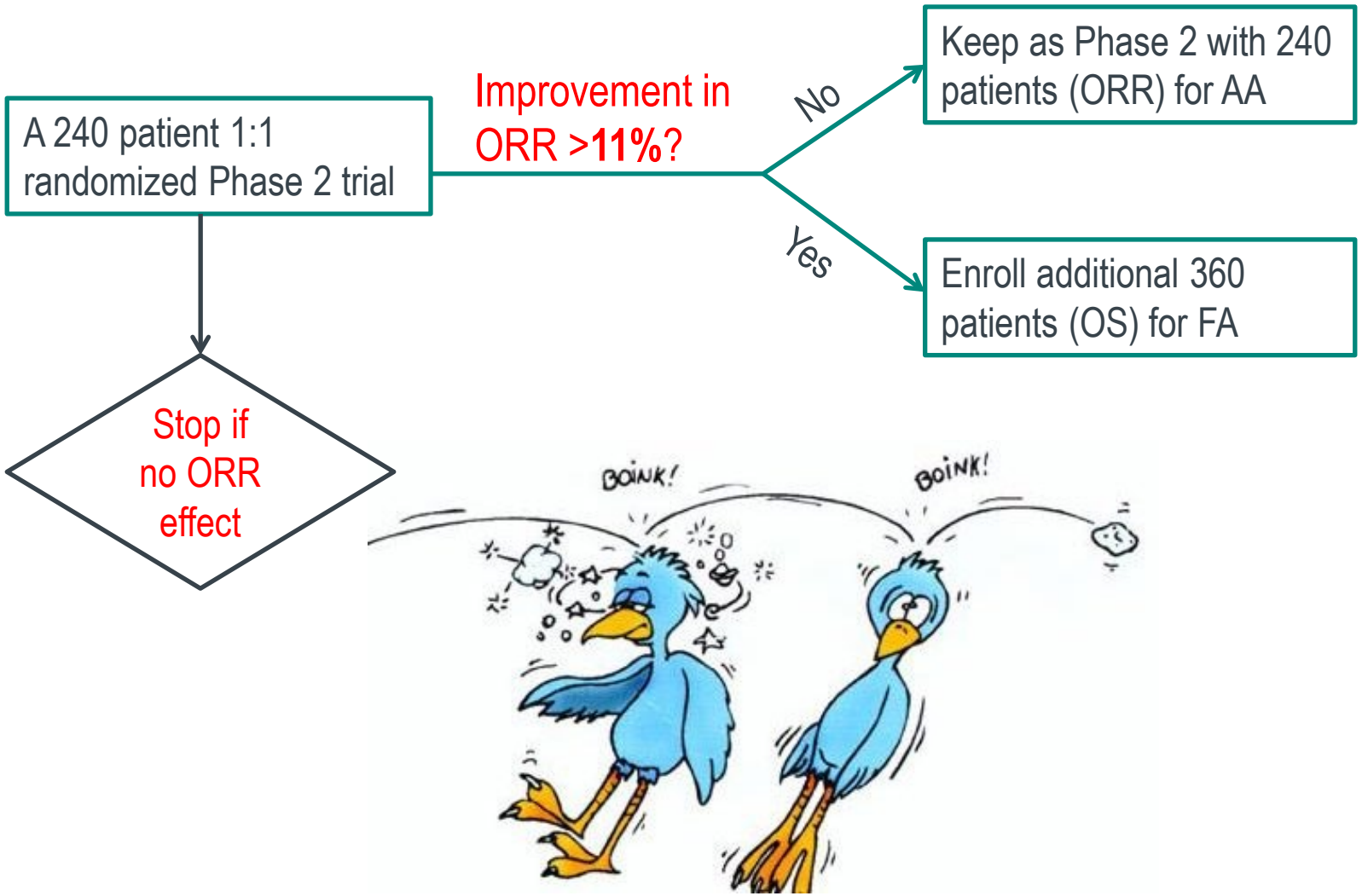
- Phase 2 (in case of no expansion)
  - With 240 patients, it has 88% power for detecting an ORR increase of **20%** at 2.5% (one-sided) alpha level
  - A futility analysis will be conducted mid-way to stop the trial early in case of no ORR improvement
  - P-value<0.025 for ORR (and positive totality of data) leads to possible filing for AA
- Phase 3 (in case of expansion)
  - With 460 OS events (600 patients in total), it has 90% power for detecting a hazard ratio (HR) of **0.74** at 2.5% (one-sided) alpha level
  - P-value<0.025 for OS leads to filing for FA
- Expansion decision targets one month ahead of Phase 2 accrual completion (~160 patients with adequate follow-up for ORR) to ensure seamless expansion

