Two Novel Designs for Small Populations: The Confirmatory Basket Trial and the Informational Design

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THE CONFIRMATORY BASKET TRIAL
Acknowledgements

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  – Zoran Antonijevic, Amgen
  – Rasika Kalamegham, Genentech

• Pathway design subgroup, additional members:
  – Christine Gausse, Merck
  – Sebastian Jobjorrnsson, Chalmers
  – Lingyun Liu, Cytel
  – Sammy Yuan, Merck
  – Yi (Joey) Zhou, Ultragenyx
  – Advisor: Sue-Jane Wang, FDA

• Pathway design subgroup is one of 5 working subgroups of the DIA Small Populations Workstream, a group of 50 statisticians and clinicians from industry, academia, and national health authorities (FDA and EMEA)

• Small populations workstream is part of DIA Adaptive Design Scientific Working Group (ADSWG), a group of 180 statisticians and clinicians from industry, academia, and national health authorities (FDA and EMEA)

• Email me at eniac1915@gmail.com if you would like to join either of these groups
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.
Approaches to development based on predictive biomarkers

- Optimized co-development of a single drug and its companion diagnostic
  - Gives a clear hypothesis and answer and still has a role in selected instances
  - Will be challenging to do in niche indications

- “Umbrella” trials
  - One tumor type with multiple drugs and predictive biomarkers
  - Patients are matched to drugs based on predictive biomarkers
  - Cooperation among multiple sponsors
  - Examples: BATTLE, I-SPY, Lung-MAP

- “Basket” or “bucket” trials
  - Multiple tumor types with one drug and predictive biomarker
  - Approval based on pooled analysis
  - Premise is that molecular subtype is more fundamental than histology
  - Single sponsor
Agenda

- Introduction
- General Design Concept for a Basket Trial
- Challenges of Basket Trials and Recommendations for Overcoming Them
- Detailed 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

- Synovial Sarcoma
  - 1/16 (6%)
- Aggressive Fibromatosis
  - 2/20 (10%)
- Dermatofibrosarcoma Protuberans
  - 10/12 (83%)
- Aggressive Systemic mastocytosis
  - 1/5 (20%)
- Hyper-eosinophilic syndrome
  - 6/14 (43%)
- Myelo-proliferative disorder
  - 4/7 (58%)

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

13 centers in consortium: North America, Europe, Australia

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

• 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 drug 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
GENERAL DESIGN CONCEPT
Consistent trend in definitive endpoint

SELECTION

PRUNING (External Data)

PRUNING (Interim endpoints)

FULL APPROVAL (Pooled analysis of definitive endpoint)

Accelerated Approval Option

May 4, 2017
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

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
- 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
  - 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
CHALLENGES OF BASKET DESIGNS AND RECOMMENDATIONS FOR OVERCOMING THEM
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.
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.
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
Challenge 3: Will the companion diagnostic assay generalize across indications?

- Analytical properties of assay may depend on tissue type
- Cutoff between biomarker positive and negative may vary between tissue types for a continuous biomarker

Addressing the challenge:
- Analytical validation of the assay for all relevant indications prior to study start
- Prior to study start, recommend biomarker stratified randomized phase 2 studies to set provisional cutoffs for continuous biomarkers in each indication to the extent feasible
Challenge 4: Availability of tissue

- Tissue sampling and processing are variables that can greatly affect the outcome of a study based on a predictive biomarker.
- Basket studies will require cooperation and uniformity across departments organized by histology.
- Addressing the challenge:
  - The sponsor must have extensive contact with the pathology department and relevant clinical departments at all investigative sites and provide standard methods for tissue sampling, handling, and processing.
  - The sponsor should engage an expert pathologist who is dedicated to training prior to trial start, and troubleshooting during the trial.
Challenge 5: 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 6: High Screen Failure Rate

- **Pro:** patients will have access to tailored therapy
- **Con:** patient has a high risk of being a screen failure if biomarker positive subgroup is low prevalence

**Addressing the challenge:**
- Study should provide a broad-based test like NGS which will give the patient some guidance on alternative therapies if they are screen failures for basket study
Challenge 7: Interim endpoints may not predict definitive endpoints

- Addressing the challenge:
  - Prefilter indications based on maturing definitive endpoint data from phase 2
    - See Figure 2
  - Require consistent trend in definitive endpoint for final full approval
Phase 2 Influencing Phase 3 Adaptation: The Phase 2+ Method

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
DETAILED DESIGN CONSIDERATIONS
Designs to Be Compared

- Sample size changes after pruning
  - D0: No pruning and no change (benchmark)
  - D1: No increase to sample size after pruning
  - D2: Sample size in pooled analysis after pruning remains same as planned for the trial (SS)
  - D3: Sample size for trial remains same after pruning as planned for the trial (SS)

<table>
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<th>Designs</th>
<th>Overall Trial</th>
<th>Pooled Population</th>
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</tr>
<tr>
<td>D3</td>
<td>SS</td>
<td>&lt;SS</td>
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</table>
Type I error control

• 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 > \( \alpha_t \)

