Designing a phase II clinical trial of personalized targeted therapy in oncology

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Introduction

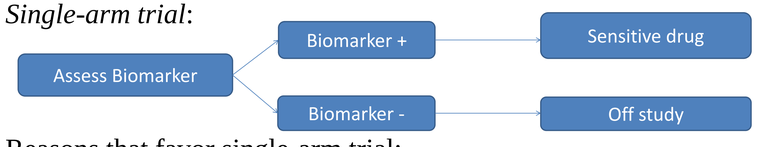
Designing a phase II clinical trial for the evaluation and validation of a biomarker-guided personalized targeted therapy can be challenging.
We outlined two design considerations illustrated by an example named TTAML (targeted therapy for acute myeloid leukemia) trial.

Background

The TTAML trial evaluates <u>five</u> widely used FDA approved drugs for AML patients.
Goal of the trial: to validate the clinical utility of a newly developed in-vitro screening technique for personalized drug selection based on drug sensitivity assay for AML patients with identifiable targets of tyrosine kinases.
Primary *objective*: to evaluate whether receiving a sensitive drug brings more therapeutic benefits than receiving a non-sensitive drug.
Primary *endpoint*: treatment response, a binary variable indicating whether the reduction in white blood cell counts is more than 25% from the baseline in 30 days.
Note:
-- Each patient has it's own set of "sensitive" and "non-sensitive" drugs.
-- The response rate may differ for the 5 drugs, and for the same drug depending on its "sensitivity" to the patient.

Design Considerations

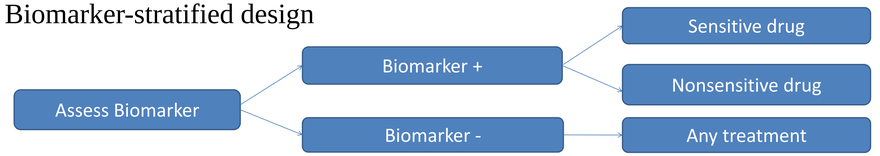
A: <u>Single-arm or randomized trial?</u>
Single-arm trial:



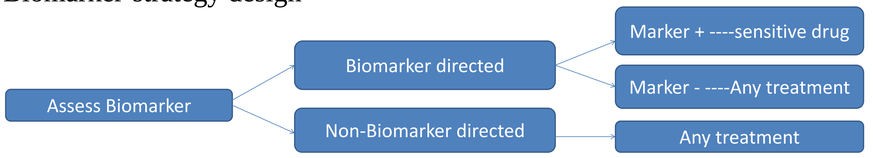
Reasons that favor single-arm trial:

- Ethical consideration: (Physician's opinion) the assay-matched targeted therapy should be at least no worse than the tradition standard treatment.
- Sample size consideration: requires relatively a small sample size compared with a randomized trial.

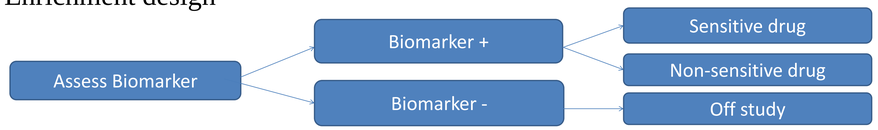
Randomized trial:
Biomarker-stratified design



Biomarker-strategy design



Enrichment design



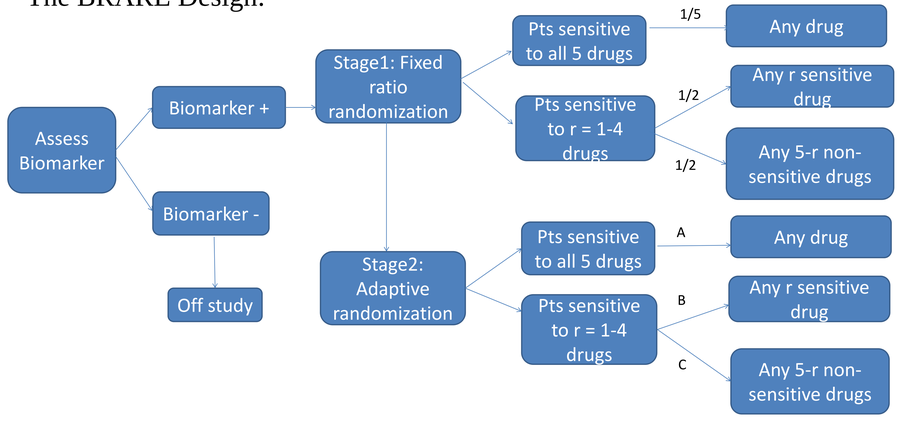
Reasons that favor a randomized trial:

- Statistically more reliable than a single-arm trial.
- Does not rely on historical data (which we lack) for the treatment effect for biomarker+ patients who have received non-sensitive treatment.

Methods for making choice: Discussion between physicians and statisticians.
Final Choice: A two-stage Bayesian response-based adaptive randomization enrichment(BRARE) design

- BRARE design serves as a compromise about the ethical concerns and statistical concerns.
- It assigns more patients to the subgroup with more favorable interim results, thus is ethically more desirable than a balanced randomized trial.
- It does not rely on historical information, thus can effectively test our hypothesis.
- The hierarchical Bayesian model allows us to borrow power across strata.
- An early stopping rule can be enforced for the sequential monitoring.

The BRARE Design:



B: <u>How to determine the adaptive allocation ratios A, B, and C?</u>
Six different allocation rules were considered:

- BRAR-01 : Allocation ratio is proportional to the estimated response rate.
- BRAR-02 : Allocation ratio proportional to $\Pr(p_j > p_{j'}, j' \in \{1,\ldots,J \mid j' \neq j\})$.
- BRAR-11: Allocation ratio partially follows RSIHR ratio. A: same as BRAR-02; B: $\frac{\sqrt{p_s}}{\sqrt{p_s}+\sqrt{p_{ns}}}$ C: $\frac{\sqrt{p_{ns}}}{\sqrt{p_s}+\sqrt{p_{ns}}}$
- BRAR-12: Allocation ratio using $\frac{[\Pr(p_s > p_{ns})]^c}{[\Pr(p_s > p_{ns})]^c + [\Pr(p_s < p_{ns})]^c}$ where c = ½.
- BRAR-14: Allocation ratio the same as BARA-12 except for c = n/2N (as proposed by Thall and Wathen).
- BRAR-16 : Apply doubly adaptive biased coin design (DBCD) to BRAR-12.

Methods for making choice: Broadly evaluate the performance (Probability of assigning patients to more effective treatment in stage 2, Power and Type I error rate) for all six allocation rules in a simulation study. Pick the allocation rule with best performance.
Final Choice: BRAR-12

- It has good power with type I error rate controlled within 5% for a total of 150 patients, 30 in the stage 1.
- Its performance is robust to the number of sensitive drugs a patient may have.
- Its probability of assigning patients to the more promising group is much higher than a traditional randomized trial with equal allocation.

Conclusion

The design considerations largely depends on the primary objective and available resources for a clinical trial.
An interactive discussion between clinical researchers and physicians is crucial in making important decisions.
The performance of different adaptive allocation ratio can be quite different. Simulation is a powerful tool in making choice of adaptive randomization ratio for the adaptive stage.

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