Clinical Trial Designs for Targeted Agents

John Crowley

Redefining Cancer Research & Clinical Trials
Primary Questions for an Anticancer Agent

Dose-finding/dose-ranging questions
• What is a **good dose and schedule** for this agent?
• What is the toxicity profile for this agent?

Activity/efficacy questions
• Does this agent have activity/efficacy for patients with cancer?
  - If so, in which tumor types?
  - For all patients, or only in **selected subsets**?
Cytotoxic Versus Targeted Agents

**Cytotoxic Agents:**
Exploit mechanisms that are important in mitosis to kill dividing cells (traditional chemotherapy agents)

**Examples for Targeted (Cytostatic) Agents:**

**Antiangiogenic Agents:** Inhibit the formation of new blood vessels, e.g. Thalidomide and Lenalidomide.

**Proapoptopic Agents:** Promote tumor cell death, e.g. Imatinib.

**Epidermal Growth Factor Receptor (EGFR) Inhibitors:** Inhibit tumor cell division, e.g. Gefitinib and Erlotinib.

**Cytotoxic agents** do not distinguish between different kinds of cells. **Targeted agents** only interfere with a specific pathway or specific cell. Difference in **degree**. Difference in **kind**.

Raises new questions that need to be addressed in Trial Designs.
Targeted Agents

- Cytotoxics
  - Target Dividing Cells
- Targeted Agents (Cytostatic?)
  - More Selective Targets
    - Collateral Damage (Toxicity)
    - Collateral Benefit (Unplanned Targets)
**Definitive TX**
Reg #1
Projected 840 pts

CDDP 50 mg/2
d 1, 8, 29, 36
VP-16 50 mg/m2
d 1-5, 29-33
XRT 1.8-2 Gy

Accrued: 620
Eligible: 575

**Consolidation**
Reg #2

DOCETAXEL 75 mg/m2 x 3 cycles

Accrued: 574
Eligible: 412

**Maintenance**
Reg #3
642 pts (80%)

PLACEBO

GEFITINIB 500 mg/day
250 mg/day (5-1-03)

Accrued: 263
Eligible: 255
Overall Survival

N | gefitinib 124 | Placebo 131
---|---------------|-------------
Events | 43 | 32
Median in Months | 19 | 29

Months After Randomization
Phase I Trials

- Safety
- Dose Finding
  - Cytotoxics
    - Monotone Dose-Toxicity Curve
  - Cytostatics
    - Unknown Dose-Toxicity Curve
Traditional Phase I paradigm (give as high a dose as possible)

• Estimate the Maximum Tolerated Dose (MTD), ie. the dose where Dose Limiting Toxicity (DLT) occurs with a specified probability, \( p_{MTD} \) (typically 20-40%)
• Avoid treating patients at doses too far above the MTD (to avoid more extreme toxicity)
• Avoid treating patients at doses too far below the MTD (since such doses are unlikely to be effective)
• Use relatively small numbers of patients (15-30)
Dose settings

- Almost all Phase I studies involve a set of pre-specified dose levels, representing points along a continuous range for a drug (often in combination with others).

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Modified Fibonacci</th>
<th>Half-log</th>
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<tbody>
<tr>
<td>1</td>
<td>$d_1$</td>
<td>$d_1$</td>
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<tr>
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<td>$2 \cdot d_1$</td>
<td>$3 \cdot d_1$</td>
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<tr>
<td>3</td>
<td>$1.67 \cdot d_2$</td>
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<td>$1.5 \cdot d_3$</td>
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<td>$3 \cdot d_5$</td>
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<tr>
<td>7</td>
<td>$1.33 \cdot d_6$</td>
<td>$10 \cdot d_5$</td>
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</table>
Design paradigms

• ‘Traditional’ algorithmic designs (e.g. 3+3)
  – use empirical algorithms based on outcomes in a small number of patients
  – at each dose level, there is a decision either to escalate or stop the trial and declare the MTD found
  – there is no (explicit) statistical basis for the algorithm

• Newer designs (e.g. CRM)
  – explicitly incorporate a statistical dose-response model, either to define dose escalation or final estimate of MTD
  – permit both escalation and de-escalation
  – some are Bayesian in nature
Dose-Toxicity Curve for Cytotoxic Agents
Dose-Toxicity and Dose-Response
Targeted Therapies: What is Different?

