Statistical Designs in Phase III Studies in the Era of Targeted Agents

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CANSSI Workshop

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Cytotoxic Versus Cytostatic Agents

Cytotoxic Agents:

- Exploit mechanisms that are important in mitosis to kill dividing cells (traditional chemotherapy agents)
- Do not distinguish between different kind of cells.

Examples for Cytostatic (Targeted) Agents:

Antiangiogenic Agents: Inhibit the formation of new blood vessels, e.g. *Thalidomide* (Celgene) and *Lenalidomide (*Revlimid, Celgene).
Proapoptopic Agents: Initiate tumor cell death e.g. *Imatinib* (Gleevec, Novartis) small molecule drug approved by the FDA to treat CML.
Epidermal Growth Factor Inhibitor: Inhibits tumor cell division, e.g. Iressa (ZD1839 or Gefitinib) and Tarceva (Erlotinib) used to treat lung cancer.

- Targeted agents only interfere with a specific pathway or specific cell.
- Raise new questions that need to be addressed in Trial Designs

Questions to be addressed for Targeted Agents in Ph III Clinical Trials

- Should all patients of a particular tumor type be treated with a targeted agent or should only those patients who are positive for the target (or marker) be so treated?
  - Targeted agents can have collateral benefit.
  - E.g. Imatinib, developed to target CML also destroys tumor cells that are c-kit positive (GI stromal tumors)
  - E.g. There is evidence that Trastuzumab has some effect on Her-2 negative breast cancer patients.
- Is there a (genetic) subgroup where such treatments are effective (or more effective) and how should study design be modified where feasible?

- What is the most appropriate trial design to validate tumor markers and to determine the subgroup of patients with good prognosis and the group of patients most likely to benefit from a new therapy?

Questions to be addressed for Targeted Agents in Ph III Clinical Trials

S0819: A Randomized Ph III Study Comparing
Chemotherapy (Carboplatin/Paclitaxel/(Bevacizumab)) **+/- Cetuximab (EGFR Inhibitor)**
in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)
(Roy Herbst, MD PhD; Mary Redman, PhD)

Hypotheses:

- *Cetuximab* will increase efficacy of concurrent chemotherapy patients with advanced NSCLC.
- EGFR FISH positive patients will benefit more from the addition of Cetuximab than the general NSCLC patient population.

Questions:

- Should all NSCLC patients be treated with the targeted agent (Cetuximab) or should only EGFR FISH+ patients be so treated?

- What is the most appropriate trial design to validate the new tumor marker and to determine subgroups of patients most likely to benefit from a new therapy?

Prognostic versus Predictive Markers

Prognostic Marker
Information about disease outcome **independent** of treatment

Example : ***PSA in prostate cancer***
Elevated levels of PSA: ➡ *higher risk for poor outcome*
Low levels of PSA: ➡ *lower risk for poor outcome*

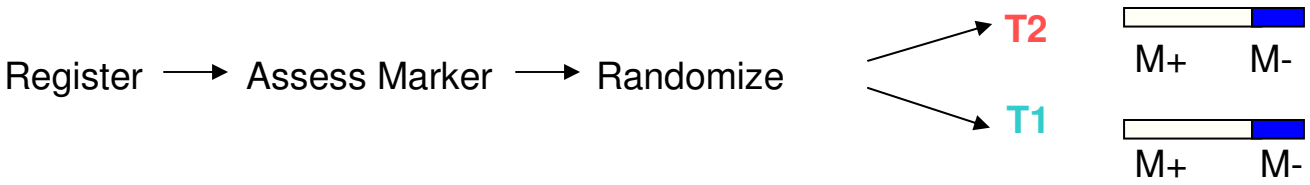
Predictive Marker
Information on disease outcome **based on a specific treatment**

Example : ***Estrogen receptor***,
ER+ : ➡ *50-60% probability of response to hormonal treatment*
ER- : ➡ *<10% probability of response to hormonal treatment*

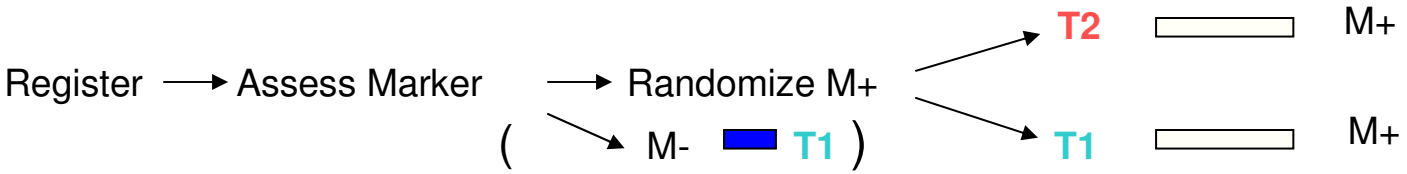
Only **predictive** markers can be used to indicate which patients should be treated with a particular **targeted** agent.

Clinical Trial Designs for Phase III Trials for Targeted Therapy

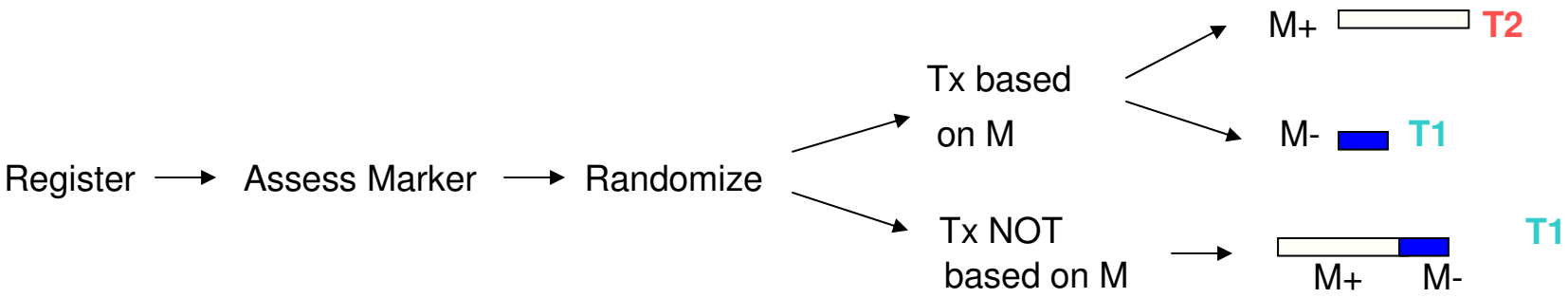
§ **Randomize-All Design**: Randomize all patients, measure marker.



§ **Targeted Design**: Randomize marker positive patients only.



§ **Strategy Design**: Randomize to marker based versus not marker-based.



M+: marker positive pts. ▭; M-: marker negative pts. ▬ ; T1: standard of care; T2: targeted agent.

Hypotheses Tested by the various designs

- **Randomize-All Design**:
  - Is treatment beneficial to for all patients?
  - Possible subset analysis, addressing: Is treatment beneficial (or more beneficial) for M+ patients?
- **Targeted Design:**
  - Is treatment beneficial for M+ patients?
- **Strategy Design:**
  - Is marker-based treatment better than everyone receiving standard of care (T1)?

Example of a SWOG trial with continuous marker: S1007

A Phase III, Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy **+/- Chemotherapy** in Patients with 1-3 Positive Nodes, Hormone Receptor-Positive and HER2-Negative Breast Cancer

With Recurrence Score (RS) of 25 or Less

Ana M. Gonzalez-Angulo, M.D, William Barlow, Ph.D.

Primary Hypotheses to be tested:

- Chemotherapy benefit based on Oncotype Dx Risk Score
- Survival benefit of chemo increases with Risk Score

Primary Analysis:

