Population Enrichment – The Future of Drug Discovery

Ankur Mukherjee, Cytel
Pune, India
ankur.mukherjee@cytel.com

Background

Population Enrichment is prospective use of any patient characteristic to obtain a study population in which detection is more likely than it would be in an unselected population.

Types of Population Enrichment:

- **Decrease Heterogeneity** (Recruiting from homogenous population based on certain characteristic)
- **Prognostic Enrichment** (Identifying high risk patients based on biomarkers)
- **Predictive Enrichment** (Identifying patients more likely to respond)

Issues:

- Cost of clinical trials is increasing.
- Discovery of blockbuster drugs is on the decline. Slowly moving away from one size fits all idea.
- High failure rate of molecules (90%). Rate even lower in major diseases.

Importance:

- Enrichment can help identifying high responsive group, which can help detecting treatment effect with lower sample size.
- Most importantly a drug can work in a subpopulation, failed molecules from one study may succeed in a different group.

Examples:

- **Opdivo** failed as a immunotherapeutic drug in lung cancer study by **BMS** where as **Merck** competitor **Keytruda** succeeded. Merck enriched their study population by including only patients with **high level of PDL-1**.
- **ISPY2** trial identified different combination therapies across different biomarker (genetic) subgroups.

Method and Assumptions

- The method is based on **predictive enrichment**.
- The study population is divided into two populations (subpopulation and complement) based on a predefined biomarker.
- Study will happen in two independent cohorts. The first cohort will recruit from the full population. The recruitment of the second cohort will depend upon an interim analysis based on the first cohort data only.
- Based on the interim analysis it will be decided whether to continue with the full population, sub population or to stop the trial for futility.
- The subpopulation prevalence will be user specified and accrual will depend upon this quantity.

Motivating example

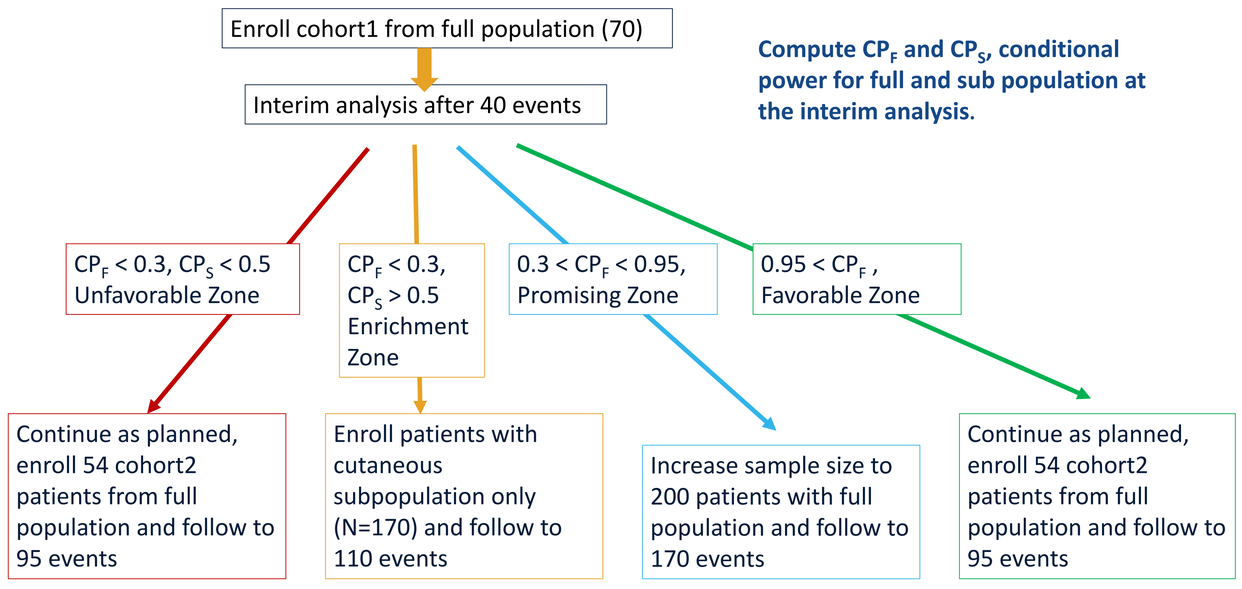
- The study is for **angiosarcoma** (AS) – cancer of inner lining of blood vessels.
- A two arm randomized trial with **single agent pazopanib and pazopanib +TRC105** in patients with unresectable angiosarcoma.
- Randomized 1:1, stratification cutaneous (sub population of interest) vs non-cutaneous , prevalence = 0.5.

