Design Concept for a Confirmatory Basket Trial

Robert A. Beckman, MD[1] and Cong Chen, PhD[2]

[1]Professor of Oncology & of Biostatistics, Bioinformatics, and Biomathematics

Lombardi Comprehensive Cancer Center and Innovation Center for Biomedical Informatics

Georgetown University Medical Center

Founder and Chief Scientific Officer, Oncomind, LLC

[2]Executive Director, Biostatistics and Research Decision Sciences, Merck & Co, Inc.

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  - **Cong Chen—led group; co-led concept development; led all statistical and simulation work**
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- Pathway design subgroup, additional members:
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  - Advisor: Sue-Jane Wang
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- Small populations workstream is part of **DIA Adaptive Design Scientific Working Group (ADSWG),** a group of > 200 statisticians and clinicians from industry, academia, and national health authorities (FDA and EMEA)

Small Populations Within A Common Disease

- The increasing discovery of molecular subtypes of cancer leads to small subgroups that actually correspond to orphan or “niche” indications, even within larger tumor types
- Enrolling enough patients for confirmatory trials in these indications may be challenging.
- The shift to a molecular view of cancer requires a corresponding paradigm shift in drug development approaches
- Exclusive use of “one indication at a time” approaches will not be sustainable

Basket Trials

- Multiple tumor types with one drug and predictive biomarker
- Evaluation often based on pooled analysis
  - In some designs, pooling can be partial, based on Bayesian hierarchical model. Degree of pooling can be adjusted based on data
  - In some designs, indications are considered individually. Basket is then more of an operational tactic
- Premise is that molecular subtype is more fundamental than histology
- Can be single sponsor or consortium
- Opportunity for multiple indications for the sample size of one

Agenda

- Introduction
- General Design Concept for a Confirmatory Basket Trial
- Challenges and Recommendations for Overcoming Them
- Performance Simulations and Design Considerations
- Conclusions

The Original Basket: Imatinib B2225

186 patients with

40 different malignancies with known genomic mechanisms of activation of imatinib target kinases

KIT, PDGFRA or PDGFRB

Imatinib 400- 800 mg BID primary Endpoint ORR

1/16 (6%) 2/20 (10%) 10/12 (83%) 1/5 (20%) 6/14 (43%) 4/7 (58%)

13 centers in consortium: North America, Europe, Australia

Lead to supplemental indications for these 4 subsets after pooling with other trials and case reports

Blumenthal. Innovative trial designs to accelerate the availability of highly effective anti-cancer therapies: an FDA perspective, AACR 2014

Features of These Designs

- A similar design to Imatinib B2225 was endorsed at a Brookings/Friends Conference in 2011
- Common features:
  - Exploratory and opportunistic in nature
  - Single-arm trials with ORR as primary endpoint
  - Intend to use pooled population for primary analysis to gain broader indication across tumor types (individual tumor type is not adequately powered)
  - Involve ***possibly*** transformative medicines in patients with great unmet need and ***seemingly*** exceptionally strong scientific rationale