- Test of interaction of RS with randomized treatment assignment

Biomarkers are often continuous

Model Assumptions

Markers are often based on

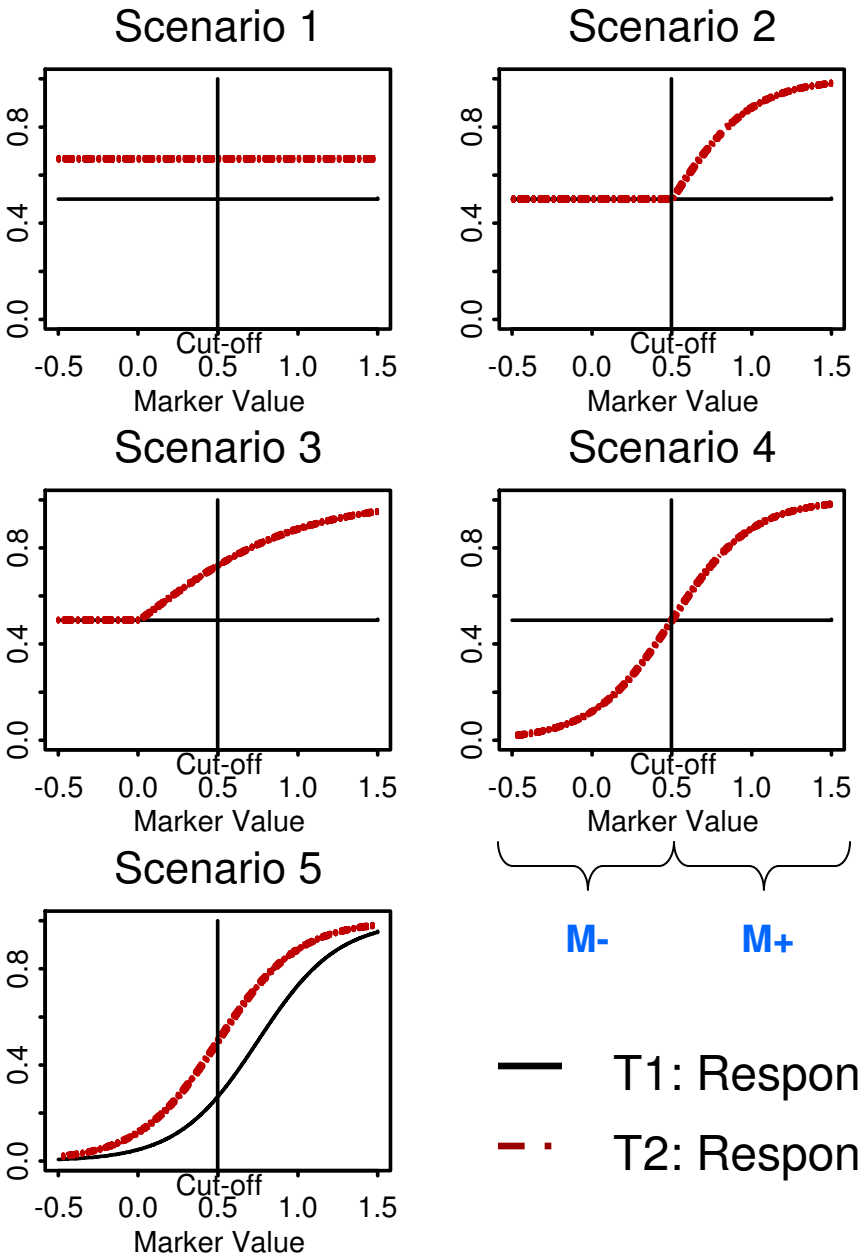
- specific chemicals in the blood or in other tissue compartment
- abundance of certain proteins or peptides
- combination of Gene Expression Profiles

→ The underlying marker distribution and response distribution to marker value is often **continuous.**

→ Using a continuous marker distribution

- is more realistic.
- takes into account marker prevalence.
- allows us to evaluate effects of a cut-point that is not precisely determined.

Possible Underlying Marker Scenarios



M+ : Marker positive,
Marker value > Cut-off

M- : Marker negative,
Marker value < Cut-off

Scenario 1: **No true Marker**

Predictive Markers:

Scenario 2: T2 helps M+, but not M- pts.

Scenario 3: T2 helps M+ and M- pts, but effect on M+ pts. is greater.

Scenario 4: T2 benefits M+ pts, but is harmful to M- pts (total interaction)

Scenario 5: **Prognostic Marker**

T1: Response to Standard of Care

T2: Response to Targeted Treatment

Model Assumptions

Marker Distribution: $f(X)$ with $X \sim N(\mu, \sigma^2)$

Response distribution to treatment j=1,2 : $g_j(X) = a_{0j} + a_{1j}X.$

- M+ patients are parameterized as: $M+ = \{X : X > c\},$

Fraction of M+ pts: $v_{M+}(c) = \int_{s>c} f(s)ds$

For binary outcomes, the outcome for the subgroup of M+ pts, assuming a logit link:

$$\eta_j(c, M+) = \int_{s>c} \frac{e^{g_j(s)}}{1+e^{g_j(s)}} f(s)ds$$

Simulation Studies

- Simulate the underlying log-marker distribution from a normal distribution:

$$X \sim N(\mu, \sigma^2)$$

- Evaluate the response distribution to the marker using the distribution functions from the various scenarios.

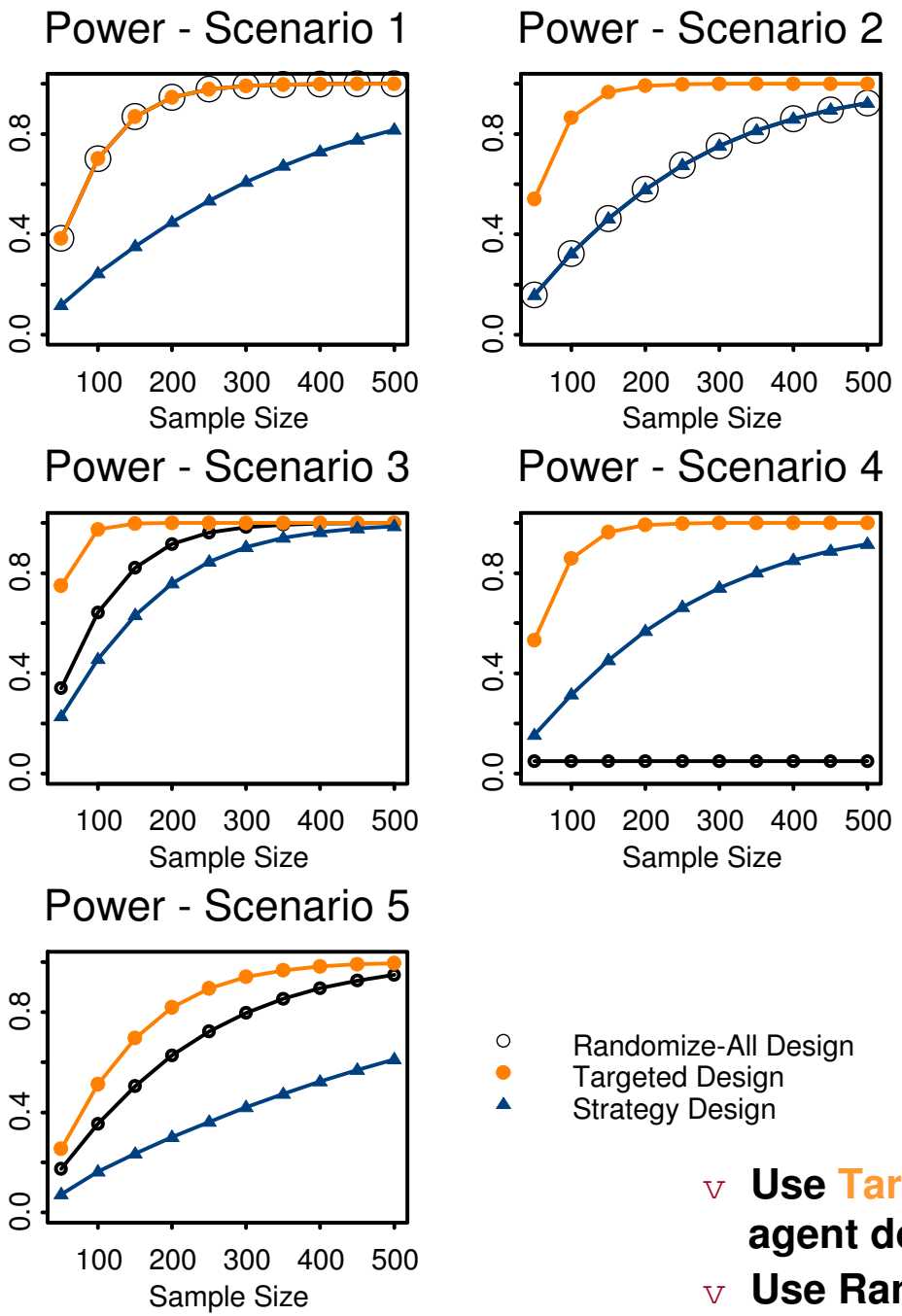
- Perform 5000 simulations to calculate response probability for M+ and M- patients: $\eta_j(c, M+)$ and $\eta_j(c, M-)$

- Evaluate power or sample size using these derived quantities for the different scenarios assuming an underlying binomial distribution.

- For the sample size calculations we used a power of 0.90 with one-sided α of 0.05.

- *For the power calculations we used a sample size of N=100 and a one-sided α of 0.05.*

Power as a Function of Sample Size



Scenario 1: No true marker,T2 better than T1
Scenarios 2-4: Predictive marker
Scenario 4: Total interaction
Scenario 5: Prognostic marker

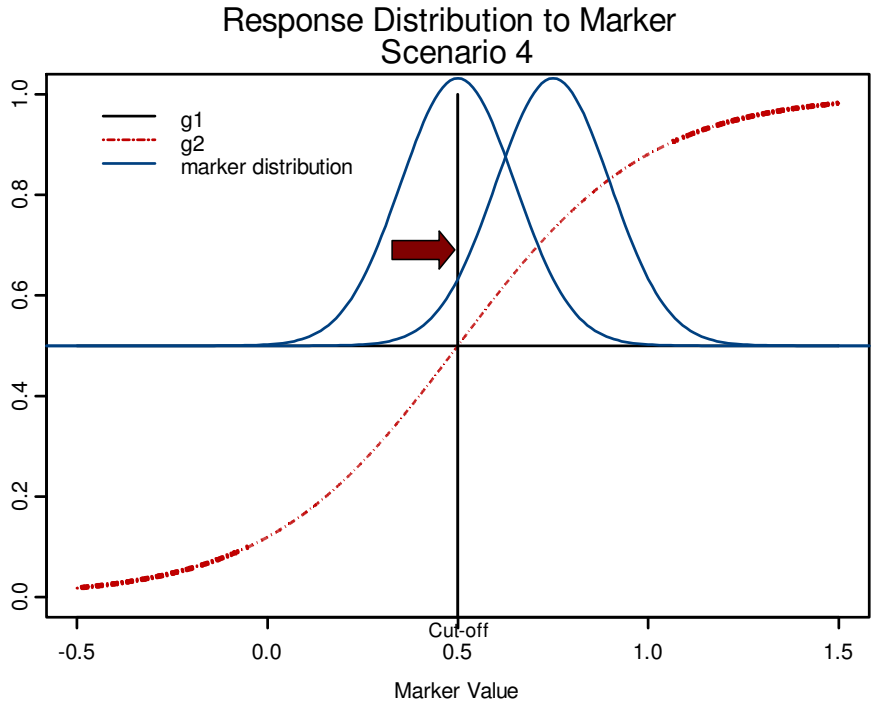
Targeted Design (•) outperforms other designs, but no information gained on M- patients.

