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The Utility of Adaptive Enrichment Designs in the Era of Developing Personalized Medicine

Yili L. Pritchett, Ph.D.

MedImmune

Workshop on Perspectives and Analysis Methods for Personalized Medicine

Singapore, July 10-14, 2017

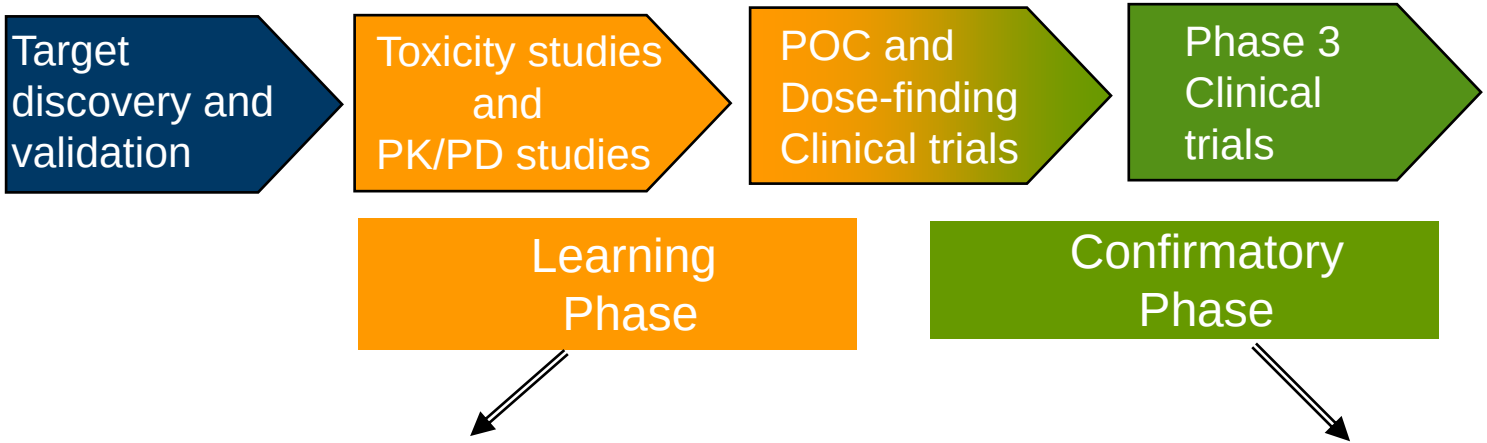
Outline

- Background
- Our practice
- Challenges remain with initial findings on a sub-population
- Enrichment designs with predictive enrichment strategy
- A Bayesian adaptive subgroup-identification enrichment design
- Concluding remarks

Background

- Many unknowns when a new molecular entity enters to clinical development.
- Expectations from efficacy to safety are clearly specified by the Target Product Profile (TPP), which is built upon the medical need, competitors' data, market research, and regulatory requirements where known.
- TPP generally sets up "goal posts" for a compound's efficacy: minimally acceptable, target and potential upside threshold values (Lalonde et al., 2007)
- Clinical trials should be distinguished by phase, "learning" or "confirmatory", based on their objectives (Sheiner,1997)

An Overview of Drug Development Process



PK=Pharmacokinetics; PD=Pharmacodynamics; POC=Proof-of-Concept.

An Evolving Process – Targeted Patient Population

Empirical Medicine

- Treatments that target on a patient population with broad clinical characteristics

Precision Medicine

- Treatments that interact with a specific biological target or pathway to provide desired therapeutic effect

Personalized Medicine

- Treatments prescribed based on individual's molecular profile
- Especially suitable for finding effective treatment for complex and heterogeneous diseases such as cancer (Hanahan and Weinberg, 2011)

“Subgroup Analysis”

- Conducting “subgroup analysis” for clinical trial data is to investigate consistency or heterogeneity of the treatment effect across subgroups, defined based on background characteristics (Alosh et al., 2015).

- It mostly focuses on testing whether the findings from a clinical trial are generalized to the overall population or are limited to a subgroup

- It has its own issues and challenges

“Subgroup Identification”

- “Subgroup identification” is the first step toward developing a “precision medicine” or “personalized medicine”

- It is to search for a sub-population that might have enhanced treatment effect, especially when
  - The test compound failed to show efficacy in the overall population
  - The MOA suggested that better efficacy would be seen in a subgroup characterized by a biomarker signature, genomic or protonic expression

- It is a concept and practice in line with the objectives in “learning phase” of new drug development

Our Practice – Conventional Approach

- Doing subgroup analysis for potential biomarkers one at a time and conducting treatment group comparisons at each level of the subgroup

- The drawbacks
  - Very labor intensive
  - Struggling with the right cut point for continuous variables
  - Can easily report false positive findings
  - Can still miss the right subgroup