• The pooled analysis will be conducted at \( \alpha^* \) so that the overall Type I error is controlled at \( \alpha \) when there is no treatment effect for any tumor \( (H0) \)

• What is \( \alpha^* \)?
Solving for adjusted alpha (\(\alpha^*\))

- 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

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

or

\[
Q_0(\alpha^*|\alpha_t, m) = \Pr_{H_0}(\bigcap \{Y_{i1} > Z_{1-\alpha}, \text{ for } i=1, ..., m\}, V_m > Z_{1-\alpha^*})(1 - \alpha_t)^{(k-m)}
\]

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

\[
\sum_{m=1}^{k} c(k, m)Q_0(\alpha^*|\alpha_t, m) = \alpha
\]
$\alpha^*$ under different design options

$\alpha^*$ decreases with increasing $k$ as expected, but its relationship with $\alpha_t$ is complicated with the interplay between cherry-picking and futility stopping.
Comparison of operating characteristics

- k=6 tumor indications with total planned event size (kN) 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

<table>
<thead>
<tr>
<th>Planned events</th>
<th>Number of active tumors</th>
<th>Power (%) for a positive study</th>
<th>Exp. number of events for pooled population</th>
<th>Exp. number of events for overall study</th>
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</thead>
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<tr>
<td></td>
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<td>300</td>
<td>3</td>
<td>60</td>
<td>64</td>
<td><strong>84</strong></td>
</tr>
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</table>
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
  – 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 $\rho=0.5$
  – Observed hazard ratio ~0.79 or lower for a positive trial in pooled population (vs ~0.84 under D0)

• Potential to gain approvals in 6 indications based on comparable sample size to a conventional Phase 3 trial
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


INFORMATIONAL DESIGN
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Key collaborators on this work:
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- Carl-Fredrik Burman
- Franz Koenig
- Sebastian Jobjornsson
- Thomas Ondra
- Nigel Stallard

This work is the product of three subgroups from the DIA small populations workstream:
- The Pathway Subgroup (Leader: Cong Chen)
- The Predictive Biomarker Subgroup Methodologies Subgroup (Leader: Carl-Fredrik Burman)

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Agenda

- Challenges of drug development in rare diseases
- Natural history studies and questions
- Informational design
  - Adaptive alpha allocation
  - Subgroup identification
  - Speculative: study sizing and endpoint identification
Challenges in Development of Drugs for Rare Diseases (NEED Subgroup)

- Limited information on disease natural history
  - Natural/temporal history
  - Relevant prognostic subgroups
  - Incidence is unknown and/or “changes” in response to increased knowledge, awareness, treatment options

- Limited information on the underlying pathophysiology of the disease
  - Underlying biology
  - Potential biomarkers

- Limited research capability
  - Insufficient number of patients
  - May be widely distributed among practitioners

- Unprecedented research
  - No standard therapy
  - No precedent from earlier clinical development program
  - Validation of clinical endpoints lacking
  - Difficult to identify “acceptable” primary endpoint
Incentive to Develop in Rare Diseases (Predictive Biomarker Subgroup Methodologies Subgroup)

- Health authorities have provided incentives for development in rare diseases
- Nonetheless, evaluation of benefit-cost utilities shows divergence between the sponsor perspective and the public health perspective for rare subgroups
- Under average scenarios of probability of success and pricing, sponsors may not be incentivized to develop drugs in rare diseases
Natural History Studies

FDA draft guidance on rare diseases:
- Provided comprehensive discussion of rare diseases and the challenges of developing them
- Recommended study of the natural history of the disease to resolve questions about natural history and endpoints prior to therapeutic studies

Questions:
- Pharmaceutical company likelihood of investment?
- Can patient advocacy groups trigger these studies in conjunction with academic consortia and public funding?
- Will one such study provide information about endpoints germane to therapies with different mechanisms of action?
- How long will it take to conduct adequately powered natural history studies followed by adequately powered therapeutic studies?
- Will people with these diseases support the idea of waiting for the results of these studies?
The Informational Design

- Add an analysis at end of the Phase III trial in a representative subset of patients (*sub-study*) for subpopulation selection and adaptive hypothesis adjustment
  - Two of every 10 patients are randomly selected if 20% of the trial information will be used in the analysis (e.g.)

- The subgroup analysis is equivalent to a Phase II trial conducted under the same clinical design at same time in same population at same sites as the Phase III trial
  - Likely more informative than separate phase 2

- The patients in sub-study are included in final analysis with appropriate statistical penalties to control the false positive rate (type I error = $\alpha$)
Informational analysis vs interim analysis

Interim analysis is conducted mid-trial in all enrolled patients.

Informational analysis is conducted at end of the trial in a subgroup of patients.