Randomize-All Design (o) outperforms Strategy Design (Δ), except in scenario 4 (total interaction) .

General Guidelines

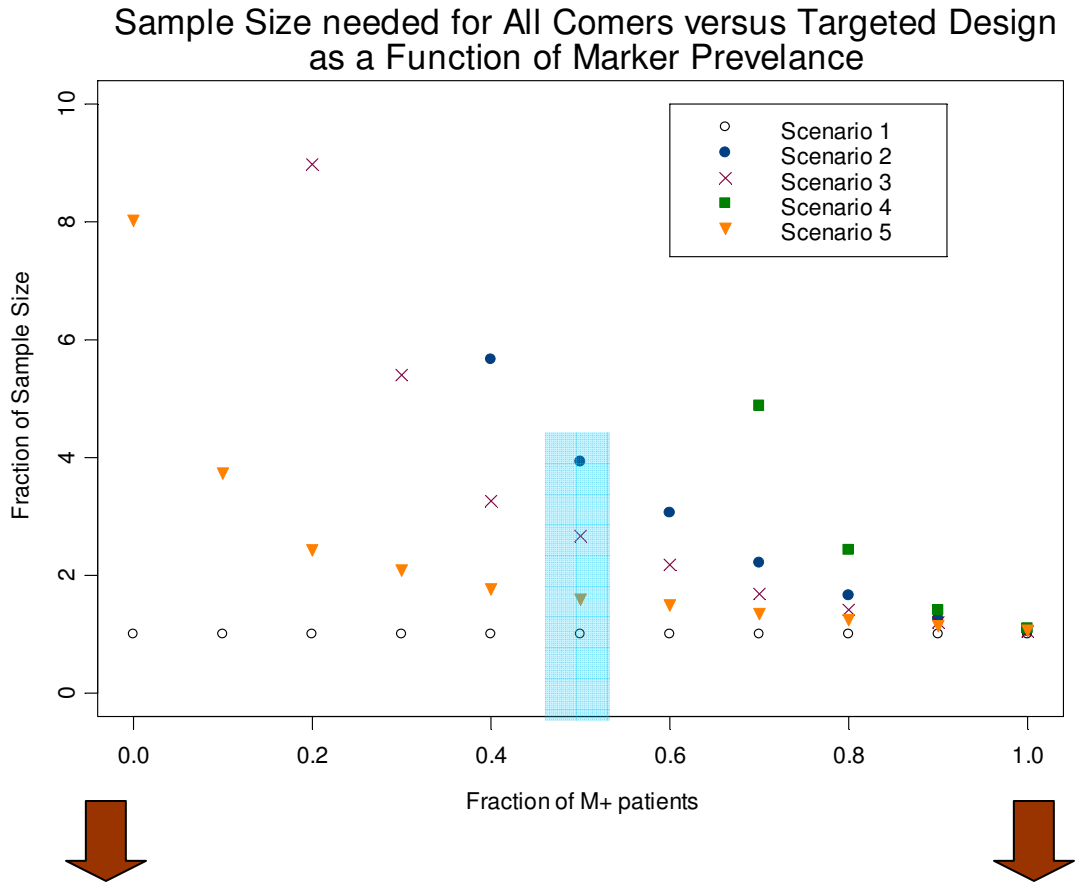
- **Use Targeted Design if there is certainty that the new agent does not help M- pts.**
- **Use Randomize-All design over Strategy Design.**

Example for Moving the Normal Distribution



Correct cut-point

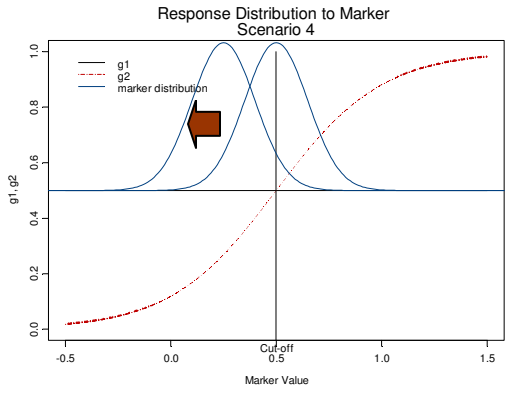
- Shifting the normal distribution shifts mass of distribution, changes marker prevalence.
- No effect on randomize- all design; potentially large effect on targeted and strategy design.

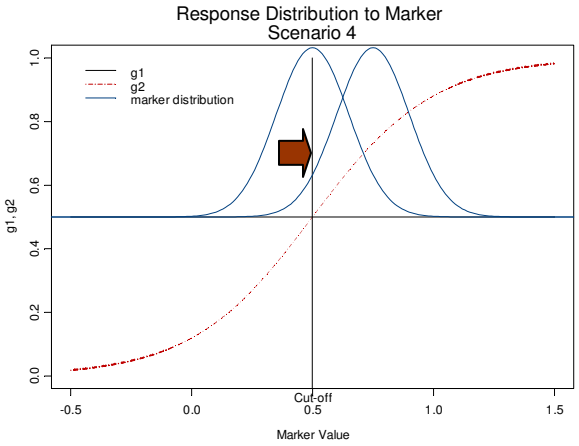


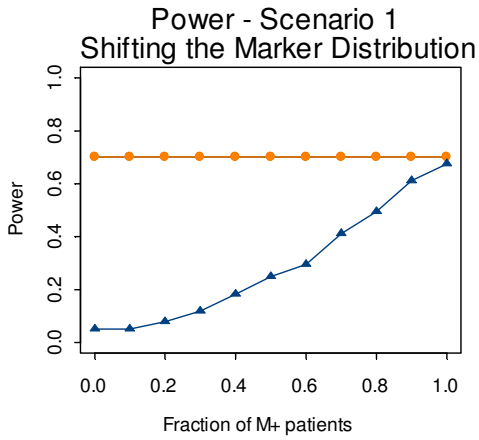
Scenario 1*:* no true marker, T2 better than T1