Our Practice – Improved Approach

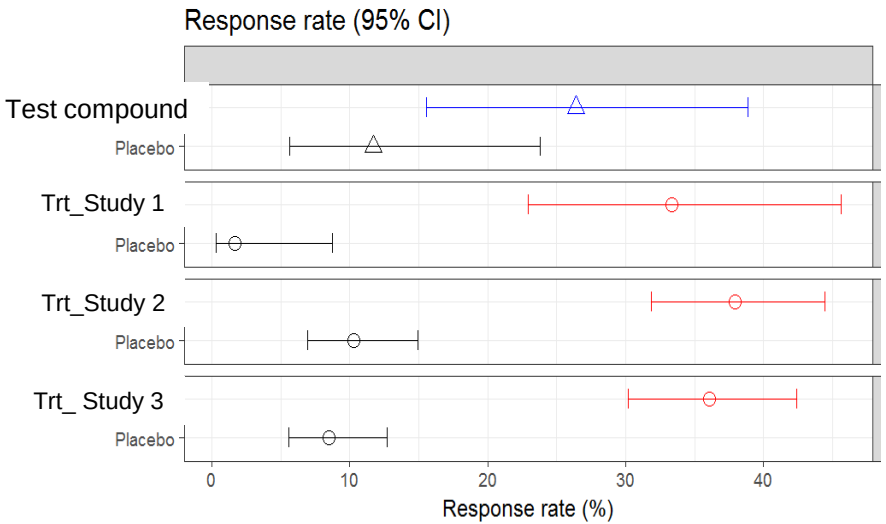
- Rapidly developed statistical methods and software have enabled much more efficient and accurate search (Loh 2002, Lipkovich et al., 2011, Foster et al., 2011, Loh et al., 2015).

- Recently, we brought in the method of Subgroup Identification based on Differential Effect Search (SIDES) and created a user-friendly software with Windows interface.

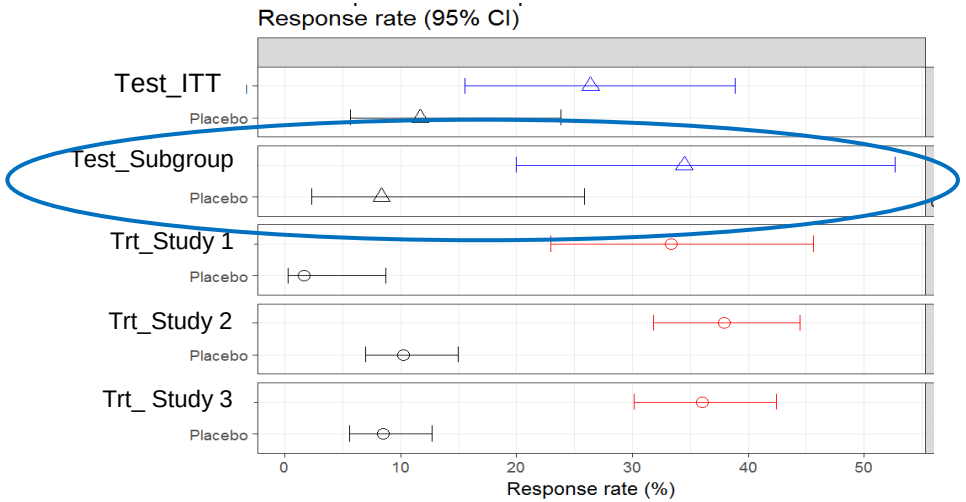
- “Subgroup Identification” undertaken with greater speed and broader scope with demonstrated benefit across different therapeutic areas.

An example of SIDES application: a subgroup with enhanced treatment effect has been identified

Response rate in comparison with an approved treatment - ITT Population



Response rate in comparison with an approved treatment --- A Biomarker High Subgroup



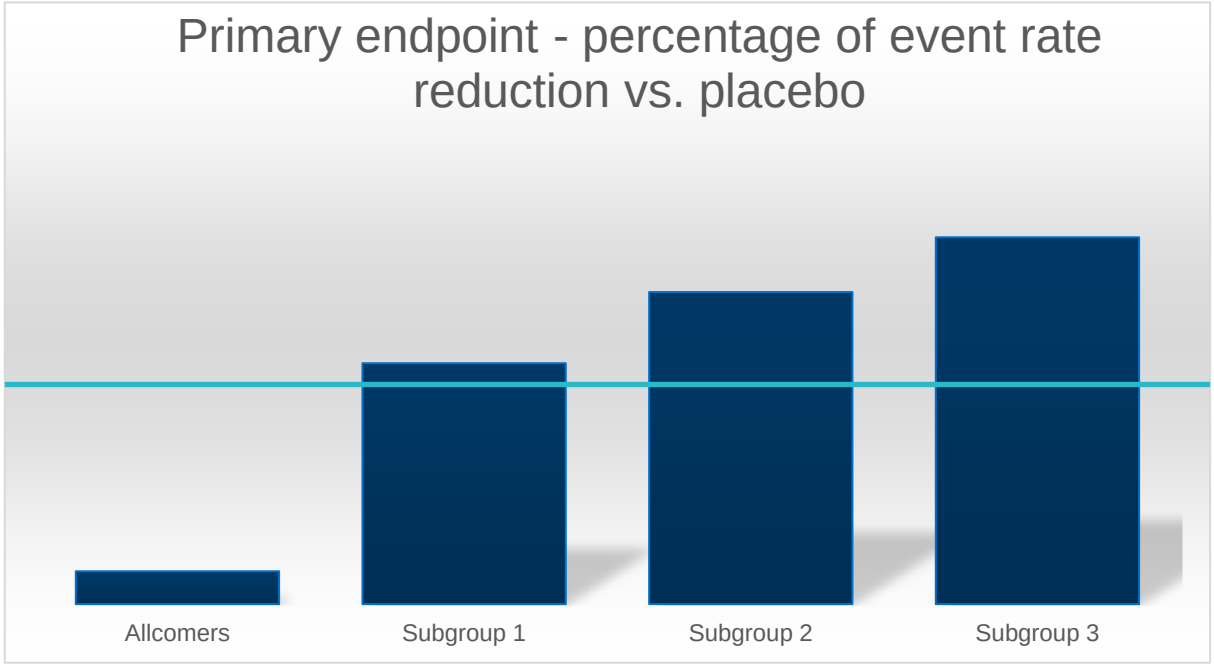
Hypothesis Supporting Biologics Development