Selecting Expansion Bar Using BCR Analysis

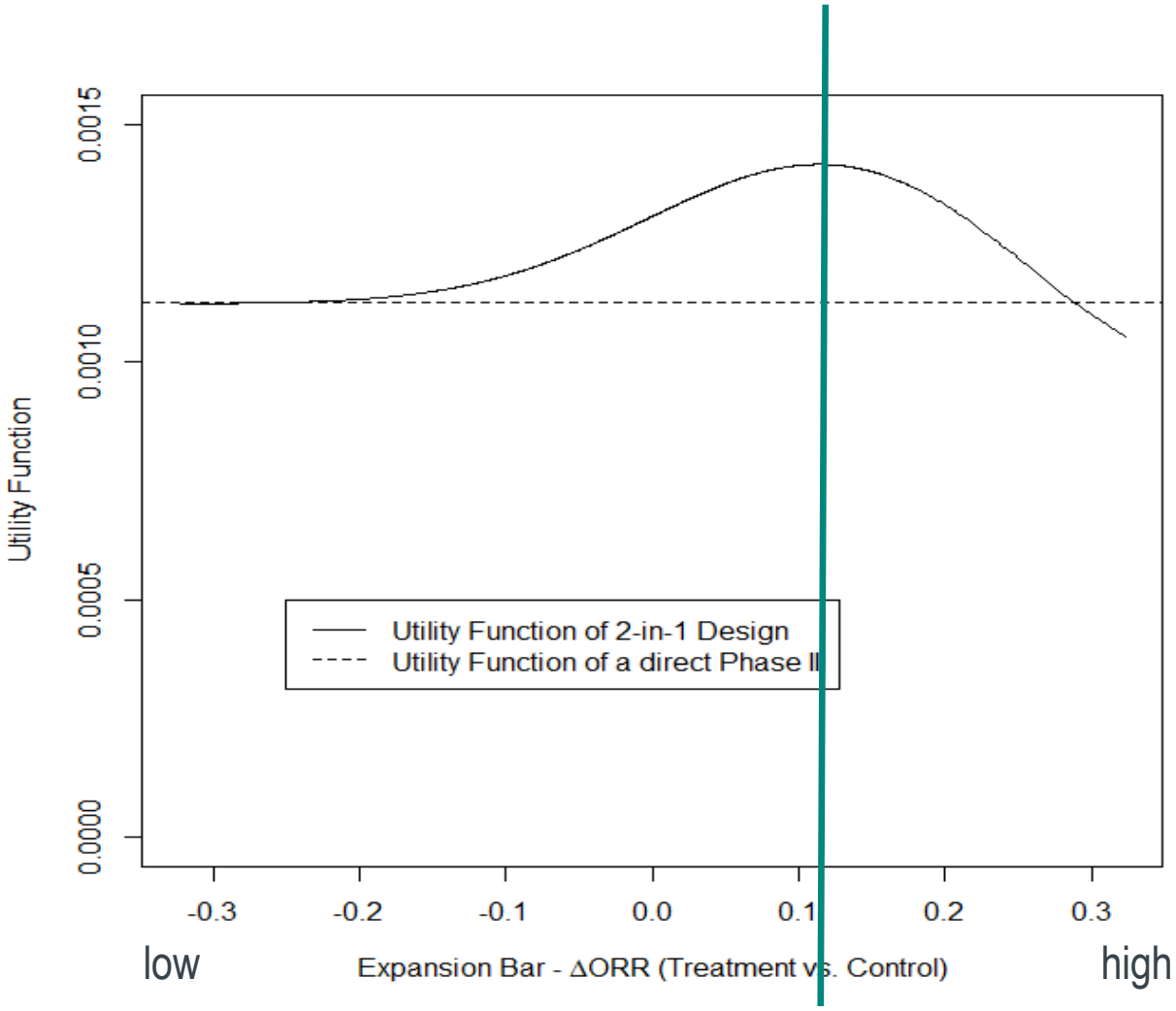
- The null and alternative hypotheses are assumed to have equal probability
  - **Null**: ORR difference=0, HR(OS)=1
  - **Alternative**: ORR difference=20%, HR(OS)=0.74
- Benefit: value adjusted probability of a true positive trial
  - 1/4*prob(true positive Phase 2)+3/4*prob(true positive Phase 3)
- Cost: expected overall sample size for the study
  - 240+{prob(expansion|null)*prob(null)+prob(expansion|alternative)*prob(alternative)}*360
  - Alternatively, one may replace sample size with actual trial cost