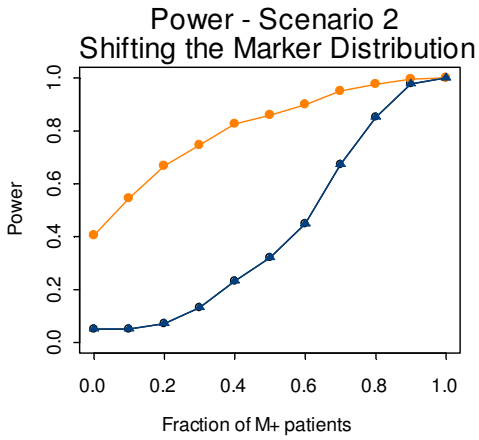
Scenarios 2-4: Predictive marker

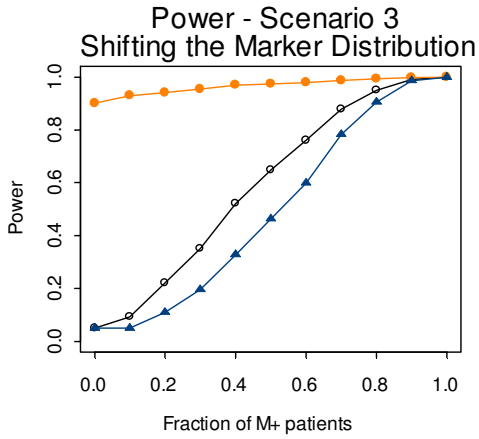
Scenario 5: Prognostic marker

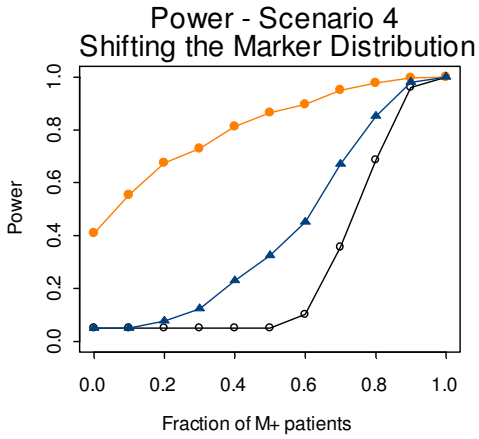


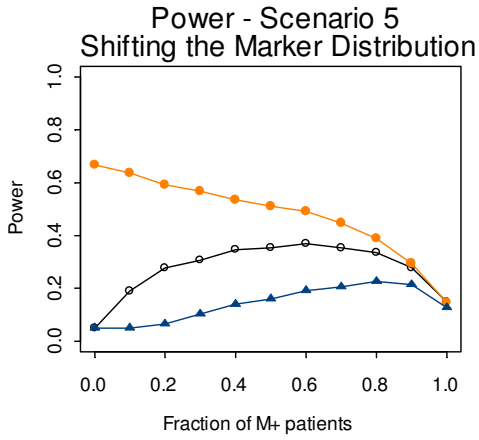


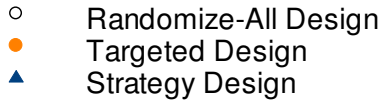












Shifting Normal Distribution

Effect on Power with fixed sample size

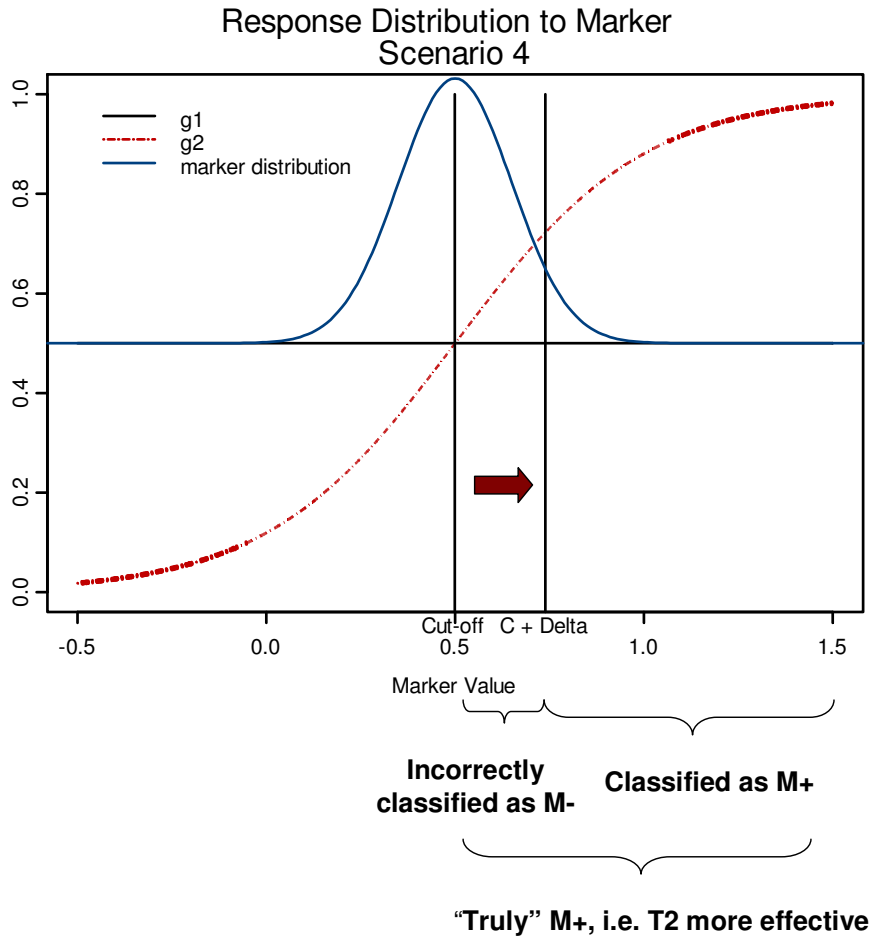
Scenario 1*:* no true marker, T2 better than T1

Scenarios 2-4: Predictive marker

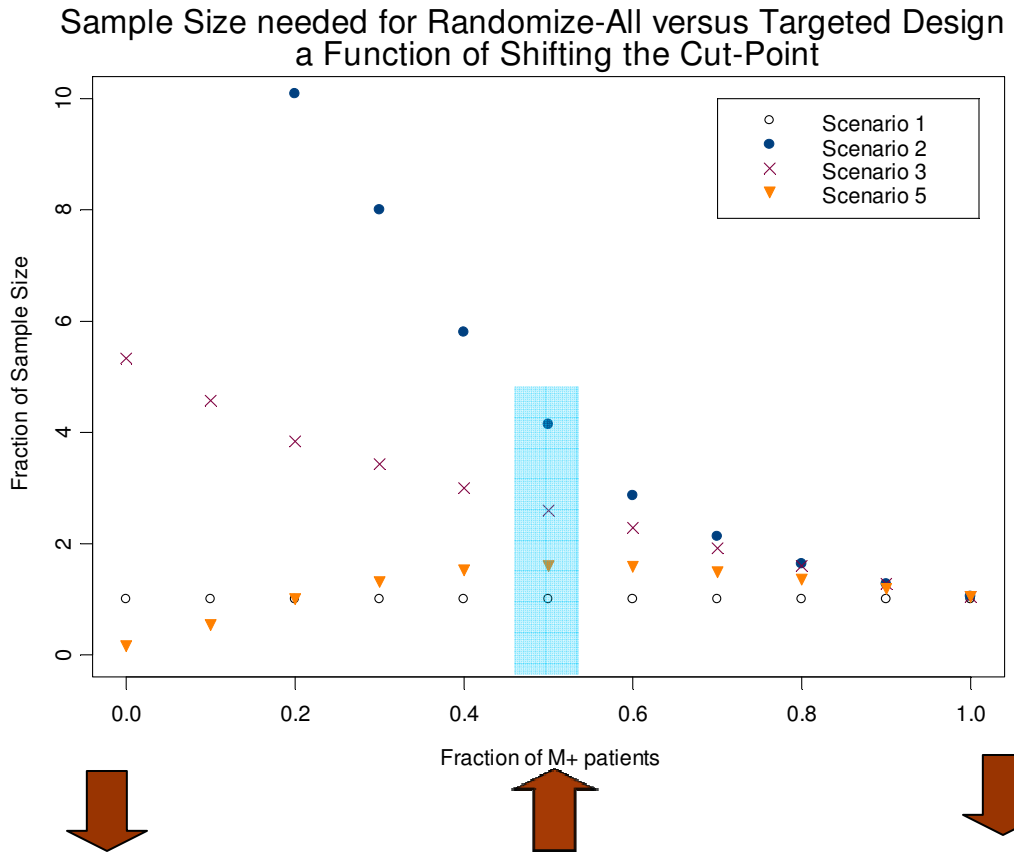
Scenario 5: Prognostic marker

In general, targeted design outperforms the randomize-all and strategy design if fraction of M+ patients is small (small prevalence).

Example for Moving the Cut-Point



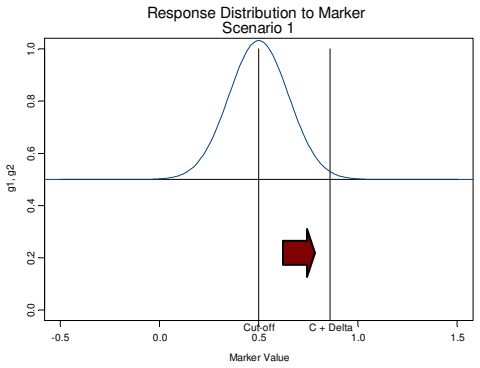
- Changes the fraction of pts that is classified as Marker positive. Shifting the cut-point results in some pts. being incorrectly classified as M- when they are truly M+ and vice versa.
- No effect on randomize- all design; potentially large effect on targeted and strategy design.



Scenario 1*:* no true marker, T2 better than T1

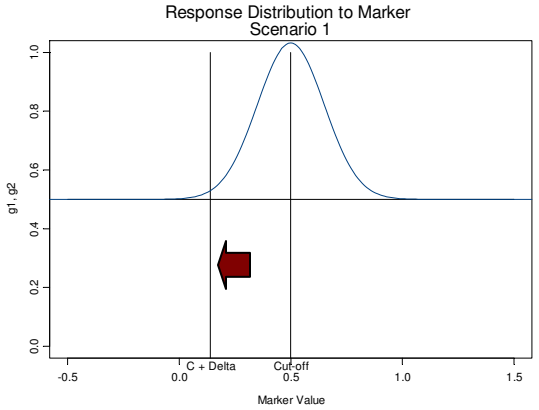
Scenarios 2-4: Predictive marker (scenario 4 outside range)

Scenario 5: Prognostic marker

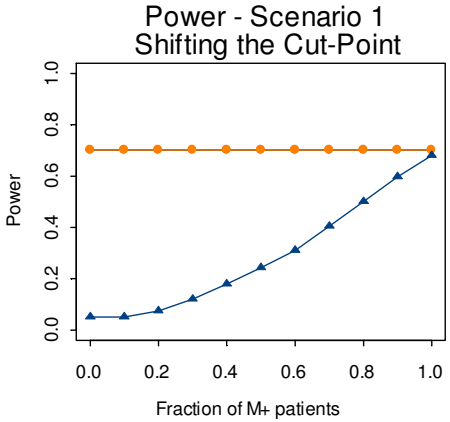


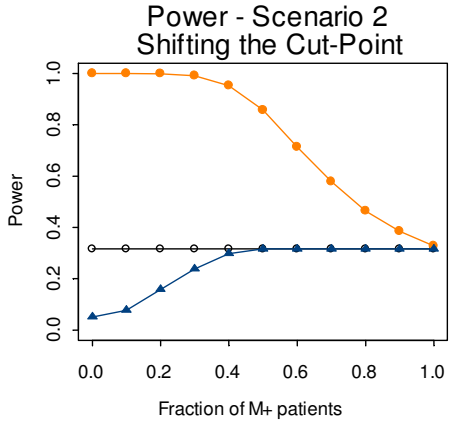
Correctly classified

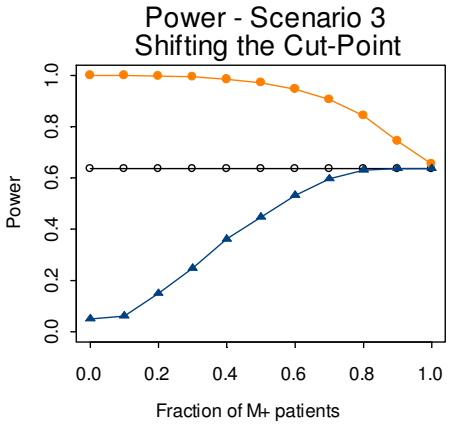
All pts are classified as M- and only the most extremes are correctly classified as M+. The difference between the two response distributions is largest.