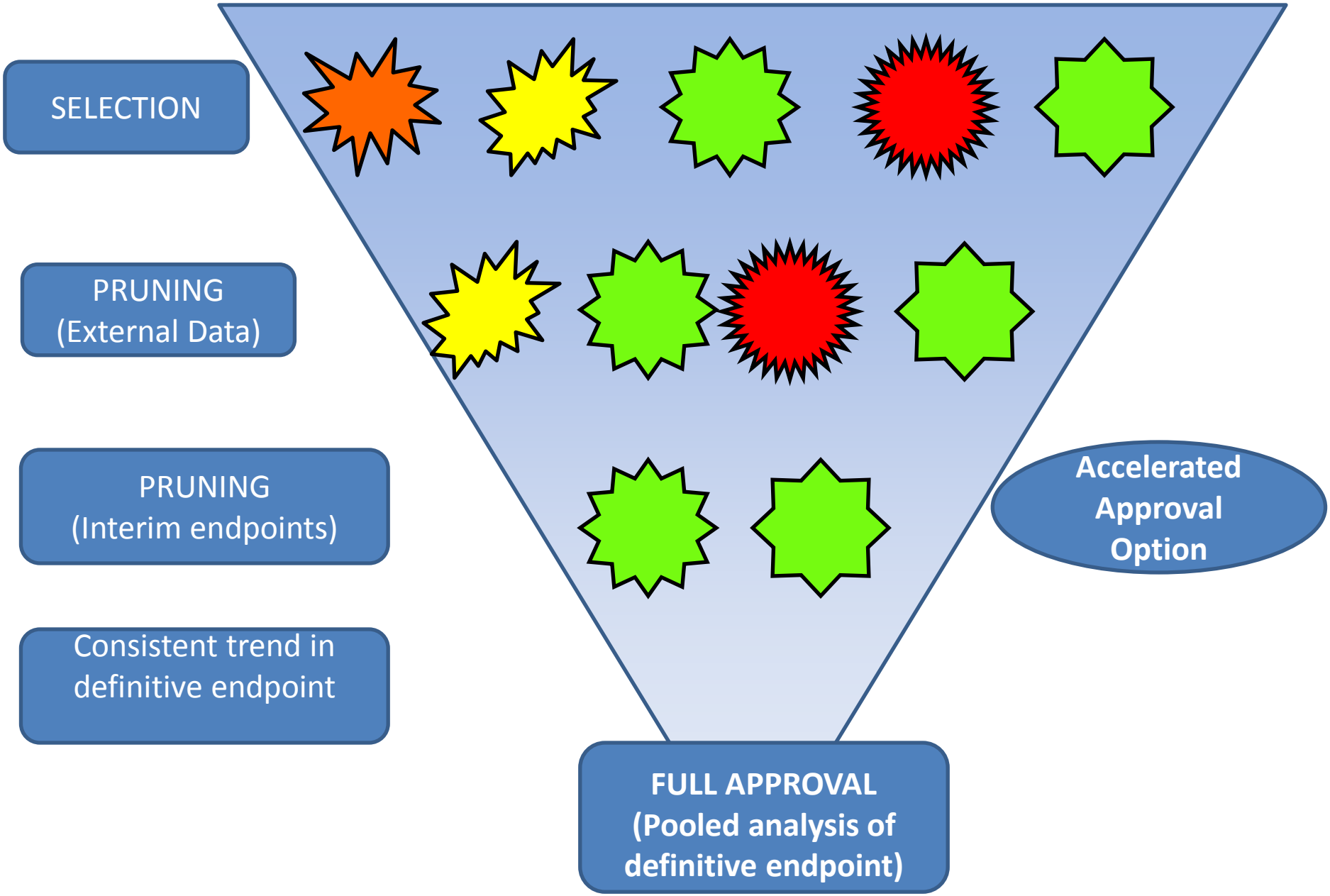
Issues

- Clinical data to support pooling may be limited, and treatment effect may differ between tumor types
  - Vemurafenib works in melanoma with BRAF V600E mutation but not colorectal cancer with same mutation
- Not all drugs hoped to be transformational live up to this promise
- Response rate may not predict overall survival
- Single arm trials are subject to patient selection bias
- Predictive effect of a biomarker is confounded with the prognostic value which is often unknown
- Health authorities can be non-committal upfront

DIA Small Population Pathway Subteam

- Can we develop a generalizable confirmatory basket design concept with statistical rigor?
  - Applicable not only to exceptional cases, but to all effective medicines in any line of therapy
  - Follow existing accelerated and standard approval pathways to increase potential approvability
- This would have multiple benefits
  - Increase and accelerate access to effective medicines for patients in niche indications
  - Provide sponsors with cost-effective options for development in niche indications
  - Provide health authorities with more robust packages for evaluation of benefit and risk
  - **MOST OF DRUG DEVELOMENT RESOURCES ARE SPENT IN THE CONFIRMATORY PHASE**

GENERAL DESIGN CONCEPT


SELECTION
PRUNING
(External Data)
PRUNING
(Interim endpoints)
Consistent trend in
definitive endpoint
Accelerated
Approval
Option
FULL APPROVAL
(Pooled analysis of
definitive endpoint)

Features of the Design (I)

- Tumor histologies are grouped together, each with their own control group (shared control group if common SOC)
- Randomized control is preferred
  - Single arm cohorts with registry controls may be permitted in exceptional circumstances as illustrated by imatinib B225 and others
- In an example of particular interest, each indication cohort is sized for accelerated approval based on a surrogate endpoint such as progression free survival (PFS)
  - This may typically be 25-30% of the size of a Phase 3 study
- In another approach, an interim evaluation of partial information on the definitive endpoint may be used
- Initial indications are carefully selected as one bad indication can spoil the entire pooled result

Features of the Design (II)