Max BCR = Min total sample size for a value-adjusted indication

Resulting Design



BCR Changes with the Expansion Bar



Robustness of Input Variables

Prior distribution of treatment effect for OS		Relative value of a positive Phase 2 vs. a positive Phase 3	Approximate optimal expansion bar in ΔORR
P(HR = 0.74)	P(HR = 1)		
1/3	2/3	1:3	12%
		1:5	10%
1/2	**1/2**	**1:3**	**11%**
		1:5	9%
2/3	1/3	1:3	10%
		1:5	8%

Relative sample size (or trial cost) of Phase 2/Phase3 has the biggest impact on optimal expansion bar, which fortunately can be well assessed when planning the study

Comparison with Other Adaptive Designs

- 2-in-1 design allows use of an intermediate endpoint for timely and cost-effective adaptation
  - Same endpoint is often used for both adaptation decision and hypothesis testing in the adaptive design literature, but adaptive tests based on follow-up–wise separation may not control the Type I error rate when a different endpoint is used
- 2-in-1 design allows declaration of a positive outcome even without expansion, providing more incentive to stop enrollment than a vanilla Phase 3 futility analysis (**for good**)
- 2-in-1 design is more consistent with conventional wisdom of drug development (i.e., GO only when data are exciting) than some sample size re-estimation methods (e.g., promising zone)
  - The fallback plan of making it a bona fide POC trial is appealing to decision makers

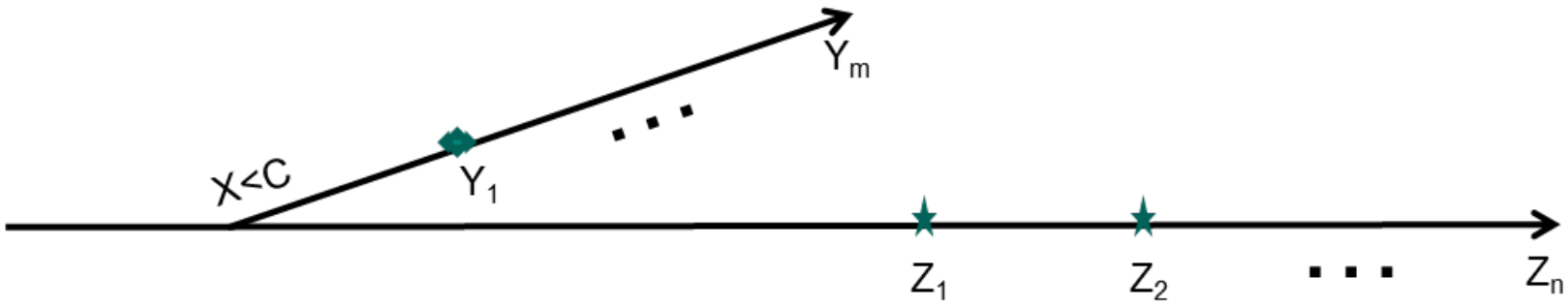
Similar Penalty-free Designs for Population Expansion

- A Phase 3 oncology trial starts with biomarker+ patients only
  - Expand to an all-comer study if treatment effect at an interim analysis is more impressive than expected, suggesting broader activity
  - In case of expansion, split alpha between biomarker+ and all-comers
- A Phase 3 all-comer oncology trial with a biomarker hypothesis (i.e., either a win biomarker+ or a win in all-comers is a win based on pre-specified alpha-split)
  - Add more biomarker+ patients in case data in biomarker- patients is less impressive than expected, suggesting lower POS in all-comer population
- The underlying mathematical reasons for Type I error control are different from 2-in-1

Sponsors usually don't like the idea of stopping a subpopulation (or arm/dose) during the study for fear of wrong decision and negative impact on accrual, especially at the expense of penalty for multiplicity control associated with population selection