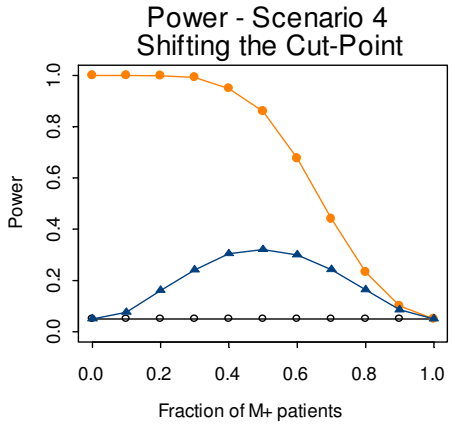


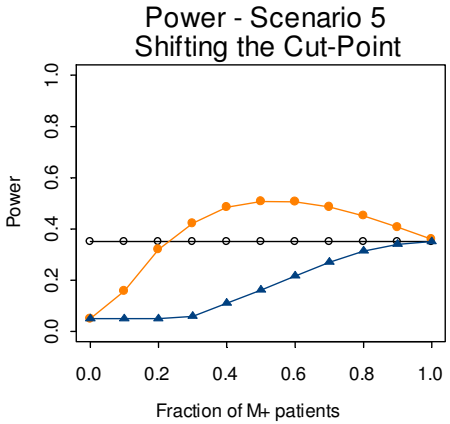
All pts are classified as M+ and thus treated identically to the Randomize-all design.

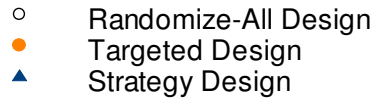












Shifting Cut-Point

Effect on Power with fixed sample size

Scenario 1*:* no true marker, T2 better than T1

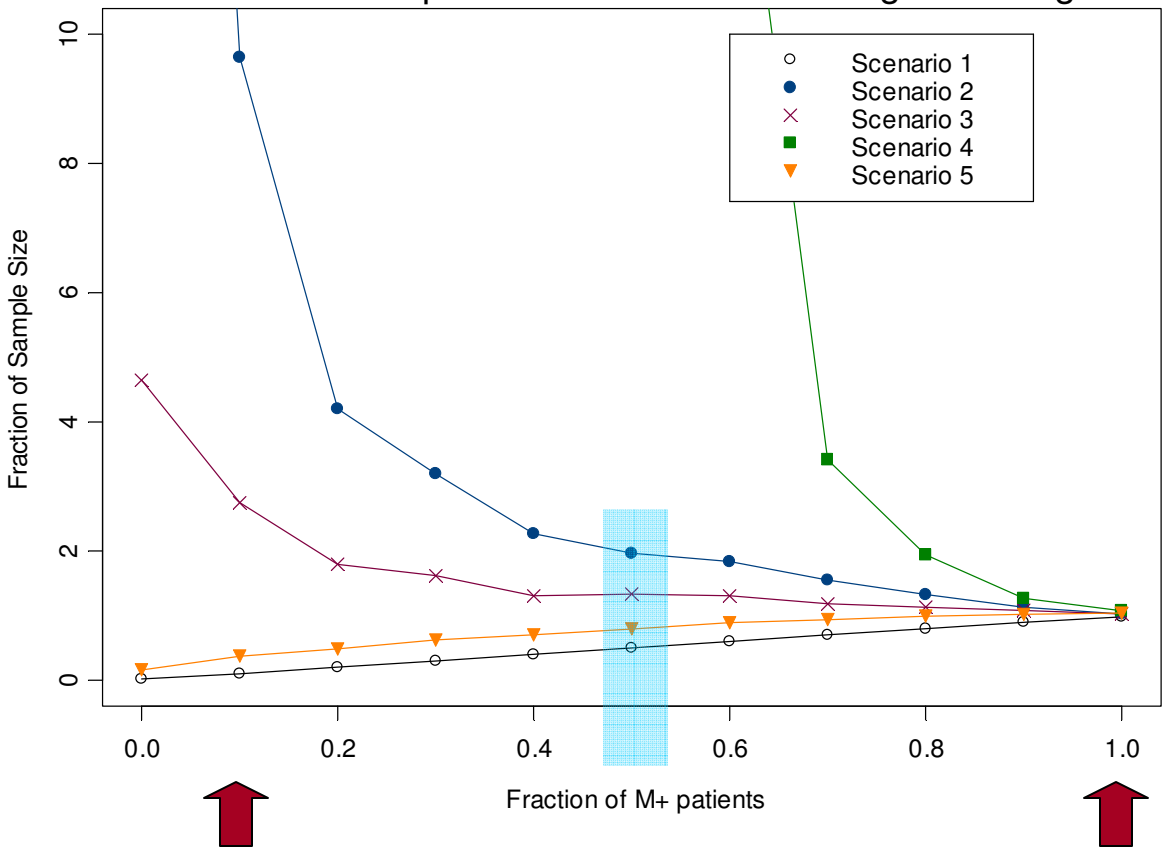
Scenarios 2-4: Predictive marker

Scenario 5: Prognostic marker

Scenario 1: Targeted=Randomize All

In general, targeted design outperforms the randomize-all and strategy design if fraction of M+ patients <1.

Ratio of the number of patients randomized in the randomize-all design
and number of patients screened in the targeted design



Scenario 1: *No true marker, T2 better than T1*
Scenarios 2-4: *Predictive marker*
Scenario 5: *Prognostic marker*

N pts **screened** in the targeted design = N **randomized** in targeted design / fraction of M+ pts

For predictive markers:

- The smaller the fraction of M+ pts, the more pts need to be screened.
- But even more patients need to be randomized in a Randomize-All Trial than screened on a Targeted Trial.

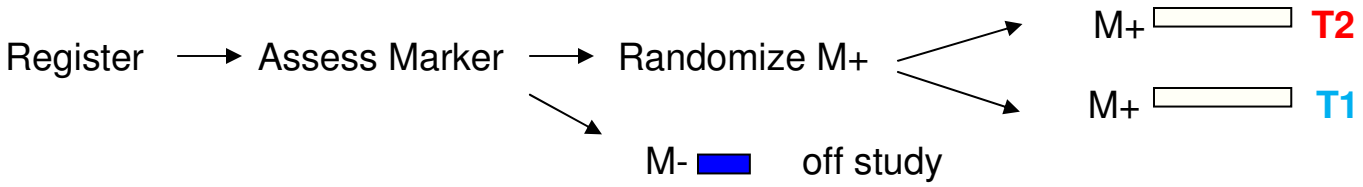
If fraction of M+ = 1

- N screened = N randomized
- Targeted and Randomize-All designs are the same.

General Guideline:

Use Targeted Design for small marker prevalence.