Mechanism of action is not straightforward

- Unknown dose-efficacy curves
- Dose-toxicity relation may not be monotonic
  - Monotone non decreasing
  - Quadratic
  - Increasing with a plateau
Dose-Toxicity Curve for Cytostatic Agents
Dose-Toxicity and Dose-Response
Finding a Good Dose for Cytostatic Agents Based on Phase I/II Trial

- Use a traditional Phase I trial design (such as 3+3 or CRM) to determine MTD.
  - Clinical Investigators participate hands-on in Phase I trials and are familiar and comfortable with these type designs.
  - Clinicians typically want to test a new agent for toxicity first even if the agent is presumed not to be toxic.
- Test 2 different dose levels (MTD and dose level immediately below) in a Phase II selection design.
  - Gain information on efficacy and toxicity on a larger cohort (~20 patients). 3 to 6 patients is often too small a sample size to determine efficacy and toxicity of a dose.
  - Patient population of Phase I and Phase II trials is typically different; this design allows for a more general patient population for the Phase I part and a patient population with a specific tumor type (for which the agent is designed to target) in the Phase II part.
Model Assumptions for Simulation Studies

- Toxicity and efficacy are modeled from a correlated binomial with the odds ratio as a measure of association between toxicity and response.
- Let the marginal probabilities (for toxicity and efficacy) logistic

\[
\Pr(Y = 1) = \frac{\exp(x\beta)}{1 + \exp(x\beta)}
\]

- Let \( p_{ij} \) be the joint probability for toxicity \( i = (0,1) \) and efficacy \( j = (0,1) \). The odds ratio \( \psi \) is defined by \( \psi = p_{11} p_{00}/p_{10} p_{01} \). The joint probability \( p_{11} \) can be expressed in terms of the marginal probabilities \( p_1 \) and \( p_2 \) as follows:

\[
p_{11} = \begin{cases} 
1/2(\psi - 1)^{-1} \left( a - \sqrt{a^2 + b} \right) & \text{for } \psi \neq 0 \\
p_1 p_2 & \text{for } \psi = 0,
\end{cases}
\]

where

\[
a = 1 + (p_1 + p_2)(\psi - 1)
\]

\[
b = -4\psi(\psi - 1)p_1 p_2
\]
Simulation Studies

- Phase II modified selection design
  - Randomize 40 pts to two arms:
    - Arm 1: Dose level determined by phase I portion
    - Arm 2: Dose level immediately below Arm 1
  - Determine power of test statistic of each arm individually by performing a simple hypothesis test.
    - H₀: p ≤ 0.05; Hₐ: p ≥ 0.30.
  - Determine probability of dose level being too toxic in ph II.
  - Determine the probability of picking dose with higher efficacy, while maintaining acceptable toxicity level.

- Phase I/II combined
  - Determine probability of reaching “best” dose in ph I/II
  - Determine probability of reaching “good” dose in ph I/II
  - Compare our results to traditional ph I/II design (single arm ph II) using the same sample size N=40.
Conclusions/Discussion

- Straight-forward, easily implemented design.
- 40 patients in the Phase II portion yields good power/significance for testing efficacy at 2 dose levels.
- The traditional design fares better if the true efficacy is close to the alternative hypothesis and if toxicity is negligible.
- In all other scenarios our proposed design fairs better than or the same as the traditional design.
- A possible future consideration would be to randomize patients to three dose levels; the dose level determined to be the MTD by the Phase I trial, the dose levels right below and right above that dose.
- This would obviously require continuous toxicity monitoring in the Phase II portion and appropriate toxicity stopping rules for the higher dose levels.
Phase II Trials

• Efficacy
• Endpoints
  – Response
  – Disease Control Rate
  – Progression-Free Survival
  – Overall Survival
Single Arm Phase II Designs

- Formulated as test of $H_0: \ p=p_0 \ vs \ H_A: \ p=p_A$
  - $p$ is the probability of response (or DCR or PFS at a specific time point)
  - $p_0$ insufficient activity to pursue
  - $p_A$ activity of interest
Standard Two Stage Design
“Cocker Spaniel”

• Accrue patients in two stages
• Stop early only if unpromising (futility)
• Stop after the first stage if the alternative is rejected at the .02 level
• Conclude active if null is rejected at final stage
• [http://www.crab.org/Calculators.asp](http://www.crab.org/Calculators.asp) – two stage
Example of Cocker Spaniel Design

• Test Null Hypothesis of 5% vs Alternative of 25%
• Two Stage Design
• 0/15, Stop. Else Proceed to 25
• 4/25 Means Success
Phase II Trials for Cytostatics

• Endpoints Other Than Response May Need to be Used
  – Disease Control Rate
  – Progression Free Survival at 6 Months
Phase II Trials with Multiple Subgroups

- Due to patient or tumor heterogeneity, patients within a traditional Phase II study may not respond equally to a new treatment.