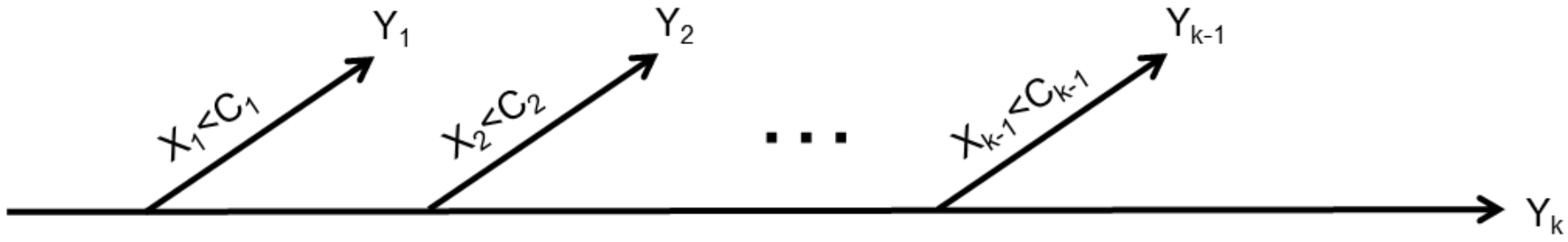
Application of Group Sequential Method to 2-in-1

- An alpha-spending function is pre-specified for each scenario (expansion or not) that controls the Type I error under each at the α level.
  - The overall Type I error is controlled at the α level if $\rho_{XY_m} \geq \rho_{XZ_1}$, or roughly speaking the first interim analysis in case of expansion should be no sooner (or based on more information) than the final analysis in case of no expansion
  - A rigorous proof is now FINALLY available (Zhang et al. 2021)



Multiple Adaptive Decisions Overtime (*K*-in-1)

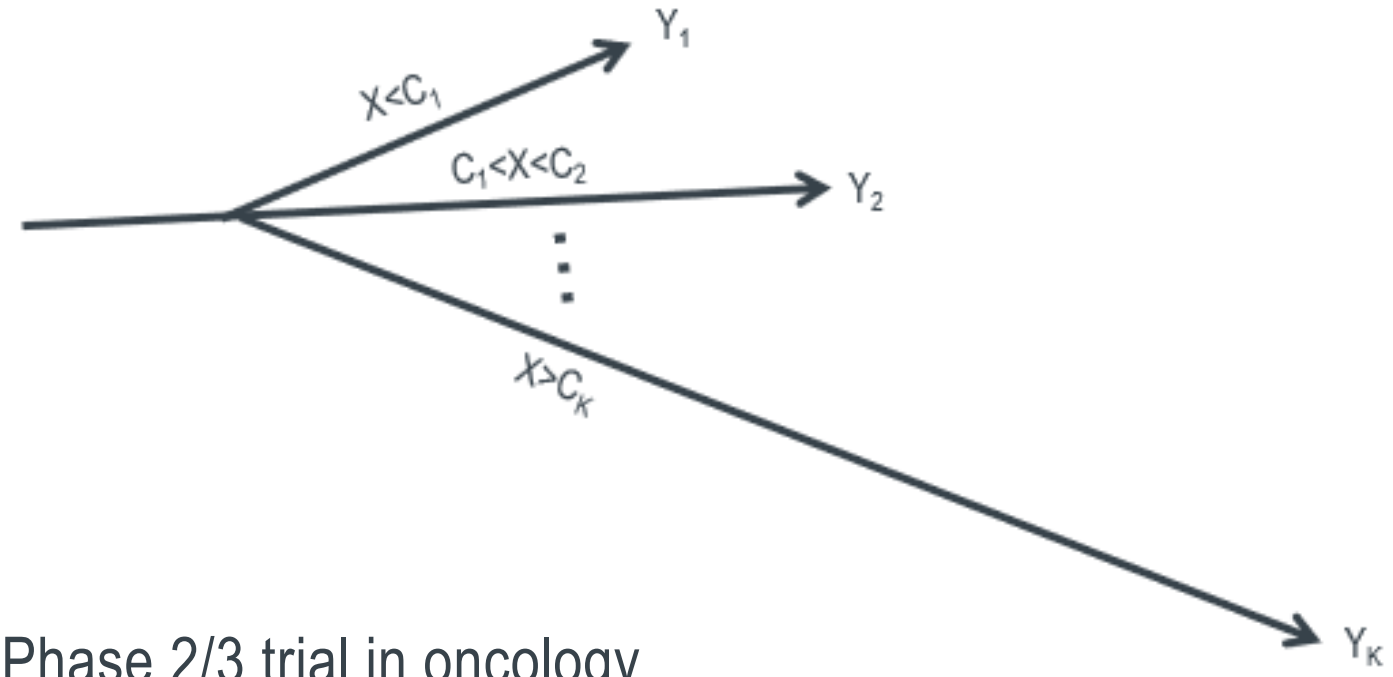
- **Sample size increases each time an expansion bar is crossed**
  - Y_j's can all be tested at the α level if corr(X_j, Y_l) is non-increasing in l $(j \leq l \leq K)$, which is generally expected to hold due to the nested structure of the study populations