- Indications are further "pruned" if unlikely to succeed, based on:
  - External data (maturing definitive endpoint from Phase 2; other data from class)
  - Internal data on surrogate endpoint OR partial information on definitive endpoint
- Sample size of remaining indications may be adjusted based on pruning
- Type I error threshold will be adjusted to control type I error (false positive rate) in the face of pruning
  - Pruning based on **external** data does not incur a statistical penalty
  - Discussed in more detail later in talk
- Study is positive if pooled analysis of remaining indications is positive for the primary definitive endpoint
  - Remaining indications are eligible for full approval in the event of a positive study
  - Full pooling chosen for simplicity
  - Some of the remaining indications may not be approved if they do not show a trend for positive risk benefit as judged by definitive endpoint

Another Possible Source of External Data

- Real World Data (RWD) from Off-Label Use
- Impact of RWD on basket trial performance is currently under study in a project led by postdoctoral fellow Daphne Guinn

CHALLENGES OF BASKET DESIGNS AND RECOMMENDATIONS FOR OVERCOMING THEM

Challenge 1: Risks of Pooling

- One of more bad indications can lead to a failed study for all indications in a basket
- Histology can affect the validity of a molecular predictive hypothesis, in ways which cannot always be predicted in advance
  - Vemurafenib is effective for BRAF 600E mutant melanoma, but not for analogous colorectal cancer (CRC) tumors
  - This was not predicted in advance but subsequently feedback loops leading to resistance were characterized

Addressing challenge 1

- Basket trials are recommended primarily after there has been a lead indication approved (by optimized conventional methods) which has validated the drug, the predictive biomarker hypothesis, and the companion diagnostic
  - Example, melanoma was lead indication preceding Brookings trial proposal in V600E mutant tumors
- Indications should be carefully selected
- Indications should be pruned in several steps before pooling

Challenge 2: Clinical validity of the predictive biomarker hypothesis

- The clinical validity of the predictive biomarker can only be verified by inclusion of “biomarker negative” patients in the confirmatory study
- Addressing the challenge
  - Recommend a smaller pooled, stratified cohort for biomarker negative patients, powered on surrogate endpoint
    - Would need to expand the biomarker negative cohort (to evaluate definitive endpoint) if surrogate endpoint shows possible benefit
  - Prior evidence should permit this if:
    - An approved lead indication has already provided clinical evidence for the predictive biomarker hypothesis
    - Prior phase 2 studies support the predictive biomarker hypothesis in other indications

Challenge 3: Adjusting for Pruning

- Pruning indications that are doing poorly on surrogate endpoints may be seen as cherry picking
  - This can inflate the false positive rate, an effect termed "random high bias"
- Addressing the challenge:
  - Emphasize use of **external data**, especially maturing Phase 2 studies, for pruning
    - Pruning with external data does not incur a penalty for random high bias
  - Apply statistical penalty for control of type I error when applying pruning using **internal data**
    - Methods for calculating the penalty are described in stat methods papers (see key references)
    - Rules for applying penalty must be prospective
    - Penalty is not large enough to offset advantages of design

Type I error control under global null hypothesis

- k tumor indications each with sample size of *N* and all with 1:1 randomization
- An interim analysis is conducted at information fraction *t* for each tumor indication and a tumor will not be included in the pooled analysis if p-value>α_t
- The pooled analysis will be conducted at α^* so that the overall Type I error is controlled at α when there is no treatment effect for any tumor (H0)
- What is α^*?

Solving for adjusted alpha (α^*)

- Let Y_{i1} be the test statistics based on information fraction t, and Y_{i2} be the test statistics based on the final analysis of data in the i-th cohort (i=1, 2,…,k)
- Suppose that m cohorts are included in the final analysis ($m \geq 1$), and let V_m be the corresponding test statistics. The probability of a positive outcome in pooled analysis is

$$Q_0(\alpha^*|\alpha_t, m) = \Pr_{H_0}(\cap\{Y_{i1} > Z_{1-\alpha_t} \text{ for } i=1,\ldots,m\}, \cap\{Y_{j1} < Z_{1-\alpha_t} \text{ for } j=m+1,\ldots k\}, V_m > Z_{1-\alpha^*})$$

or $$Q_0(\alpha^*|\alpha_t, m) = \Pr_{H_0}(\cap\{Y_{i1} > Z_{1-\alpha_t} \text{ for } i=1,\ldots,m\}, V_m > Z_{1-\alpha^*})(1-\alpha_t)^{(k-m)}$$

- α^* is solved from below where c(k, m) = k!/((k-m)!m!)