- Biologics entering clinical development often come with a known mechanism of action (MOA)
- The MOA suggests that some biomarkers might have predictive property for clinical outcome
- Phase 2 clinical trials are often designed with the best effort to test the hypothesis
  - Collecting relevant biomarker data
  - Allocating sample size for the potential biomarker positive subpopulation
  - Performing pre-specified and ad hoc analysis

A Real World Case

- A new biologic compound came to Phase 2
- Its MOA had suggested several potential predictive biomarkers
- The study was sized to allow adequate power for a biomarker positive subpopulation to detect a desired treatment effect
- It was assumed that median was the cut point to classify a biomarker high or low group
- Clinical outcomes and MOA related biomarkers were collected

Findings from the study



The desired treatment effect

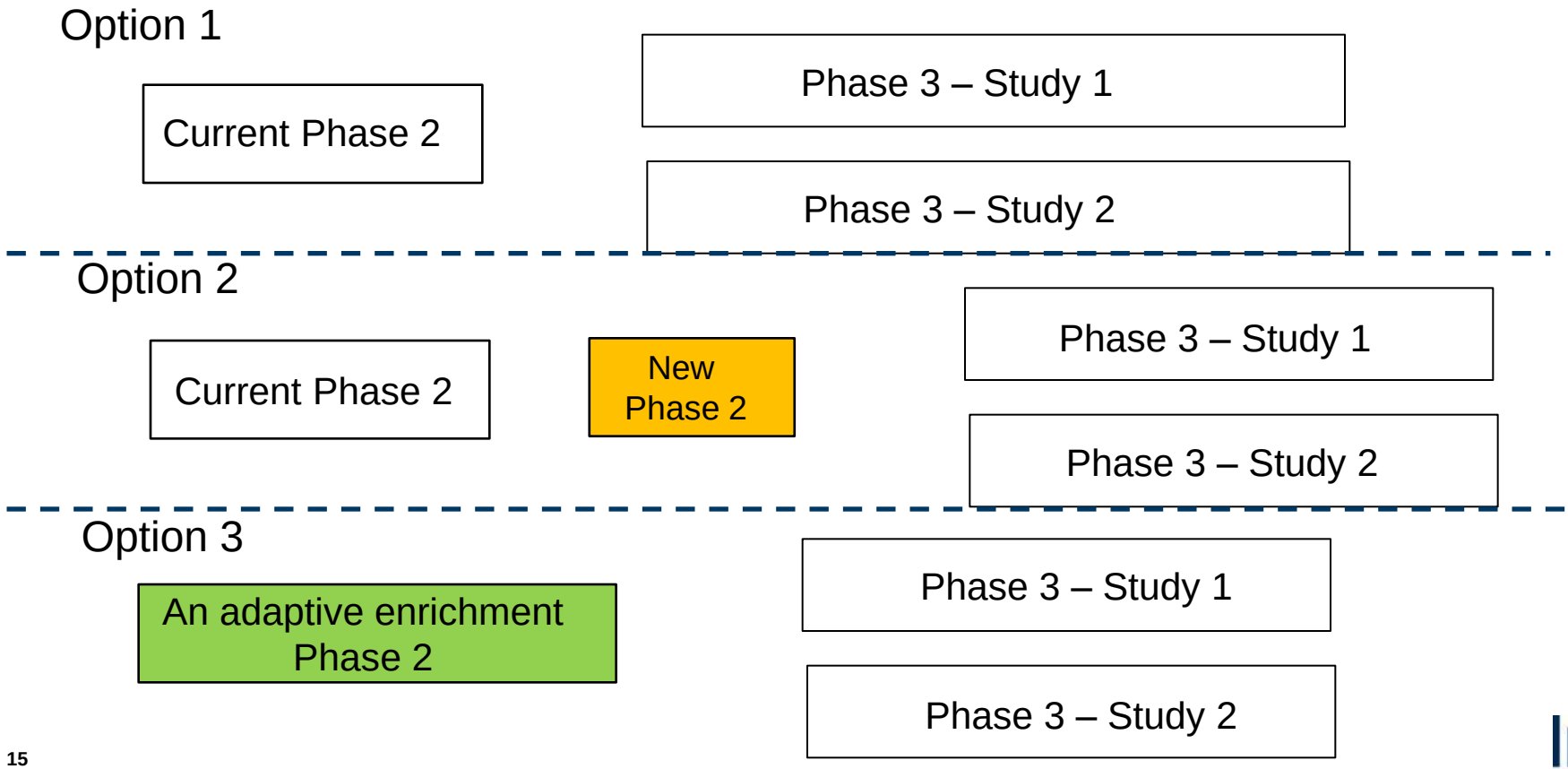
Sample size:	N	27% of N	13% of N	10% of N