- Potential subgroups of patients include different histologies or genetically defined subgroups.
A Single Trial versus Multiple Smaller Trials

- Conducting a single Phase II study across subgroups can be problematic. A stratum where there is activity would be combined with other strata without activity and lead to an overall false negative conclusion.

- Alternatively, conducting multiple Phase II studies each with a separate accrual goal may be logistically difficult and inefficient, with no joint learning across subgroups.
Single Study versus Multiple Subgroup Phase II Studies

![Diagram showing one study versus three subtype specific studies.]

Two Classes of Multi-Strata Phase II Studies

![Diagram showing multi-subgroup study versus targeted subgroup study.]

Basic Idea: Extend Simple Two Stage Phase II

• Consider each subgroup and stop if insufficient activity in that subgroup
• Also stop the entire study if minimal overall activity
• Target alternative response rate will be larger for a given subgroup than the overall study
• Look at data after every 5-10 patients for the entire study, after some minimum subgroup sizes have been met
Hypothetical Example: Soft Tissue Sarcoma with 3 Subtypes

- Frequencies of subtypes (A, B, C) (50%, 30%, 20%)
- Null hypothesis $H_0: R = .05$
- Alternative for a subtype $H_{As}: R = .25$
- Minimum (15) and maximum (25) sample sizes generated by a standard two stage design
- Overall alternative for the study $H_A: R = .15$
- Futility monitoring for subgroup and overall
Generate Many Hypothetical Phase II Studies

• Anticipated Realities
  – No improved activity; (.05,.05,.05)
  – Improved activity in frequent subtype (.25,.05,.05)
  – Improved activity in infrequent subtype (.05,.05,.25)
  – Limited activity in all subtypes (.15,.15,.15)

• Generate 5000 simulated studies

• Tabulate the results
No Improved Activity across Subgroups

<table>
<thead>
<tr>
<th>Accrual</th>
<th>Response</th>
<th>N(Simp)</th>
<th>Power(Simp)</th>
<th>N(Comb)</th>
<th>Power(Comb)</th>
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<td>0.50</td>
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<td>20.01</td>
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<td>20.77</td>
<td>0.04</td>
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</table>

Experiment-wise Power (Simp) = 0.1042, Experiment-wise Power = 0.0916

18% reduction in patients

Sample size reduction under Null
Improved Activity in Frequent Subtype

Retains sample size and power of best single arm

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<table>
<thead>
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<tbody>
<tr>
<td>0.50</td>
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<tr>
<td>0.30</td>
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<td>0.20</td>
<td>0.05</td>
<td>20.44</td>
<td>0.03</td>
<td>20.22</td>
<td>0.04</td>
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Experiment-wise Power (Simp) = 0.9026, Experiment-wise Power (Comb) = 0.9054.

Retains good subgroup properties
Ordered Activity
(Targeted Phase II)

- Consider targeted subgroup and overall study
- Test for futility for both targeted subgroup and overall study
- If the subgroup is determined inactive then entire study is closed
- Generate 5000 simulated studies
- Tabulate the results
Targeted Subgroup

<table>
<thead>
<tr>
<th>Accrual</th>
<th>Rate</th>
<th>N(Simp)</th>
<th>Power(Simp)</th>
<th>N(SubT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.50</td>
<td>20.01</td>
<td>0.04</td>
<td>17.95</td>
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<tr>
<td>2</td>
<td>0.30</td>
<td>20.13</td>
<td>0.03</td>
<td>14.09</td>
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<td>3</td>
<td>0.20</td>
<td>20.72</td>
<td>0.04</td>
<td>12.46</td>
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</table>

Power (Simp) = 0.0988
Power (Comb) = 0.0788
Target Specific Power = 0.0288

27% sample size reduction

But retains good power under alternative
Alternative: activity in targeted subset of patients

<table>
<thead>
<tr>
<th></th>
<th>Accrual</th>
<th>Rate</th>
<th>N(Simp)</th>
<th>Power(Simp)</th>
<th>N(SubT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.50</td>
<td>0.20</td>
<td>24.60</td>
<td>0.76</td>
<td>24.44</td>
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<tr>
<td>2</td>
<td>0.30</td>
<td>0.05</td>
<td>19.86</td>
<td>0.04</td>
<td>19.75</td>
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<tr>
<td>3</td>
<td>0.20</td>
<td>0.20</td>
<td>24.64</td>
<td>0.75</td>
<td>24.24</td>
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</table>

