

Sequential Enrichment Designs for Early Phase Clinical Trials Xin Zhang, Satrajit Roychoudhury **Pfizer Inc. New York, United States**

1. Background	4. S
Early phase clinical trials in oncology	Dema
 Single-arm design with limited sample size Subgroup identifications are typically done via post-hoc-analysis 	• / s p
 Exact binomial test and Simon two-stage design are commonly used Need evidence-based and clinically meaningful quantitative framework to facilitate patient subpopulation for further development 	Goal • / ii • I C
Objective	
 Developing a robust GO/NO-GO decision- making framework by considering both statistical significance and clinical relevance Identify the right population to increase likelihood of success 	 5. 5 Se Stu All-c Bay
We propose a Bayesian adaptive enrichment strategy and dual criterion design for sub- population selection in early phase trials.	 Pr(Po Pr(
2. Example	(ac
 Study objective PoC study of Drug A to evaluate its anti-tumor activity in gastric cancer 	The t in F i • Ba
Endpoint	1. Pr(
• Objective response rate (ORR)	2. Po
 Study population All patients irrespective of status for biomarker of interest Y Study design 	• Mi All-c Y+ p Samp
 Single-arm with biomarker of interest Y 3. Dual Criteria Design 	signi
 Formal inclusion of statistical significance and clinical relevance in design: Decide GO 	F
 Strong evidence: effect ≥ no effect or null value (NV) Estimated effect ≥ decision value (DV) DV : minimum effect with clinical relevance; not classical alternative hypothesis Need discussion with nonstatisticians Sample size requires consideration of DV 	

- Adequate sample size is required to ensure statistical significance when clinical relevance observed
- Need simulation to calculate design operating characteristics (e.g., type-I error, power)

Subpopulation Selection in Early Phase 6. Design Characteristics (single-stage)

and for a new design

A competitor Drug B failed for all-comers but show promising efficacy in patients with Y+ in post-hoc subgroup analysis

Assess activity of Drug A for all patients irrespective of biomarker status If it is **not active for all patients**, assess activity of Drug A for Y+ patients

Single-stage Design with Population election

idy populations comers (F) = Y+ patients + Y- patients yesian triplet criterion for all-comers $(ORR (F) \ge 16\% | data) \ge 0.975$ osterior median (F) $\geq 24\%$ $(ORR (Y-) \ge 16\% | data) \ge 0.75$ ctivity assurance in Y- patients) third criteria ensures that the effect of Drug A is not solely driven by Y+ yesian dual criteria for Y+ patients $(ORR (Y+) \ge 16\% | data) \ge 0.95$ osterior median $(Y+) \ge 24\%$ inimum sample size (SS_{min}) comers: 87 (with number of responders ≥ 21)

patients: 58 (with number of responders ≥ 14) ple size bigger than SS_{min} ensures statistical ficance when clinical relevance is observed

Figure 1. Grid Search for Minimum Sample Size





Stage 1

All-comers: 50 Y+: 30 Y-: 20

7. Two-stage Design with Adaptive **Population Enrichment**

• Sequential enrichment early stopping for futility.

analysis | interim data)



Use probability of success (POS) at interim to allow

- Use POS for interim decision making
- POS(F): PP(posterior median (F) \ge 24% at final
- analysis | interim data); <u>PP=predictive probability</u>
- POS(Y+): PP(posterior median (Y+) \ge 24% at final
- POS(Y-): PP (Pr(ORR (Y-) $\ge 16\% | data) \ge 0.75$ at final analysis | interim data)

• Interim decision rules

Continue with F: $POS(F) \ge 10\%$ and $POS(Y) \ge 10\%$ Continue with Y+: $POS(F) \ge 10\%$ but POS(Y) < 10%

- and $POS(Y+) \ge 10\% OR$
- POS(F) < 10% but $POS(Y+) \ge 10\%$ Otherwise stop for futility

ORR(Y+) =

ORR(Y+) =

ORR (Y+

10. References

ario	Probability of crossing interim boundary in all-comers (%)	Probability of crossing interim boundary in Y+ patients (%)	Probability of early stop for futility (%)
= ORR (Y-) 5%	24.7	16.0	59.3
-) = 32%) = 16%	60.4	35.5	4.1
-) = 1 <mark>6%</mark>) = 32%	71.3	1.6	27.1
= ORR (Y-) 2%	96.1	2.6	1.3

Scenario	Probability of crossing efficacy boundary in all-comers (%)	Probability of crossing efficacy boundary in Y+ patients (%)
) = ORR (Y-) = 16%	1.0	3.8
32%, ORR (Y-) = $16%$	15.2	73.9
16%, ORR (Y-) = $32%$	28.6	0.5
) = ORR (Y-) = 32%	88.5	7.4

9. Conclusions/Discussions

We have provided an evidence-based approach for subgroup selection in single arm trial Complement statistical–clinical criterion and

intrinsic population selection algorithm in the interim analysis

Can be extended to single-arm studies with other endpoints, such as time-to-event endpoints (e.g., 1-year PFS rate)

. Roychoudhury, S., Scheuer, N., & Neuenschwander, B. (2018). Beyond p-values: A phase II dual-criterion design with statistical significance and clinical relevance. Clinical Trials, 15(5), 452–461.