Challenges remain

- When efficacy findings that confirm MOA hypothesis are obtained from a sub-population with small sample size, unknowns still exist:
  - Is the efficacy finding replicable?
  - What is the true effect size on this sub-population?
  - What is the right dose for this sub-population?

- How to create a clinical development path to move forward with a balance of speed and probability of late phase success?

Clinical Development Plan with Multiple Choices



Population Enrichment Designs

- "Enrichment is defined as the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population" (FDA draft guidance, 2012)

- Classification of enrichment strategies
  - *Strategies to decrease heterogeneity*
  - *Prognostic enrichment strategies (studying on a high risk subpopulation to increase background event rate or to reduce placebo response)*
  - *Predictive enrichment strategies (studying on the subpopulation who are more likely to respond to a particular intervention)*

A hypothetical population enrichment design using predictive strategy

- A test compound pursuing the indication of preventing End Stage Renal Disease (ESRD, defined as needing dialysis or kidney transplant) in patients with renal deficiency
- A 20% reduction on ESRD was considered to be clinically meaningful
- This compound has demonstrated compelling efficacy in reduction of UACR (urinary albumin/creatinine ratio) in Phase 2 clinical trials
- Its effect on UACR was quickly seen after 4 weeks of treatment; 50% subjects had ≥ 30% reduction

Sample size needed for a Phase 3 time-to-event clinical trial in general population

- Primary endpoint: time-to-ESRD or death
- 90% power to detect HR=0.80 at 1-sided α=0.025
- Assume placebo event rate 6%
- Performing an interim analysis when 50% of the events have been collected for futility and sample size re-estimation
- Accrual: 2 years, follow-up: 4 years

  → *Required number of events d = 846*

  → *Required total sample size N=5192*

Can we use enrichment design to reduce the sample size and to increase probability of Phase 3 success?

Reduction in UACR predicts reduction in ESRD or Death

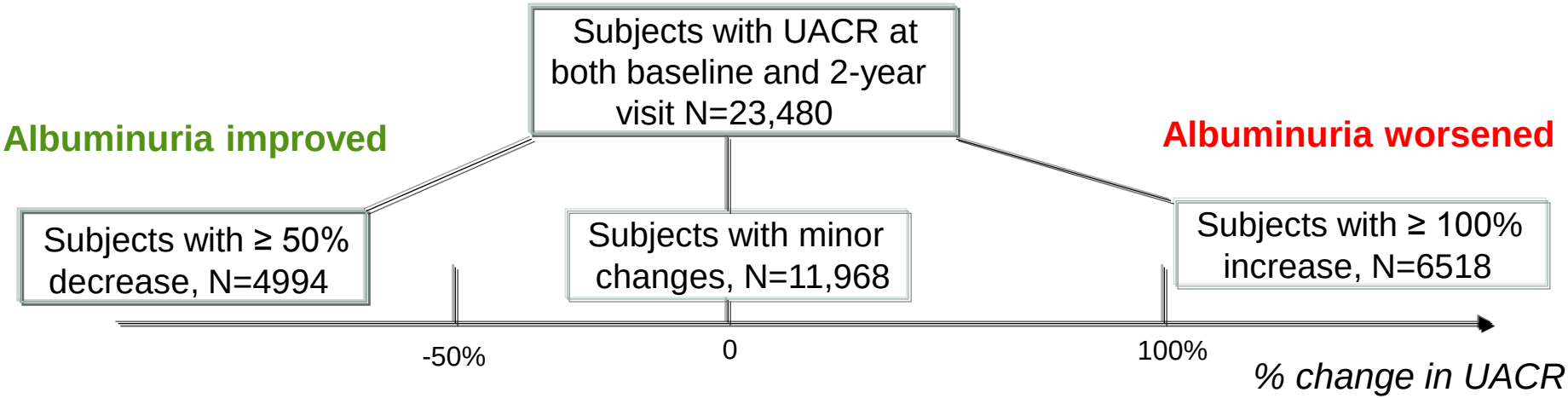
1. Analysis for combined data from two large renal outcome trials on an anti-hypertensive agent (Schmieder et at., 2011).