Power for targeted subgroup: 92%
Observations from the Simulations

- In null case, potentially substantially reduced sample size over multiple Phase II studies
- If activity in single group, good power for that group. About the same sample size as individual Phase IIs for the negative subtypes
- If modestly effective overall, then the combined analysis yields good power
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. There is evidence that *Trastuzumab* has some effect on Her-2 negative breast cancer patients.
  - E.g. *Imatinib*, developed to target CML also destroys tumor cells that are c-kit positive (GI stromal tumors)

- 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?
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.
Prognostic and Predictive Factors

- **Prognostic**
  - Main Effect
  - Effect Does not Vary with Treatment
  - All That Can Be Concluded from Single Arm Trials

- **Predictive**
  - Interaction
  - Effect Differs by Treatment
  - Can Only Be Assessed in Multi-Arm Trials
Clinical Trial Designs for Phase III Trials for Targeted Therapy

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

  Register → Randomize → Assess Marker → T2

  - T1
    - M+
    - M-
    - M+
    - M-

- **Targeted Design**: Randomize marker positive patients only

  Register → Assess Marker → Randomize M+

  (M-)

  → T1

  → T1

  → M+

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

  Register → Assess Marker → Randomize

  → Tx based on M

  → M+

  → M-

  → T2

  → T1

  → T1

  → M+

  → M-

M+: marker positive pts. ; M-: marker negative pts. ; T1: Treatment 1; T2: Treatment 2.
Possible Underlying Marker Scenarios

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
IPASS Study Design

**Patients**
- Chemonaïve
- Age ≥18 years
- Adenocarcinoma histology
- Never or light ex-smokers*
- Life expectancy ≥12 weeks
- PS 0-2
- Measurable stage IIIIB / IV disease

**Gefitinib (250 mg / day)**
1:1 randomisation

**Carboplatin (AUC 5 or 6) / paclitaxel (200 mg / m²) 3 weekly**

**Endpoints**
**Primary**
- Progression-free survival (non-inferiority)

**Secondary**
- Objective response rate
- Overall survival
- Quality of life
- Disease-related symptoms
- Safety and tolerability

**Exploratory**
- Biomarkers
  - EGFR mutation
  - EGFR-gene-copy number
  - EGFR protein expression

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*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; #limited to a maximum of 6 cycles
Carboplatin / paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor
Progression-free survival in ITT population

Gefitinib demonstrated superiority relative to carboplatin / paclitaxel in terms of PFS

HR (95% CI) = 0.741 (0.651, 0.845) p<0.0001

Primary Cox analysis with covariates
HR <1 implies a lower risk of progression on gefitinib
Progression-free survival in EGFR mutation positive and negative patients

**EGFR mutation positive**
- **Gefitinib** (n=132)
- **Carboplatin / paclitaxel** (n=129)

HR (95% CI) = 0.48 (0.36, 0.64)  
*p*<0.0001
- No. events gefitinib, 97 (73.5%)
- No. events C / P, 111 (86.0%)

**EGFR mutation negative**
- **Gefitinib** (n=91)
- **Carboplatin / paclitaxel** (n=85)

HR (95% CI) = 2.85 (2.05, 3.98)  
*p*<0.0001
- No. events gefitinib, 88 (96.7%)
- No. events C / P, 70 (82.4%)

At risk:
- Gefitinib:
  - At risk: 132
  - At risk: 108
  - At risk: 71
  - At risk: 31
  - At risk: 11
  - At risk: 3
  - At risk: 0

- C / P:
  - At risk: 129
  - At risk: 103
  - At risk: 37
  - At risk: 7
  - At risk: 2
  - At risk: 1
  - At risk: 0

Treatment by subgroup interaction test, *p*<0.0001

**ITT population**
- Cox analysis with covariates
Marker Positive

Enrichment Design

*Only marker+ patients are randomized and/or treated*

All patients → Marker assay

(R = randomization)

Marker + → New drug

Marker − → Control? → OFF study

Need to know the “right” marker and have good marker assay
Targeted (Marker+) Design for Assessment of a Targeted Therapy

• Advantages:
  – Smaller sample size
    • Example trastuzumab in HER2+ breast cancer
    • 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)
ERCC1-Customized Chemotherapy in Advanced NSCLC