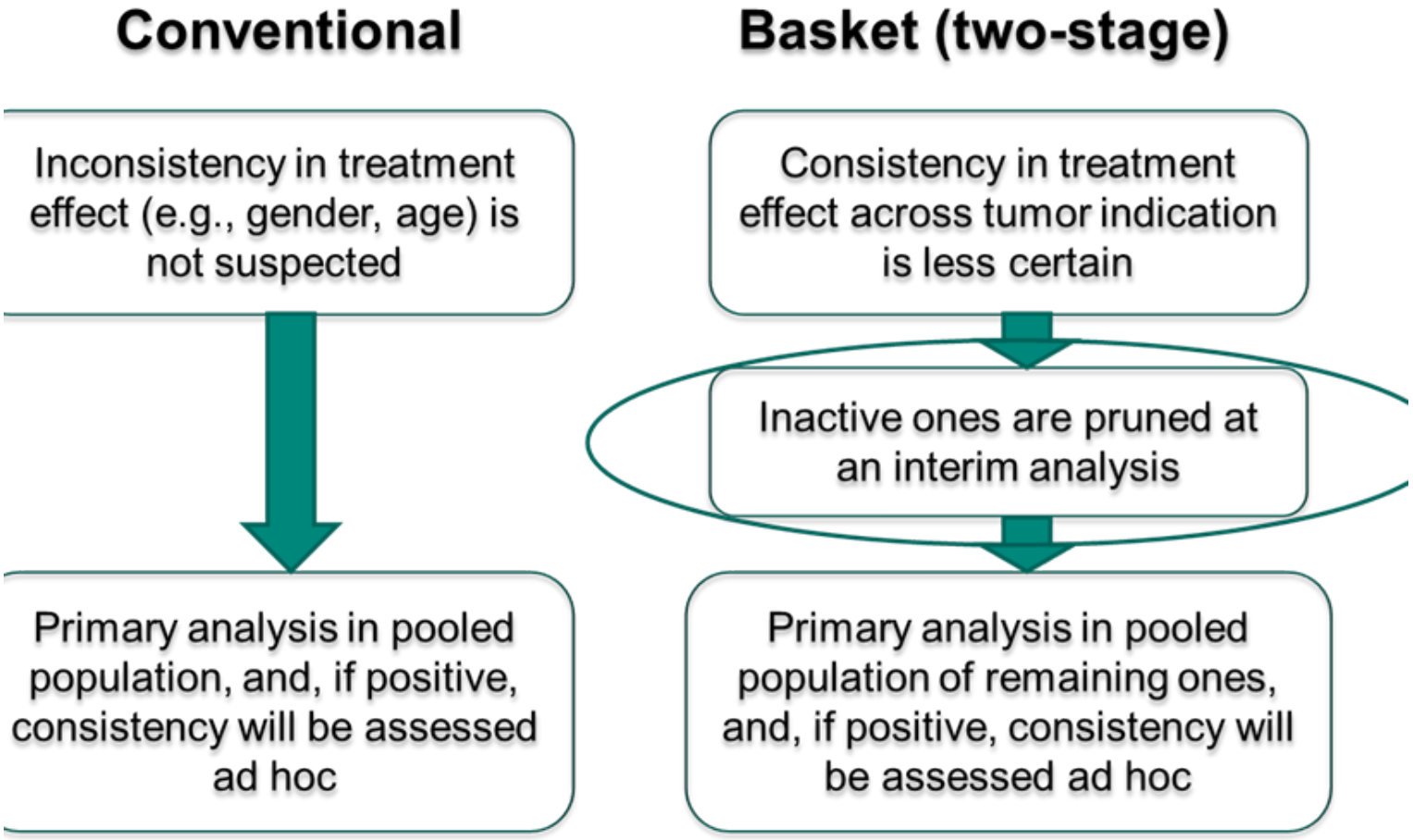
$$\sum_{m=1}^{k} c(k,m) Q_0(\alpha^*|\, \alpha_t, m) = \alpha$$

Challenge #4: Strong Control of FWER

- This problem is still open
- Challenge:
  - One or more strongly positive indications can drive an overall pooled positive result and negative indications are carried along
  - Simulation involves a large number of cases and the degree to which active indications are active affects the results
- A recent MSKCC study* simulated a popular Bayesian basket trial design and found FWER of up to 57%.
  - Authors advocate characterization of FWER by simulation

*Cunanan K et al. Specifying the True- and False-Positive Rates in Basket Trials, *J Clin. Onc. Precision Onc. ,* published online November 3, 2017

Should Basket Trials Control FWER by Indication?



Other FWER Considerations

- A basket trial with k indications replaces k independent trials that collectively would have a family-wise error rate of approximately k * 0.025
- Should we therefore allow approximately k*0.025 for FWER of a basket trial?
- Under would conditions would FDR be a better measure than FWER?