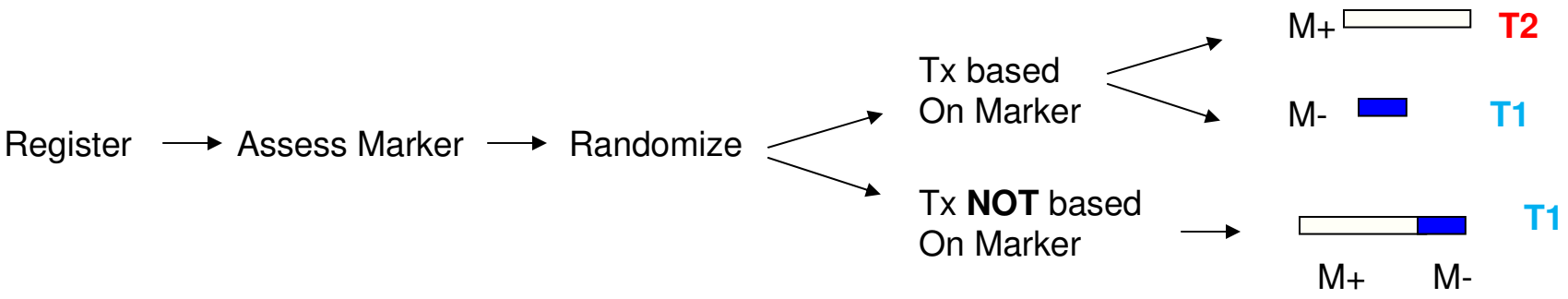
Targeted (Marker+) Design for Assessment of a Targeted Therapy



- **Advantages**:
  - Smaller sample size
  - Meets regulatory requirements for drug approval in this marker+ subpopulation
- **Disadvantages:**
  - May require large population to be screened
  - Cannot determine efficacy in Marker- patients
    - (because only Marker+ patients enrolled)

General Guideline: Use Targeted Design for small marker prevalence

Marker Strategy

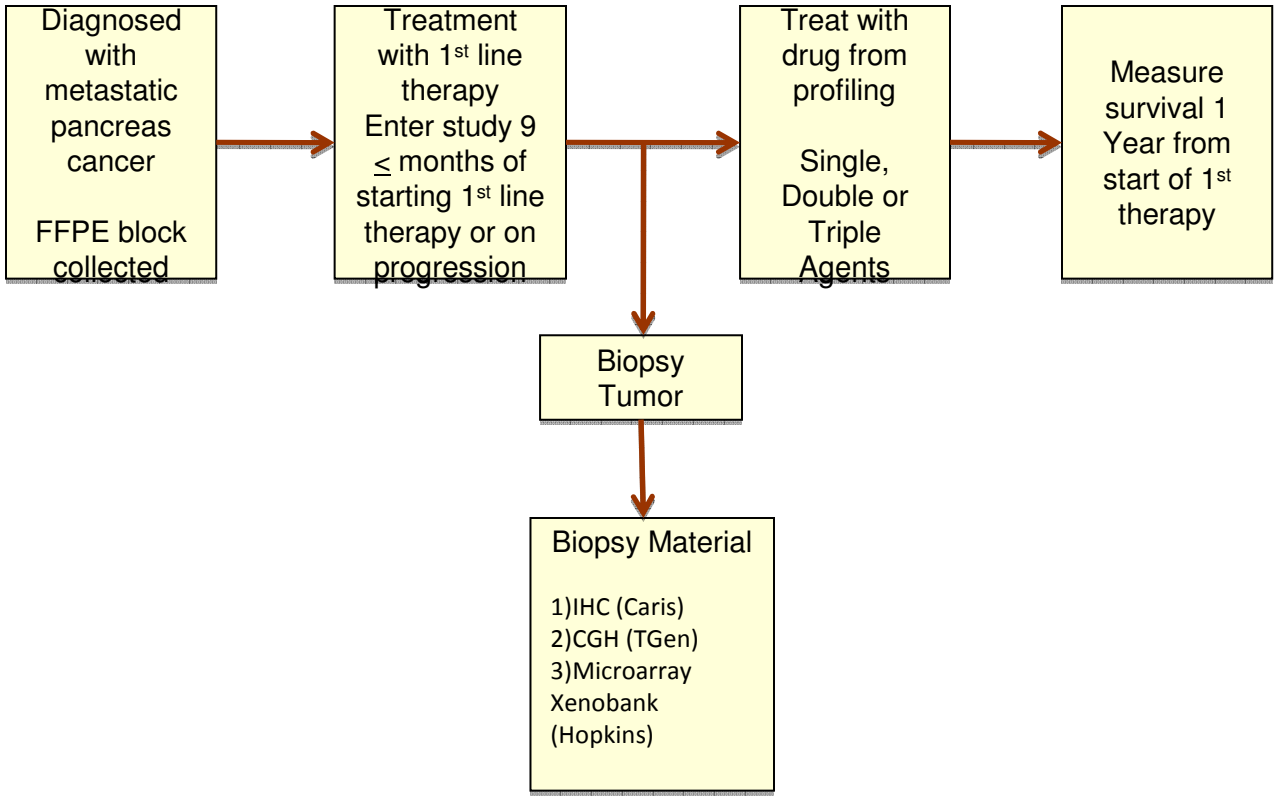


When Would You Use the Marker Strategy Design?

- When All (or Almost All) Patients Will Receive "nonstandard" Treatment (T2).
- When M+ is very prevalent.
- When truly interested in the strategy hypothesis.
- Treat by Molecular Profile (Von Hoff, JCO 2010); true personalized therapy.

STAND UP TO CANCER CONSORTIUM: PHASE II STUDY OF THERAPY SELECTED BY MOLECULAR/METABOLIC PROFILING IN PATIENTS WITH PREVIOUSLY TREATED METASTATIC PANCREATIC CANCER

R. Ramanathan, MD, D. Von Hoff, MD, Antje Hoering, PhD

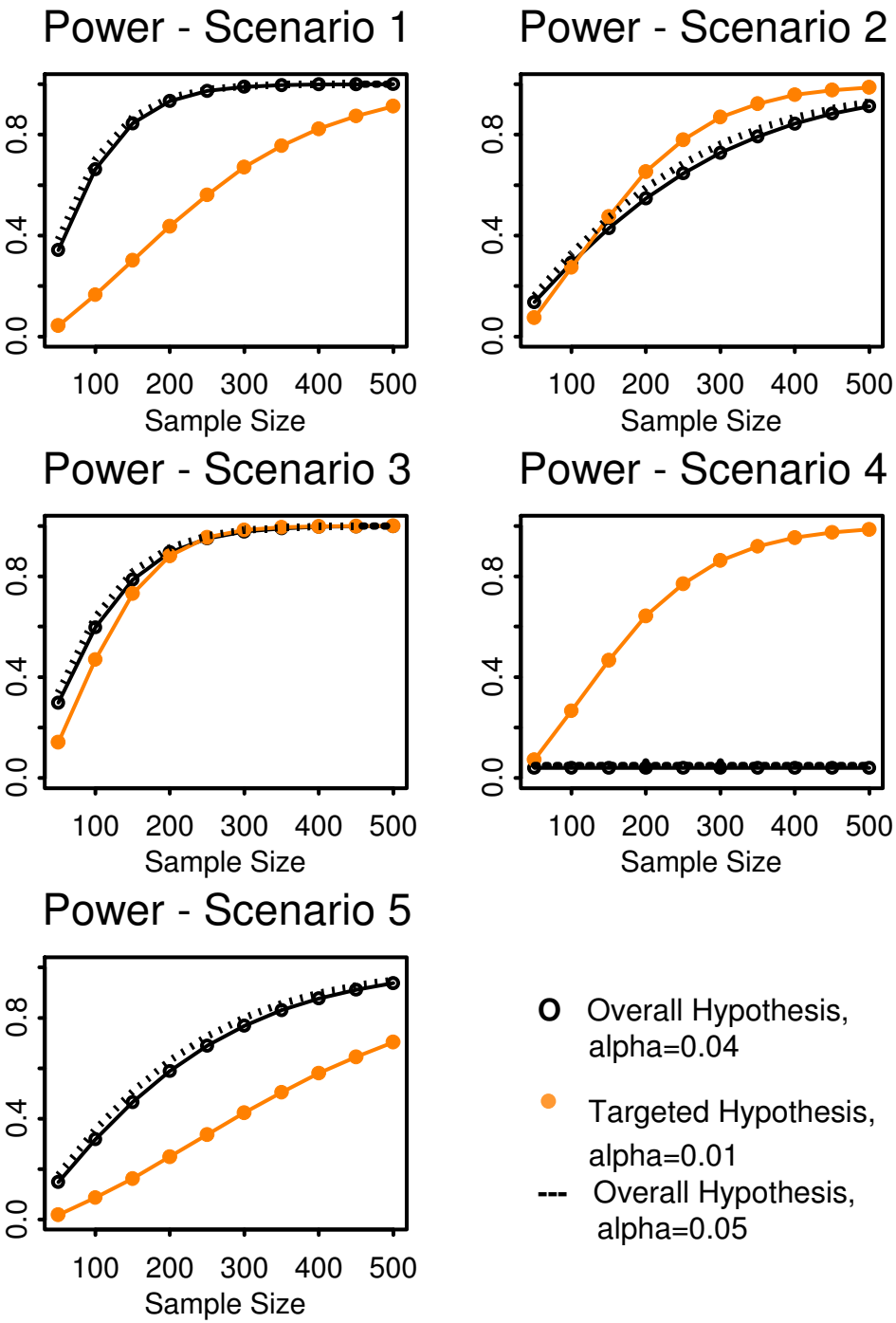


Goal: Improve one-year survival (from 5% to 20%)

Outcome: 7 out of 35 patients alive at one-year => positive study

Possible Phase III Design: Strategy Design

Randomize-All Design Split Alpha



Scenario 1: No true marker, T2 better than T1
Scenarios 2-4: Predictive marker
Scenario 4: Total interaction
Scenario 5: Prognostic marker

Scenarios 2 and 3 (predictive markers) the power of the two hypotheses is comparable.

Only a modest increase in sample size is needed to test both hypotheses.

General Guideline

Use Randomize-All Design with Split Alpha if there is the possibility of the new Agent helping M+ and M- pts.