- Control arm: docetaxel / cisplatin
- Experimental arm: ERCC1 levels
  - Low ERCC1 mRNA: docetaxel / cisplatin
  - High ERCC1 mRNA: docetaxel / gemcitabine

Planned: 340 patients; included: 300

SLCG; Response Genetics
Targeted (Marker+) vs Marker Strategy

- Proposed SWOG Trial in Advanced Nonsmall Cell Lung Cancer, PS 2
  - EGFR+ -- Erlotinib vs Chemotherapy
  - 30% EGFR+
    - Marker Positive – 200 patients, 667 Screened
    - Marker Strategy – 1700 patients
Marker Strategy

• When Would You Use the Marker Strategy Design?
  – When All (or Almost All) Patients Will Receive “nonstandard” Treatment
    • Human Tumor Cloning Assay in Extensive Small Cell Lung Cancer, SWOG 8610
    • Test of Effectiveness of Imaging Technology
    • Treat by GEP
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 is a better predictor of benefit than EGFR IHC.

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
PFS HR = 1.2
Power: 90%
\[ \alpha = 0.015 \]
N = 1546

EGFR FISH +
PFS HR = 1.33
Power: 90%
\[ \alpha = 0.02 \]
N = 618
Prevalence of FISH+ ~ 50%, power = 92%, overall alpha=.025 (1-sided)

**Hypotheses to be tested:**

**H1: Entire cohort:** Addition of Cetuximab increases median PFS 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%.

<table>
<thead>
<tr>
<th>Design</th>
<th>N</th>
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<tbody>
<tr>
<td>All Comers Design with split alpha (H1 and H2)</td>
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<td>All Comers Design (H1 only)</td>
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<td>Marker Positive Design (H2 only)</td>
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<tr>
<td>Marker Strategy Design</td>
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</table>
Designs for Targeted Agents

• What Design Strategy to Choose?
• Marker(s) Known?
  – No – All Comers, Measure Something
• Marker(s) not Measured Well – All Comers, Measure Marker(s), Possibly Split Alpha
• Else – Marker+ Design
• Marker Strategy Design only if “Strategy” Makes Sense
Possible Underlying Marker Scenarios

**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

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

**M-:** Marker negative, Marker value < cut-point
SWOG S1007 (RxPONDER)

• Excludes women with HER2 positive disease, more than 3 positive nodes, and RS > 25

• Women with RS 0-25 are randomized to
  1. Endocrine therapy and no chemotherapy or
  2. Endocrine therapy + chemotherapy
SWOG S1007

• Trial tests prediction of chemotherapy benefit based on Oncotype Dx Risk Score
  – Survival benefit of chemo (if it exists) should increase with RS
  – Optimal RS cutpoint for giving chemo will be estimated

• Assess costs of chemotherapy
• Assess QOL of chemotherapy
• Other biomarker comparisons of the two randomized groups
Schema and Patient Flow

Node-positive (1-3 nodes) HR-positive and HER2-negative breast cancer

(N= 600)
RS already Available

RS ≤ 25 ?

RS > 25

(N= 3,800)
Discuss alternative trials for high risk patients

RS ≤ 25

N= 5,600
Physician and patients discuss randomization knowing the RS

N= 4,000
Randomization stratified by
1. RS 0-13 vs. 14-25
2. Menopausal status

Accept

N= 2,000
Chemotherapy; appropriate endocrine therapy

Refuse

N= 1,600
Record chosen therapy and followed for vital status through cancer registry

N= 8,800
Patients consent to study-sponsored RS testing, discussion of potential trials, tumor tissue submission and linkage to cancer registry data

N= 2,000
No Chemotherapy; appropriate endocrine therapy
SWOG S1007 statistical models

- **Alternate hypothesis**

  \[ \lambda(t; \text{chemo}, \text{RS}) = \lambda_0(t) \exp(\beta_1 \text{chemo} + \beta_2 \text{RS} + \beta_3 \text{chemo} \times \text{RS}) \]

- **Intermediate hypothesis**

  \[ \lambda(t; \text{chemo}, \text{RS}) = \lambda_0(t) \exp(\beta_1 \text{chemo} + \beta_2 \text{RS}) \]

- **Null hypothesis**

  \[ \lambda(t; \text{RS}) = \lambda_0(t) \exp(\beta \times \text{RS}) \]
Estimating the cutpoint for chemotherapy being efficacious

Use the upper bound of the 95% CI for the estimated equivalence point $\theta$
Thanks to My Collaborators

Antje Hoering
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Mary Redman
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References


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