- A hypothetical Phase 2/3 trial in oncology
  - Both X_1 and Y_1 may be based on objective response rate (ORR) while X_2 and Y_2 are based on progression-free-survival (PFS) and Y_3 is based on the overall survival (OS)

Multiple Cutpoints at Same Time (*K*-in-1)

- **Sample size increases with expansion bar**
  - Y_j's can all be tested at the α level if corr(Y_j, X) is non-increasing in j $(1 \leq j \leq K)$, which is generally expected to hold, and overall Type I error tends to decrease with K

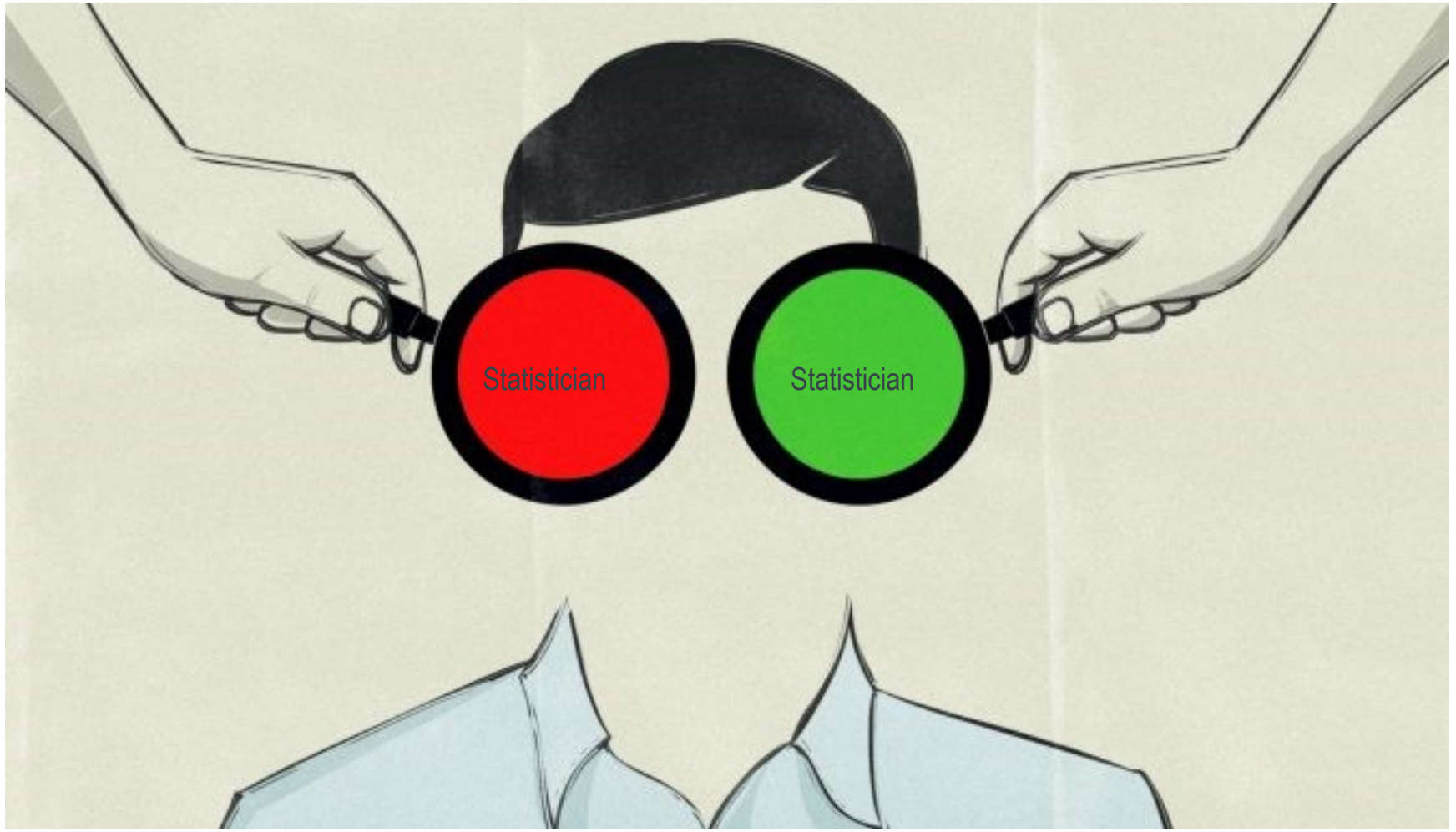


- A hypothetical Phase 2/3 trial in oncology
  - Both X and Y_1 may be based on ORR while Y_2 is based on PFS and Y_3 is based on OS