Hybrid Design: SWOG Lung Trial S0819

S0819:

A Randomized Ph III Study Comparing
Chemotherapy (Carboplatin/Paclitaxel/(Bevacizumab))
+/- *Cetuximab*
in Patients with Advanced
Non-Small Cell Lung Cancer (NSCLC)

Hypotheses:

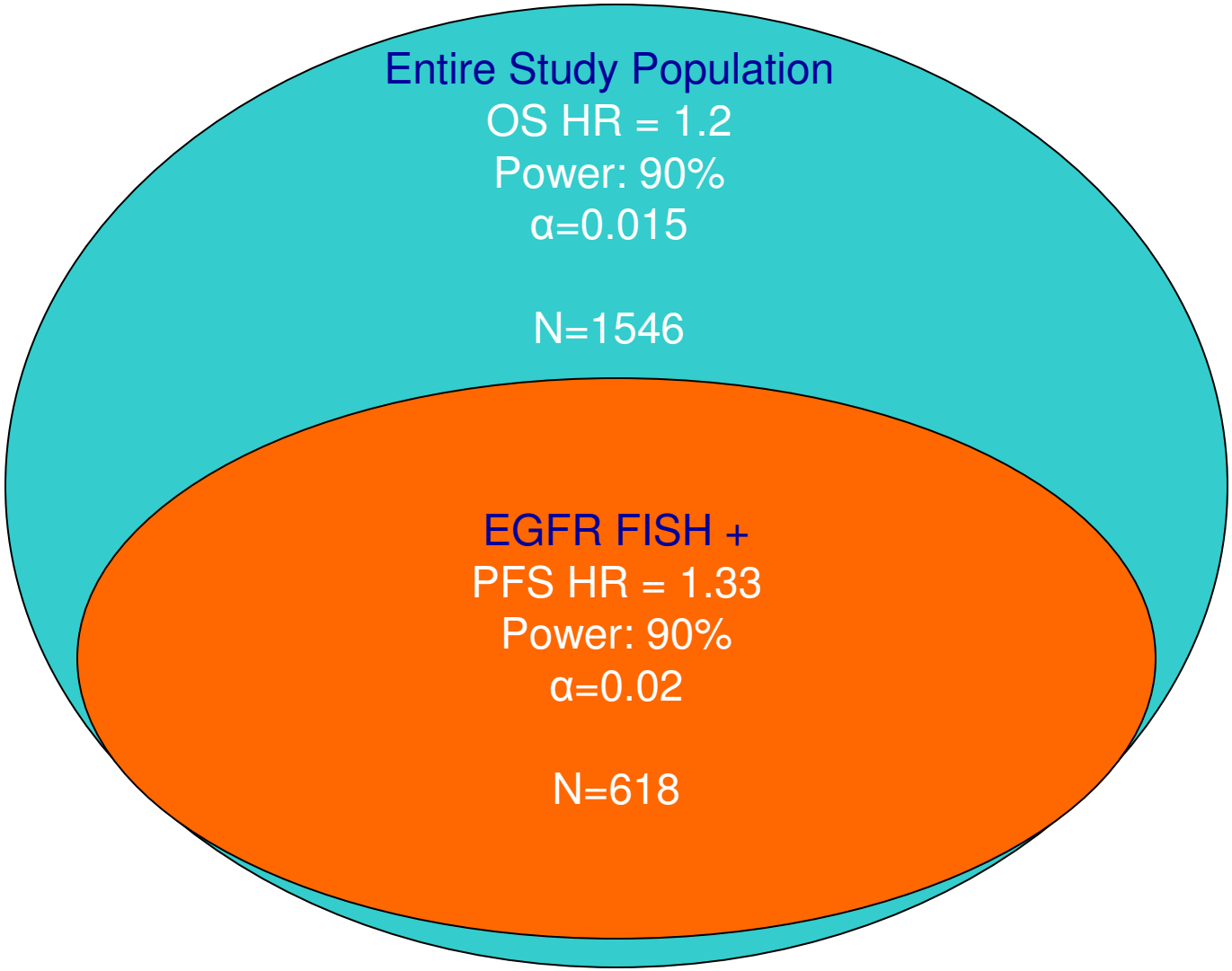
- *Cetuximab* will increase the efficacy of concurrent chemotherapy in patients with advanced NSCLC.
- EGFR FISH positive patients will benefit more from the addition of Cetuximab than the general NSCLC patient population.

Questions

Should all NSCLC patients be treated with a targeted agent or should only EGFR FISH positive patients be so treated?

What is the most appropriate trial design to validate the new tumor markers and to determine subgroups of patients most likely to benefit from a new therapy?

SWOG S0819


Entire Study Population
OS HR = 1.2
Power: 90%
α=0.015
N=1546
EGFR FISH +
PFS HR = 1.33
Power: 90%
α=0.02
N=618

SWOG S0819

Prevalence of FISH+ ~ 50%, power = 92%, overall alpha=.025 (1-sided)

Hypotheses to be tested:

H1: Entire cohort: Addition of Cetuximab increases median OS by 20%.

H2: FISH+ cohort: Addition of Cetuximab increases median PFS by 33%.

H-strategy: Strategy of (Chemo+Cetuximab for FISH+ cohort) versus Chemo only for everyone superior: Increase of median PFS in strategy arm by 15%.

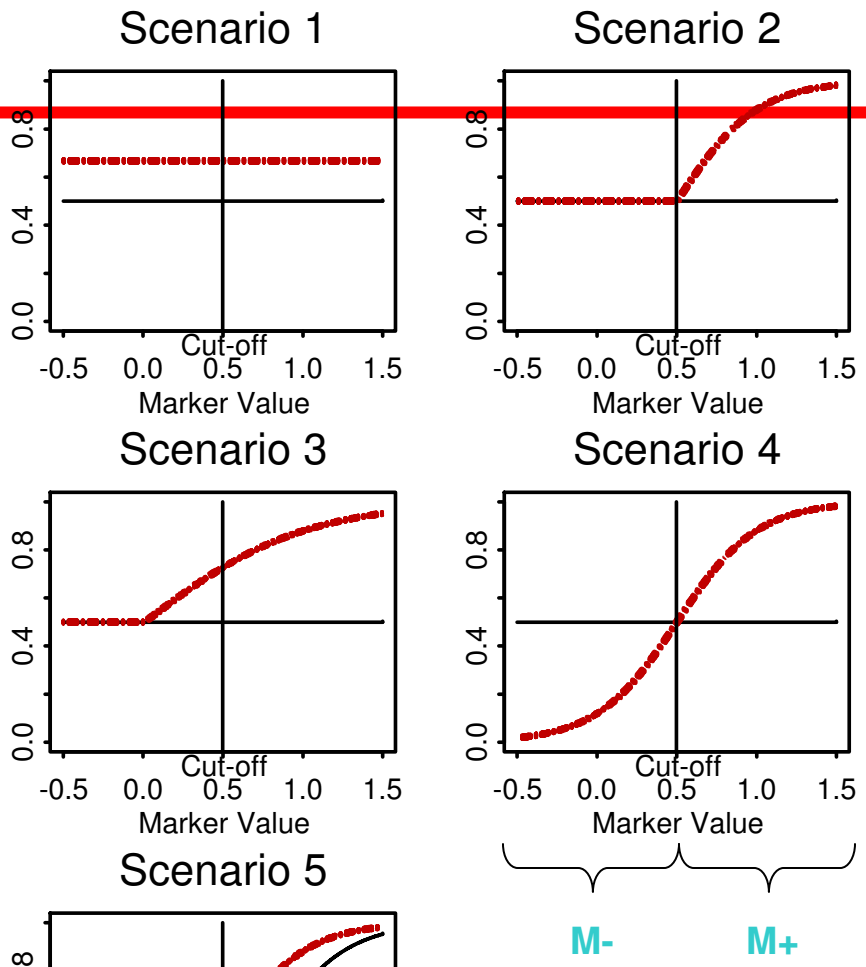
Design	N
Randomize-All Design with split alpha (H1 and H2)	618/1546
Randomize-All Design (H1 only)	1418
Marker Positive Design (H2 only)	584
Marker Strategy Design	2406

General Guidelines for Randomize-All Design

- **Use randomize-all design (possibly with power adjusted for multiple comparison) if**
  - There is the possibility that the new treatment is beneficial for marker-negative patients.
  - Marker prevalence is relatively high.

Both the overall and the targeted hypothesis can be tested with only a modest increase in sample size.

Can We Distinguish Scenario 4 from 5?



M+ : Marker positive, Marker value > cut-point

M- : Marker negative, Marker value < cut-point

Scenario 1: **no true Marker**

Predictive Markers:

Scenario 2: T2 helps M+, but not M- pts.

Scenario 3: T2 helps M+ and M- pts, but effect on M+ pts. is greater

Scenario 4: T2 benefits M+ pts, but is harmful to M- pts (total interaction)

Scenario 5: **Prognostic Marker**

T1: Response to Standard of Care

T2: Response to New (Targeted) Treatment

Example of a SWOG trial with continuous marker: S1007

A Phase III, Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy **+/- Chemotherapy** in Patients with 1-3 Positive Nodes, Hormone Receptor-Positive and HER2-Negative Breast Cancer

With Recurrence Score (RS) of 25 or Less

Ana M. Gonzalez-Angulo, M.D, William Barlow, Ph.D.