2. Meta-analysis on 9 renal outcome trials (Lambers and De Zeeuw, 2010).

3. Subgroup analysis results from the largest renal outcome study RENAAL (Brenner et at. 2010).

Analysis for combined data from two large renal outcome trials on an anti-hypertensive agent

- Two large size, event outcome studies on telmisartan were combined to evaluate the predictivity of changes in albuminuria on mortality, CV, and renal outcomes (Schmieder et at., 2011)



Change in UACR Predicted Event Outcomes

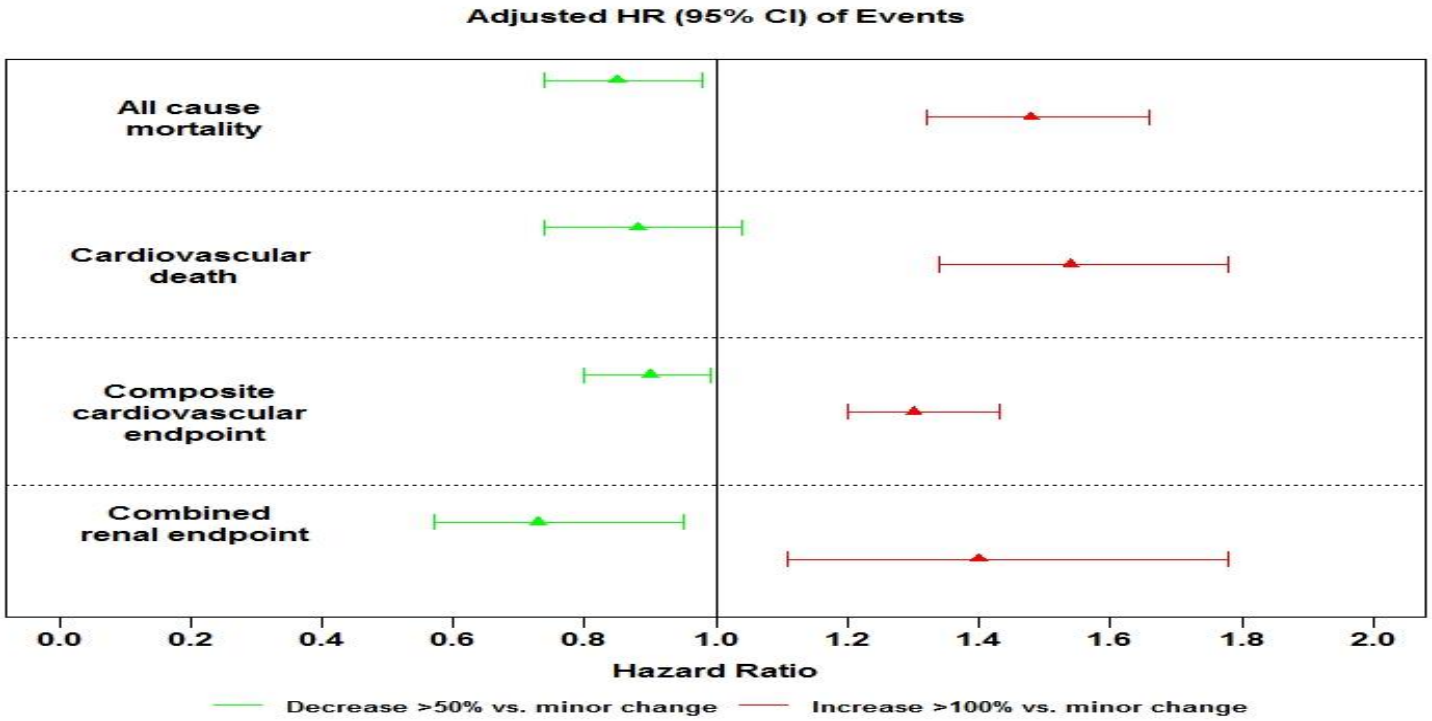


Figure 1. Schmieder et al. 2011

Meta-analysis for 9 Renal Outcome Trials

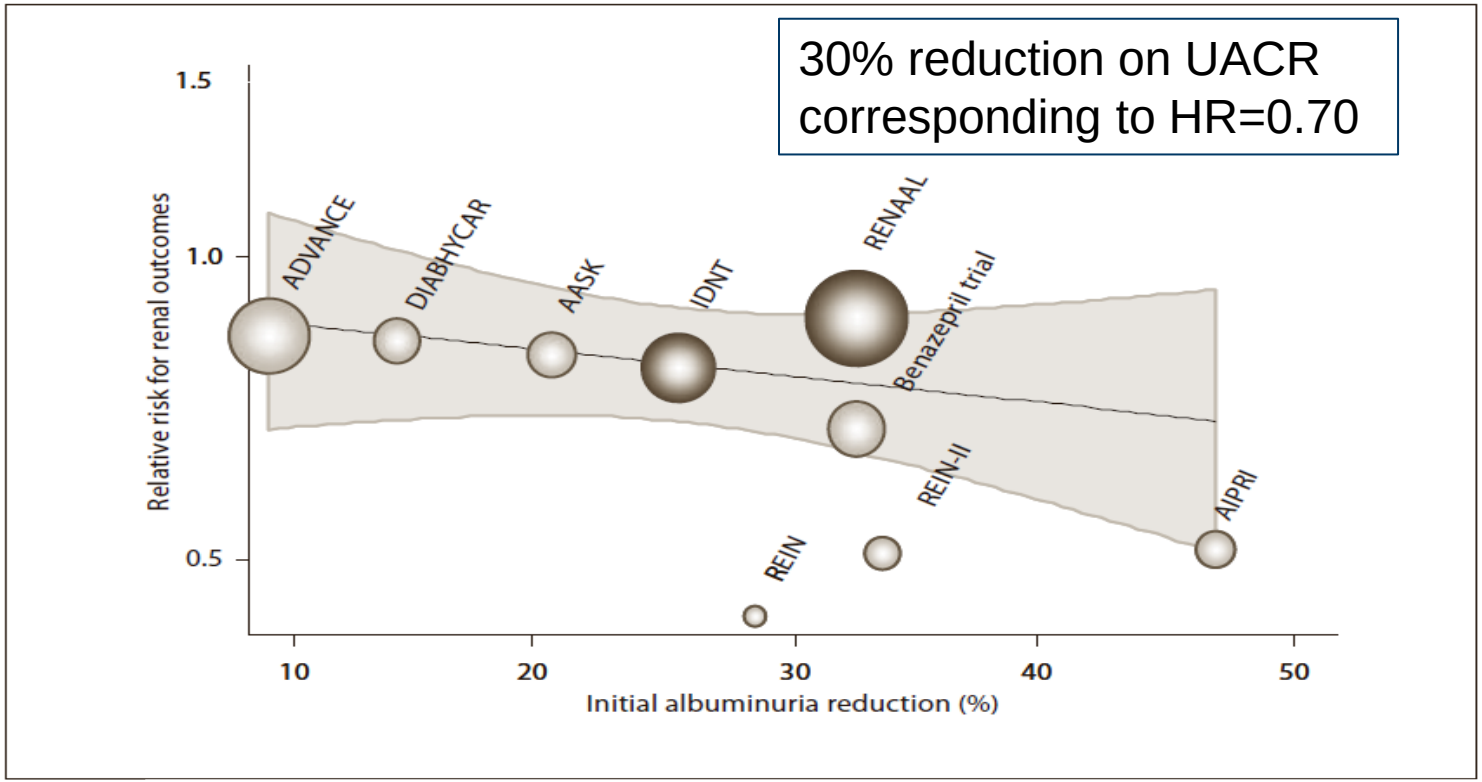


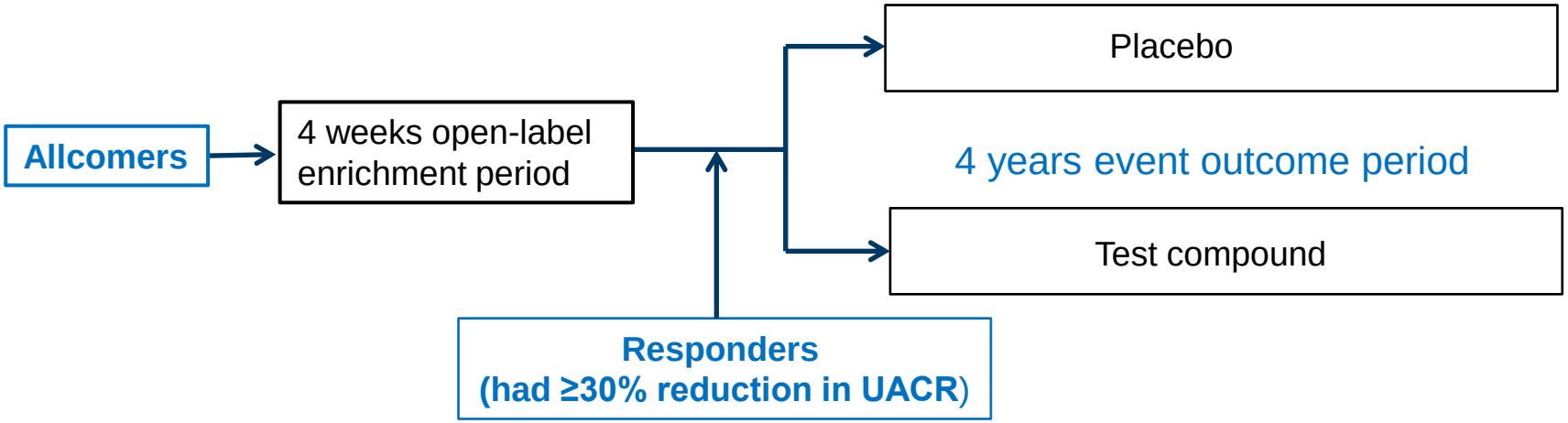
Figure 1. Lambers Heerspink and De Zeeuw Nephron. Clin. Prac. 2010

Subgroup Analysis Results from RENAAL
--- A placebo controlled Phase 3 study for losartan