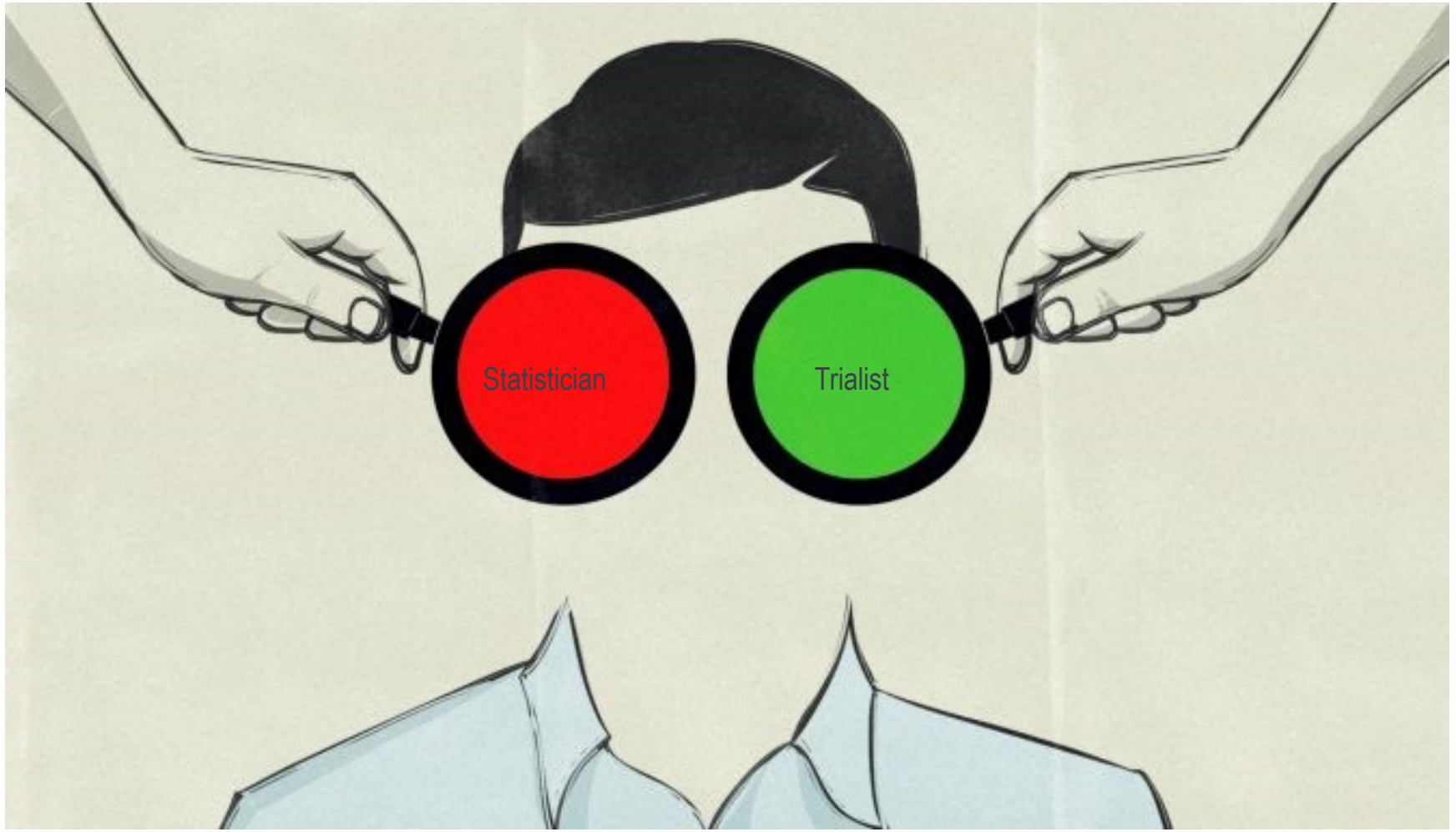
Other Advancements in 2-in-1 Design

- Application of 2-in-1 design concept to Phase 2 POC and dose-finding
  - Deng Q, Bai X, Ting N. Dynamic development paths for expanding a proof-of-concept study to explore dose range. Statistics in Medicine 2019.
- Sufficient conditions for FWER control with graphical approach are derived
  - Li W, Jia C, Zhou H, Sun L. Family-wise Type I Error Rate Control for an Extended 2-in-1 Design with Graphical Approach in Oncology Drug Development, to be submitted
- Application of group sequential method to generalized K-in-1 design