Primary Hypotheses to be tested:

- Chemotherapy benefit based on Oncotype Dx Risk Score
- Survival benefit of chemo increases with Risk Score

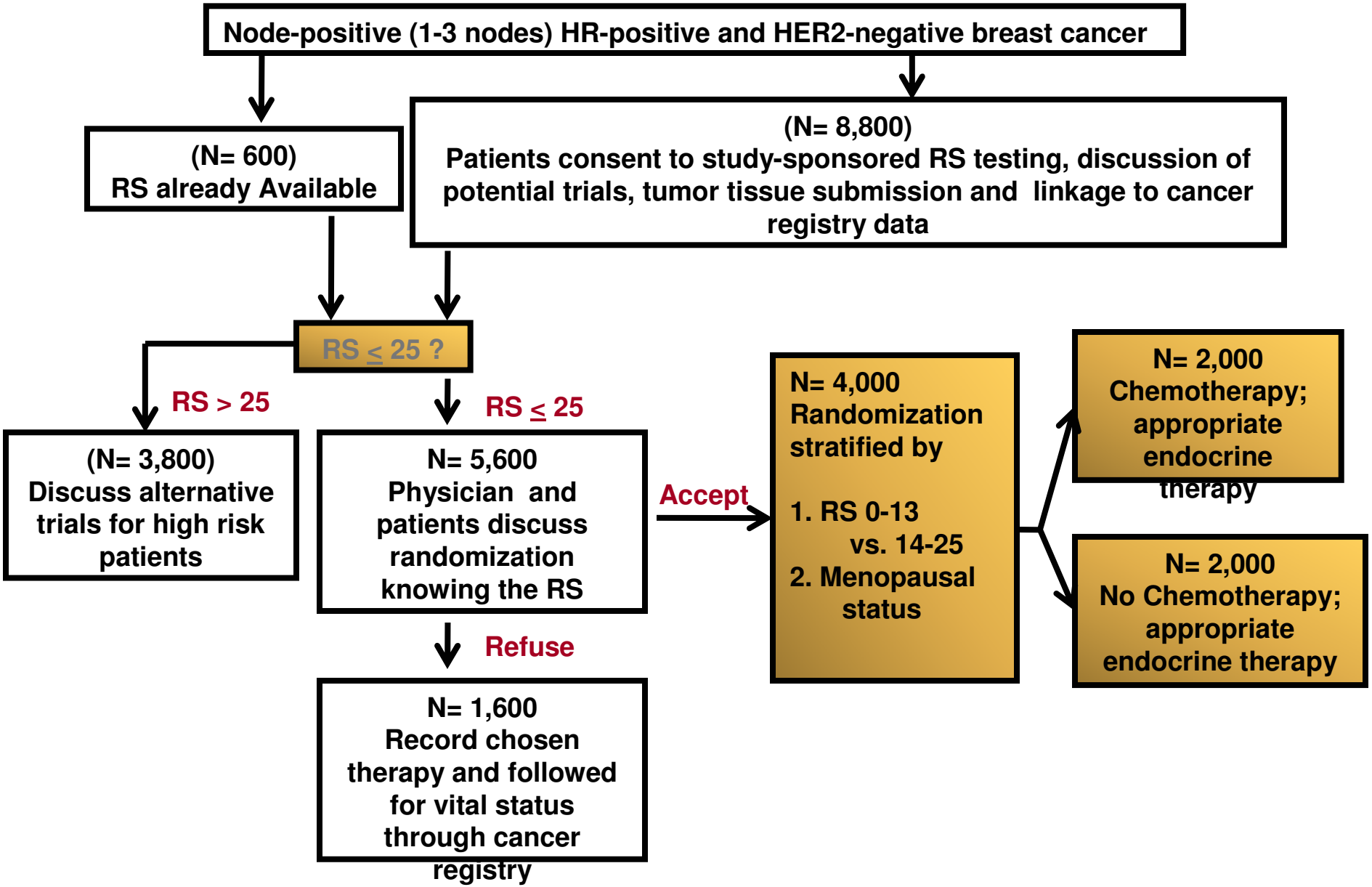
Primary Analysis:

- Test of interaction of RS with randomized treatment assignment

Other Goals:

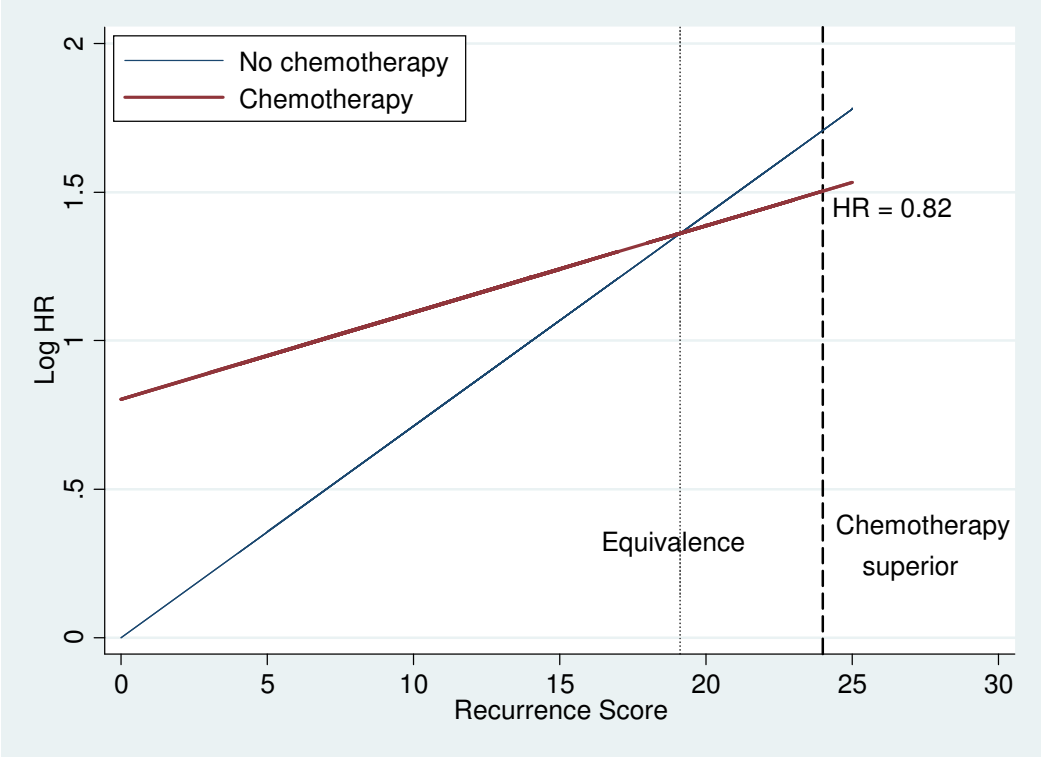
- If interaction is statistically significant, determine Cut-off of Risk Score above which chemotherapy benefits these patients.
- Assess costs of chemotherapy
- Assess QOL of chemotherapy
- Other biomarker comparisons of the two randomized groups

Schema and Patient Flow



Estimating the cut-point for chemotherapy being efficacious

- Use the upper bound of the 95% CI for the estimated equivalence point θ

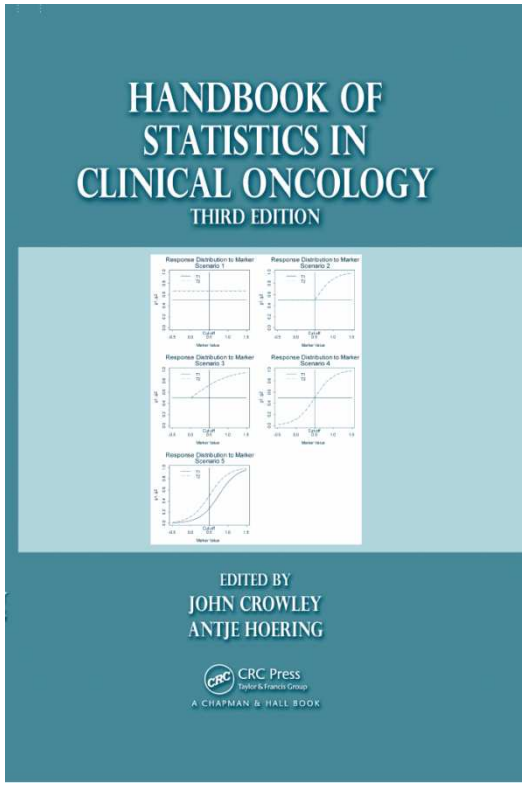


General Guidelines

- The **marker strategy design** tends to be inefficient to compare efficacy difference of two treatments. Patients in two different randomized arms are treated with the same therapy.
  - Can be used when marker is very prevalent.
- The **targeted design** performs the best in all scenarios with an underlying marker. But
  - More patients still need to be assessed for their marker status.
  - No information is gained on marker-negative patients.

  Use targeted design if
  - There is certainty that the new therapy won't help marker-negative patients.
  - Cut-point is well established.
  - Marker is rare in population.
- **Use randomize-all design with split alpha if**
  - There is the possibility that the new treatment is beneficial for marker-negative patients.
  - Marker prevalence is relatively high.

    Both the overall and the targeted hypothesis can be tested with only a modest increase in sample size.



Thank You

My Collaborators

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John Crowley, PhD

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