Population Enrichment – The Future of Drug Discovery

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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 homogeneous population based on certain characteristics.
- 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 an 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 PD-L1.
- SPY2 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

Table: Simulation Outputs

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<tr>
<th>Hazard</th>
<th>Cutaneous, Non-Cutaneous</th>
<th>Zone</th>
<th>Prob. Of Zone</th>
<th>Power</th>
<th>Average Study Duration</th>
<th>Average Sample Size</th>
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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