	HR (95% CI)
All Patients	**N=1513 (751 Losartan, 762 Placebo)**
Primary composite endpoint	0.84 (0.72 - 0.98) p=0.02
Doubling of serum creatitine	0.75 (0.61 – 0.92) p=0.006
ESRD	**0.72** (0.58 – 0.89) p=0.002
Death	1.02 (0.81 – 1.27) p=0.88
ESRD or Death	**0.80** (0.68 – 0.95) p=0.01
Doubling of serum creatitine or ESRD	0.79 (0.64 – 0.95) p=0.01
> 20% reduction in UACR	**N =1146**
Renal Endpoint (ESRD)	**0.67** (0.55 – 0.81) p<0.001
ESRD or Death	**0.66** (0.55 – 0.79) p=0.001
> 30% reduction in UACR	**N =1092**
Renal Endpoint (ESRD)	**0.61** (0.49 – 0.75) p<0.001
ESRD or Death	**0.61** (0.51 – 0.75) p<0.001
> 40% reduction in UACR	**N =1020**
Renal Endpoint (ESRD)	**0.60** (0.47 – 0.76) p<0.001
ESRD or Death	**0.63** (0.51 – 0.78) p<0.001

Brenner et at. 2010

Responder Enrichment Event Outcome Trial Design



- With enrichment strategy, greater treatment effect can be assumed as alternative (HR=0.70)
- N=2392 responders to be randomized; N= 4784 subjects are needed to enter the enrichment period (assuming 50% response rate)
- Recall: without enrichment, the sample size would be N=5789.

Adaptive Enrichment Designs

- Applicable in the situation when it is not clear whether an investigation compound works for allcomers or a sub-population nor it is clear what the predictive biomarkers are

- The idea: learn from allcomers at interim → adapt entry criteria to enrich if warranted → continue to learn more about the enriched population within the same study.

- Growing body of reports [13-17] on different types of adaptive enrichment designs with key differences in
  - The algorithm for subgroup identification
  - The decision rules for population enrichment

A Bayesian Adaptive Subgroup-Identification Enrichment Design (ASID)

- A MedImmune and John Hopkins' University collaboration project (Xu et al., under preparation)

- The design engine includes
  1. An algorithm to search for the subgroup with enhanced treatment effect in Bayesian framework
  2. Decision rules to decide on which population to continue after interim
  3. Flexible, additional adaptive elements after population adaptation:
     - sample size re-estimation
     - adding more doses for dose-finding

Note: Design details and simulation results will be presented at JSM 2017

Design Set Up

- A randomized, proof-of-concept study of two arms: an investigational compound and a control with total sample size N
- Clinical response variable can be continuous, binary, categorical, counting or survival
- K biomarkers are identified with potential predictivity based on the compound's MOA
- Interim analysis will be performed when data from N_1 subjects are available, N_1 ~ 1/3 – ½ of N

The idea for subgroup-identification: Random partition for the biomarker space

- Subject i is characterized by his/hers clinical response y_i, biomarkers $X_i = (X_{i1}, X_{i2}, \ldots, X_{ik})$, and the treatment assignment, z_i
- Denote Ω to be the biomarker space
- Define "a partition" as a family of subsets $\pi = \{S_1, S_2, \ldots, S_M\}$, where S_j are mutually exclusive and their union is Ω
- Model the probability that a biomarker will be split at each round and model the cut point based on variable type
- Prior information can be incorporated

Sampling Model

- Patient Subgroup: $\Pi = \{S_1, \cdots, S_m, \cdots, S_M\}$
- Binary Outcome: $p(y_i = 1 \mid z_i = t, \Pi, \boldsymbol{x}_i \in S_m) = \theta_{t,m}.$
- Categorical Outcome $p(y_i = c \mid z_i = t, \Pi, \boldsymbol{x}_i \in S_m) = \theta_{c,t,m},$
- Continuous Outcome $p(y_i \mid z_i = t, \Pi, \boldsymbol{x}_i \in S_m) = N(\theta_{t,m}, \sigma^2)$
- Survival Outcome $\log(y_i) = \boldsymbol{x}_i' \boldsymbol{\beta}_{t,m} + \epsilon_i$
- In summary

$$p(\boldsymbol{Y}_n, \Theta, \Pi \mid \boldsymbol{X}_n, \boldsymbol{Z}_n) \propto p(\boldsymbol{Y}_n \mid \boldsymbol{X}_n, \boldsymbol{Z}_n, \Theta, \Pi)\, p(\Theta \mid \Pi)\, p(\Pi \mid \boldsymbol{c}) p(\boldsymbol{c})$$

Where c denotes the parameters in the model that describes the random partition π

Adaptive Enrichment Design Diagram

Use interim data to learn and make decision

- Search for optimal subgroup using Bayesian random partition
- Follow decision rules to decide whether need to enrich