  - Zhang X, Chen C. Application of group sequential method for interim monitoring to the 2-in-1 design and its extensions, to be submitted
- Estimation of treatment effect
  - Li W, Bai X, Deng Q and Chen C. Estimation of Treatment Effect in 2-in-1 Adaptive Design and Some of its Extensions. Statistics in Medicine 2021. DOI: 10.1002/sim.8917.
- Some practical considerations and examples
  - Fan L, Zhao J and Li W. The extension of 2-in-1 adaptive phase 2/3 designs and its application in oncology clinical trials. Contemporary Clinical Trials 2020

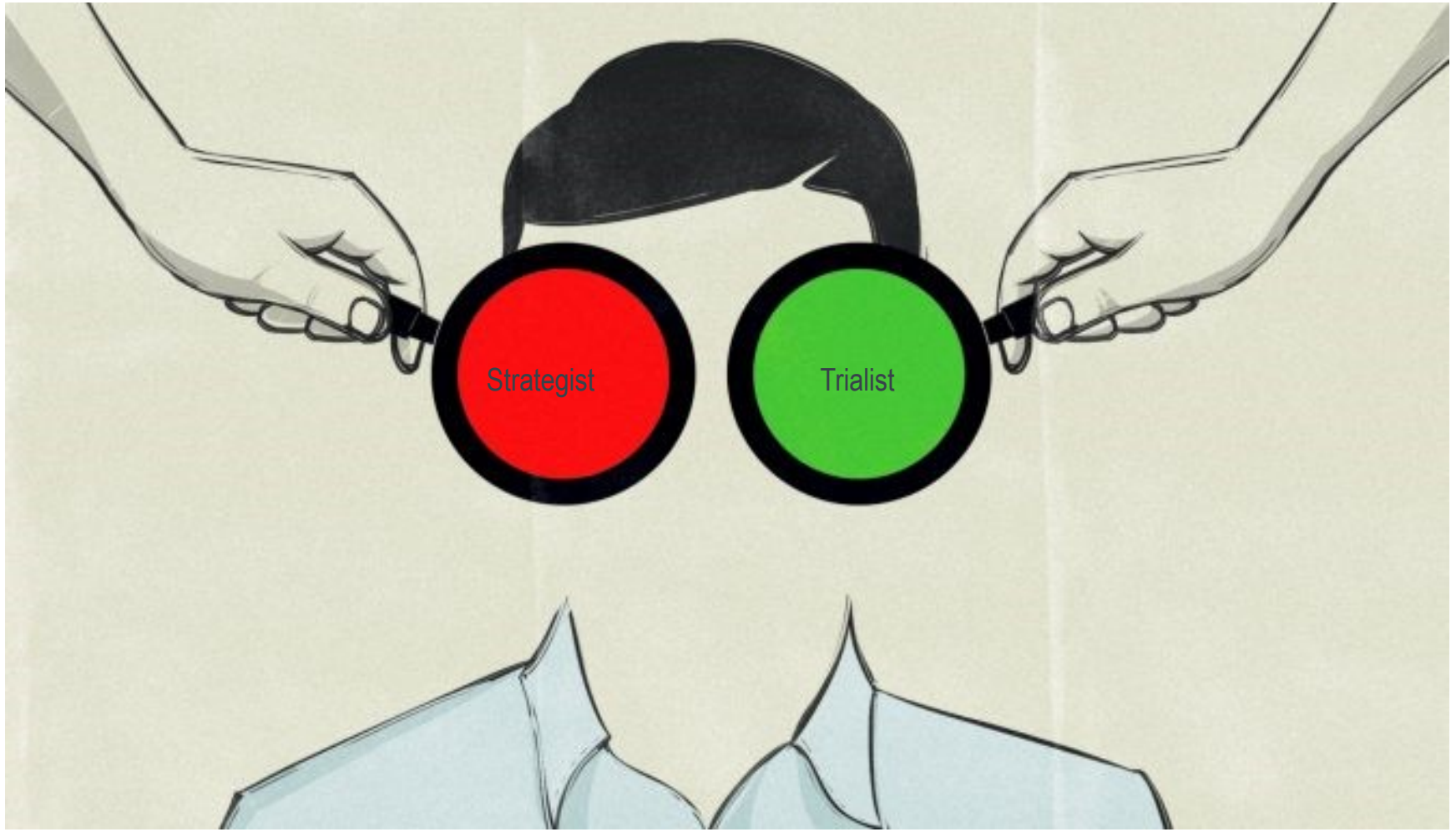
Statistician's Typical Role in Drug Development