Eligibility Criteria:

- Advanced **cutaneous and non-cutaneous** angiosarcoma (AS) not amenable to curative intent surgery
- Measurable disease by RECIST 1.1
- No prior treatment with a VEGF inhibitor
- 0, 1, or 2 prior lines of therapy
- ECOG ≤ 1

Adaptive Design Based On Interim Analysis

- Cohort 1 70 patients from full population. Interim analysis after 40 events are observed.
- Cohort 2 initial sample size 54
- 60 total events from cohort 1 and 35 from cohort 2.



Simulations Scheme

- Pazopanib (control) median survival = 4 months
- Hazard ratio cutaneous sub group = 0.55
- Hazard ratio non cutaneous sub group will be taken as (0.55, 0.7, .85, 1)
- Type I error = 0.025

Inputs

Type I Error (α): 0.025

Rejection Region: Left-Tail

Subpopulation Prevalence: 0.5

Allocation Ratio (n_t/n_c): 1

Subjects are followed: Until End of Study

Initial Sample Size

Cohort #	Sample Size	# of Events	
		Total	At IA
Cohort 1	70	60	40
Cohort 2	54	35	

Survival Information

Input Method: Median Survival Times

Subpopulation

Piece #	Med.Surv.Time		Hazard Ratio
	Control	Treatment	
1	4.000	7.273	0.550

Complement

Piece #	Med.Surv.Time		Hazard Ratio
	Control	Treatment	
1	4.000	4.706	0.850

Adaptation Parameters in Promising Zone

	Total	Coh1	Coh2
Maximum Sample Size if Adapt:	200	70	130
Maximum # of Events if Adapt:	170	60	110
Target CP for Re-estimating Events:	0.95		
Promising Zone Lower CP:	0.3		
Promising Zone Upper CP:	0.95		
Accrual Rate after Adaptation:	No change		

Adaptation Parameters in Enrichment Zone

	Total	Coh1	Coh2
Maximum Sample Size of Enriched Subgroup:	135	35	100
Maximum Events of Enriched Subgroup:	110	35	75
Enrich if CP_F < 0.3 & CP_S >=	0.5		
Terminate for Futility if CP_F < 0.3 & CP_S <	0.1		
Target CP for Re-estimating Events:	0.95		
Minimum # of Events from Subgroup:	58		
Accrual Rate after Enriched:	No change		

Note: Cohort1 and Cohort2 events contain average estimates.

Table: Simulation Outputs

* Fixed sample design shown in parenthesis

HR Cutaneous, Non Cutaneous	Zone	Prob. Of Zone	Power	Average Study Duration	Average Sample Size
0.55, 0.55	Unfavorable	16	34	21	124
	Enrich	3	84	25	162
	Promising	39	93	30	197
	Favorable	42	93	22	124
	Total	**100**	**81 (97)**	**25 (25)**	**154 (200)**
0.55, 0.7	Unfavorable	24	25	20	124
	Enrich	7	88	25	161
	Promising	37	85	30	197
	Favorable	19	88	21	124
	Total	**100**	**71 (86)**	**24 (25)**	**156 (200)**
0.55, 0.85	Unfavorable	31	18	20	124
	Enrich	12	84	24	157
	Promising	38	79	29	197
	Favorable	19	82	20	124
	Total	**100**	**61 (66)**	**24 (25)**	**155 (200)**
0.55, 1	Unfavorable	36	15	19	124
	Enrich	18	84	24	155
	Promising	34	76	29	197
	Favorable	12	76	20	124
	Total	**100**	**56 (43)**	**24 (25)**	**154 (200)**

Discussion

- Compared to a fixed sample design of 200 patients, the adaptive design provides for greater power, smaller trial size and shorter duration
- The adaptive design maintains over 80% power in the favorable, promising and enrichment zones at the hazard ratio of 0.55 for the cutaneous subgroup even with larger hazard ratios in the non-cutaneous subgroup
- In this rare disease a trial that starts out small but adapts the sample size and patient population as needed, based on interim data from the trial itself, is preferable to a larger 200 patient fixed sample trial

Reference

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