No

Continue with original population for potential success

or

Stop the study due to futility

or

Continue with original population due to inconclusive finding

Yes

Modify entry criteria to enroll more responsive sub-population

- Enroll N-N_1 subjects

  and consider to

- re-estimate the sample size
- add more doses for dose-finding

Decision Rules

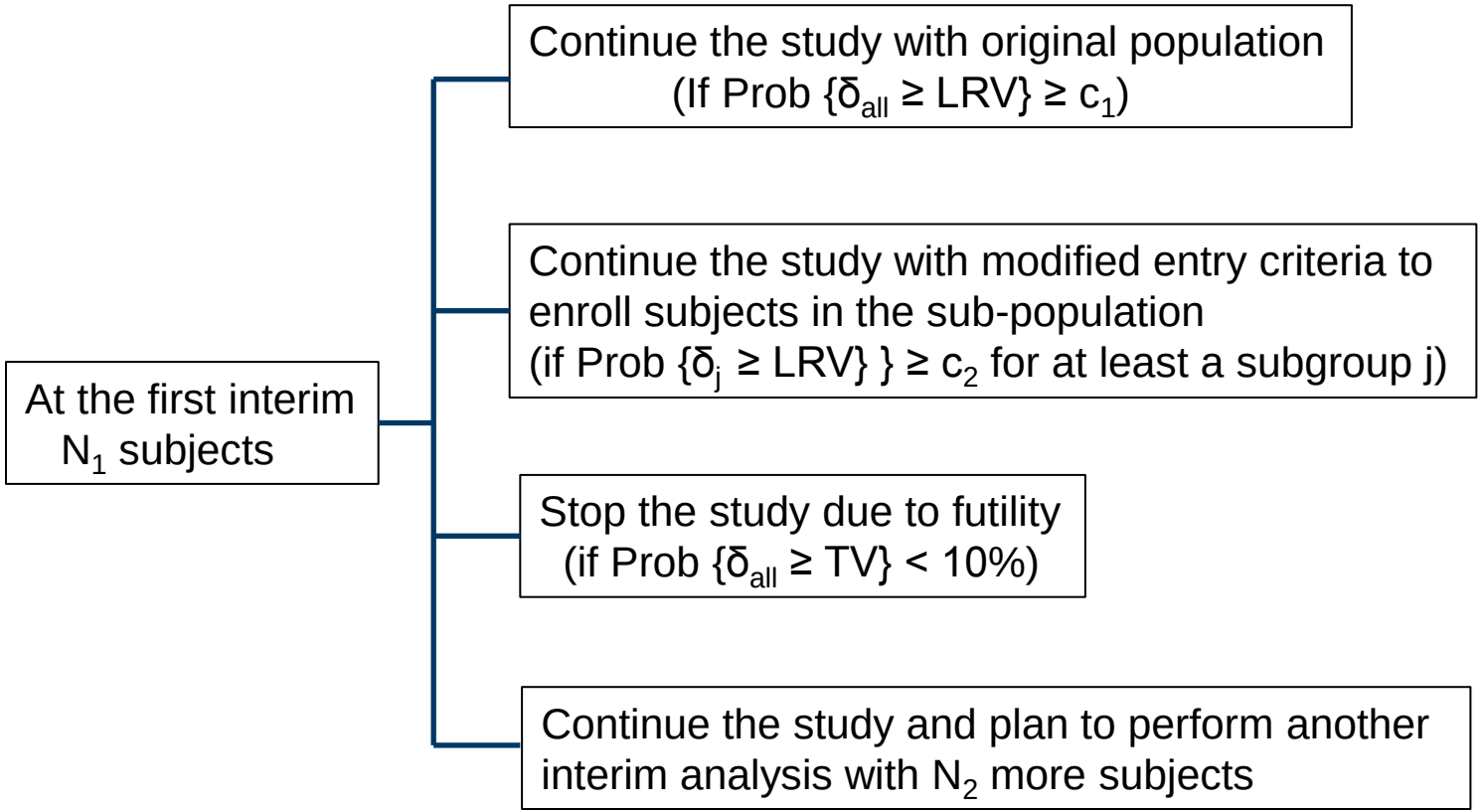
- Denote δ_{all} and δ_j to be the parameter presenting treatment effect in the overall population and Subgroup j, respectively.

- Specify probability thresholds c_1 and c_2, with $c_1 \geq c_2$

- Decision rules
  1. If Prob $\{\delta_{all} \geq LRV\} \geq c_1$ then continue with original population,
  2. Otherwise, if Prob $\{\delta_j \geq LRV\} \} \geq c_2$ for at least one subgroup j, then enrich the population to the union of the subgroups meeting condition Prob $\{\delta_j \geq LRV\} \} \geq c_2$
  3. Otherwise, if Prob $\{\delta_{all} \geq TV\} < 10\%$, stop the trial for futility
  4. Otherwise, conduct 2nd interim analysis when N_2 more subjects' data become available and repeat the steps 1-3, where $N_2 \sim 1/3$ of N.

- At the time of performing 2nd interim on N_1+N_2 subjects, if no decision can be made at Step 3, then continue the trial to finish up remaining subjects of $N-N_1-N_2$.

Potential Outcomes at the First Interim



Concluding Remakes

- Recent development of statistical methods and their companion software have enabled structured and efficient search of sub-population with enhanced treatment effect
- Challenges remain as to how to construct a clinical program to advance the compound with initially identified sub-population
- Adaptive enrichment design can learn and enrich in the same study to support a compound's advancement with the balance of speed and quality
- ASID partition biomarker space in Bayesian framework and can be an efficient adaptive enrichment design option for early phase trials

Acknowledgement

- Yanxun Xu, Ph.D., John Hopkins' University
- Dewei She, Ph.D., MedImmune
- Erik Pulkstenis, Ph.D., MedImmune

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