Patients selected for informational analysis.
Alpha allocation between subgroup and full population: comparison to other methods

- Perform separate Phase 2 and Phase 3 studies:
  - Use interim endpoint to judge Phase 2 results:
    - Slow
    - Uncertain relationship between interim and definitive endpoint
  - Use final endpoint to judge Phase 2 results:
    - Extremely slow

- Adaptive signature design (Freidlin and Simon 2005)
  - Determines the biomarker subgroup from a subset of phase 3
  - Fixed alpha allocation between subgroup and full population

- Chen and Beckman (2009)
  - Assuming subgroup is known, determine optimal alpha allocation from clinical data
  - Can use interim data from Phase 3 (with uncertain relationship between interim and final endpoints and statistical penalty)
  - OR maturing final endpoint from Phase 2 study
Comparison to seamless Phase 2/3 adaptive designs

- Seamless phase 2/3 designs with interim analyses save time and patients but involve uncertainty about relationship between interim and final endpoints.

- Achilles’s heel of a conventional adaptive design:
  - Change of patients’ characteristics after adaptation.

- Information design is a type of ideal adaptive design:
  - Some of the methods developed for adaptive design can be readily applied to informational design.
Auto-adaptive alpha-allocation with trial data

▶ For each $t$, find the alpha-allocation that maximizes the expected conditional power
  – Informational analysis provides an objective prior distribution of estimates for true treatment effects
  – Estimates of treatment effects based on external data can be further incorporated

▶ The adjusted alpha at $t$, $\alpha^*(t)$, is calculated to keep the actual Type I error controlled at $\alpha$
  – The larger the $t$ the smaller the $\alpha^*(t)$

▶ Is the $\alpha$ penalty worth it?
  – No if we have strong prior; Yes otherwise
Application example

- 1:1 randomization with a total 410 events
  - 83% power for detecting a 0.75 hazard ratio at 2.5% in overall population
  - The true (UNKNOWN) hazard ratio is 0.90 in overall population and 0.61 in the biomarker positive population
  - 17% or 34% of the events are assumed in the subpopulation

Power comparison

- The study has only 19% power if step-down from overall population
- Should the biomarker subpopulation be tested first, the study would have 54% power at $r=17\%$ and 83% power at $r=34\%$
- The informational design would have $\sim45\%$ power at $r=17\%$ and $\sim75\%$ power at $r=34\%$
- A little bit of information adds tremendous value. However, benefit of more information is offset by penalty on alpha.
Adaptively determining a biomarker cutoff using the information design ("Adaptive subgroup selection")

Suppose you have a continuous biomarker like gene expression and you don’t know the cutoff between positive and negative

- Divide the overall population into k separate bins with increasing biomarker level
- Use the information design with information fraction t to successively exclude populations based on lack of efficacy, starting from the lowest biomarker level and working your way upwards through the k bins
- Determine a false positive type I error threshold (alpha*) for testing in the remaining patients that appropriately penalizes for this use of information
A Speculative Application: Endpoint selection and Study Sizing

- Use informational design to allow combining a natural history study with a pivotal study in the setting of rare disease.
- Assume there are several potential pivotal clinical benefit endpoints.
- Due to limited information about disease and perhaps about drug, we don’t know which endpoints will be informative.
- Assume benefit on any one of the endpoints is sufficient for approval if others aren’t adversely affected.
- Use information fraction $t$ to allocate false positive rate $\alpha$ optimally among endpoints.
- May also require adaptive increase in study size depending on data.
- Endpoints chosen would have to add up to $\alpha^*$, less than $\alpha$, to appropriately penalize for the use of information.
Question for discussion

- $\alpha^*$ has been calculated to allow control of the false positive rate for the first two applications.

- If this could be done for endpoint selection (and possible adaptive study sizing), would this be allowable, i.e., a pivotal study with multiple candidate primary endpoints and selection of the primary endpoints at the end according to pre-specified rules?
Key references

BACKUPS
α* and power in the informational design alpha allocation example
\( \alpha^* \) under different \( k \)

- Equal prevalence of events by biomarker level
- \( \alpha_t = 0.5 \) (binding)
Application example

Consider a hypothetical study with 3 ordered biomarker subpopulations (i.e., low, intermediate, high).

The study targets 410 events so that the study has 83% power for detecting a 0.75 hazard ratio at 2.5% (one-sided) in the overall population.

The study may drop low, low + intermediate, OR drop all (“early” termination) if empirical effect is negative.

Log-hazard ratios are $\log(0.75)+\delta$, $\log(0.75)$, $\log(0.75)-\delta$

- When $\delta$ ranges from 0.2 to 0.4, hazard ratio ranges from 0.92 to 1.12 for the “low” group and from 0.50 to 0.61 for the “high” group.
### Operational characteristics

<table>
<thead>
<tr>
<th>δ</th>
<th>t</th>
<th>α*</th>
<th>Prob (keep all)</th>
<th>Prob (drop low)</th>
<th>Prob (drop low/intermediate)</th>
<th>Prob (drop all)</th>
<th>Overall study power</th>
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<tr>
<td>0.2</td>
<td>40%</td>
<td>0.0164</td>
<td>0.63</td>
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<tr>
<td>0.3</td>
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<td>0.42</td>
<td>0.26</td>
<td>0.01</td>
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</tr>
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The overall study has 83% power w/o population de-selection. De-selection criterion or timing is not optimized.