PERFORMANCE SIMULATIONS AND DESIGN CONSIDERATIONS

Comparison of operating characteristics

- k=6 tumor indications with total planned event size (k*N*) ranging from 150-350
  - The true treatment effect is –log(0.6), or hazard ratio of 0.6 in a time-to-event trial
- Pruning occurs at when half of the events have occurred
- Number of active indications (g) with target effect size ranges from 3 to 6, with remaining ones inactive

Study power and sample sizes under different pruning and pooling strategies

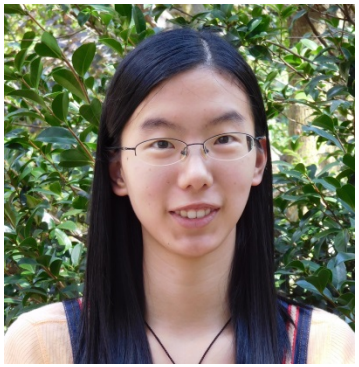
Planned events	Number of active tumors	Power (%) for a positive study				Exp. number of events for pooled population			Exp. number of events for overall study		
		D0	D1	**D2**	D3	D0/D2	D1	D3	D0/D3	D1	D2
200	6	95	85	**95**	93	200	157	179	200	179	221
200	5	85	75	**91**	86	200	144	172	200	172	228
200	4	67	62	**82**	76	200	131	166	200	166	234
200	3	44	45	**68**	61	200	119	159	200	159	240
300	6	99	96	**99**	99	300	254	277	300	277	323
300	5	96	81	**98**	96	300	232	266	300	266	334
300	4	84	81	**94**	91	300	209	255	300	255	345
300	3	60	64	**84**	79	300	187	244	300	244	356

An Application of Special Interest

- A randomized controlled basket trial with 1:1 randomization in 6 tumor indications, each targeting a hazard ratio of 0.5 in PFS with 90% power at 2.5% alpha for global null hypothesis
  - 88 PFS events and 110 patients planned for each indication
  - PFS analysis is conducted when all are enrolled
- D2 is applied to keep total sample size at 660 in pooled population targeting 430 death events
  - The study has ~90% power to detect a hazard ratio of 0.7 in OS at 0.8% alpha (after taking the penalty) assuming ρ=0.5
  - Observed hazard ratio ~0.79 or lower for a positive trial in pooled population (vs ~0.84 under D0) for alpha control **under global null**
- Potential to gain approvals in 6 indications based on comparable sample size to a conventional Phase 3 trial

Characterization of Performance Constrained by FWER (ongoing)

- Team includes Yuru Ren, Valeriy Korostyshevskiy, and Sammy Yuan
- Currently studying single TTE endpoint with normally distributed hazard ratios, mean of 1.0 for inactive, 0.7 for active
- Simulate different scenarios of how many indications in basket are inactive. Maximum Type I error (worst case scenario) is FWER
- What power is achievable when FWER must be ≤ k * 0.025?



Current Approaches

- In order to control FWER, we must add an additional post-correction step
- Each indication is tested up to twice individually*
  - at interim information time t [0,1] at significance level alpha-t, AND
  - if part of a successful pool, in a post check at significance level alpha-post

*Beckman R and Loeb LA. Multistage Proofreading in DNA Replication. Quarterly Reviews of Biophysics 26: 225-331 (1993)

Preliminary Results

- k = 6; HR = 0.7, nominal power of pool =95%; t = 0.5, **alpha t = 0.4, alpha post = 0.1:**

6	**0.5276**	**0.9467**	**0.0000**
5	0.5262	0.8954	0.0631
4	0.5079	0.8032	0.1111
3	0.4654	0.6675	0.1432
2	0.3780	0.4739	0.1451
1	0.2316	0.2402	0.0986

- k = 3; HR = 0.7, nominal power of pool =95%; t = 0.5, **alpha t = 0.3, alpha post = 0.1:**

3	0.6940	**0.9534**	**0**
2	0.6815	0.8435	0.0493
1	0.5813	0.5871	0.0731

Future Plans

- Further parameter optimization
- Application of heterogeneity detection methods (Simon)
- Study of application with using surrogate interim endpoint
- Application of RWD to study design

Conclusions

- It is feasible to create a general design concept for a basket study that is suitable for many agents
- Multiple challenges can be addressed with careful planning
- Benefits include:
  - Increased and earlier patient access to targeted therapies for small subgroups
  - Cost-effective methods for sponsors to develop targeted agents in small subgroups
  - More robust datasets for health authorities to assess benefit-risk in these small patient groups

Key References

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