Statistician's Aspirational Role



Statistician's Aspirational Role

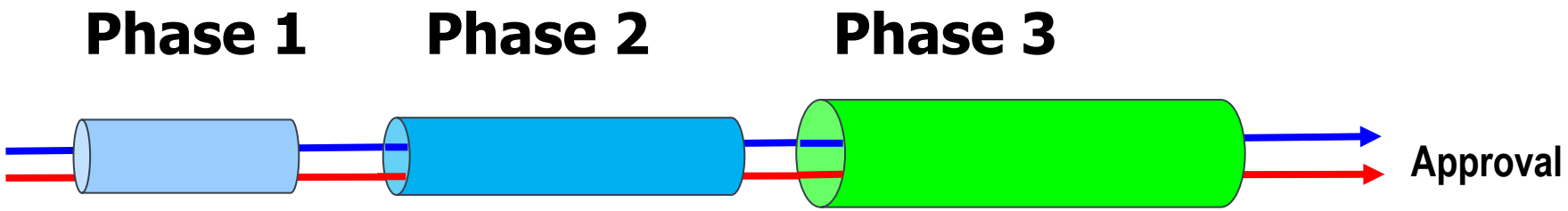


Key References

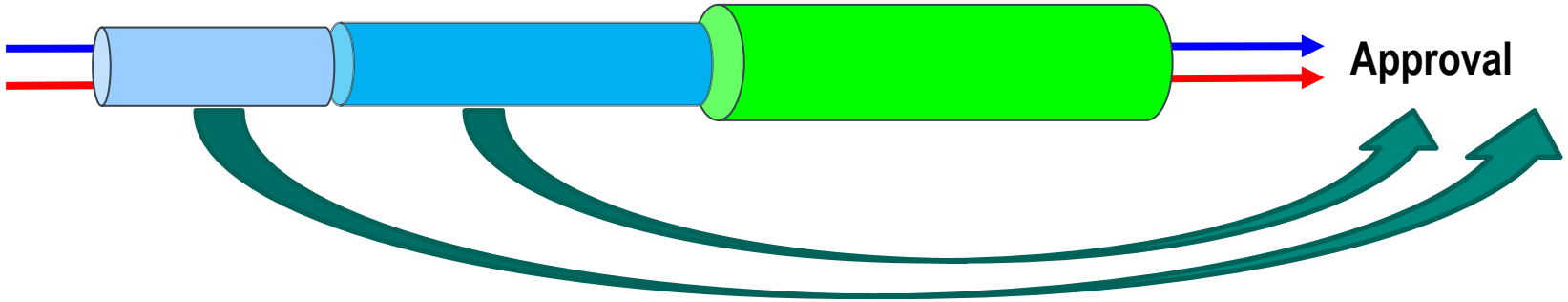
- Chen C, Anderson K, Mehrotra DV, Rubin EH and Tse A. A 2-in-1 Adaptive Phase 2/3 Design for Expedited Oncology Drug Development. Contemporary Clinical Trials 2018; 64:238-242.
- Sun LZ, Li W, Chen C, and Zhao J. Advanced Utilization of Intermediate Endpoints for Making Optimized Cost-Effective Decisions in Seamless Phase II/III Oncology Trials, Statistics in Biopharmaceutical Research 2019. DOI: 10.1080/19466315.2019.1665578.
- Chen C, Li W, Deng Q. Extensions of the 2-in-1 Adaptive Design. Contemporary Clinical Trials 2020. DOI: 10.1016/j.cct.2020.106053.

A New Era in Oncology Drug Development

- Traditional paradigm



- Evolving new paradigm



Unmet medical need and compelling data on surrogate endpoints (e.g., RR and PFS) likely predictive of benefit (e.g., OS)