Design considerations for Phase II trials incorporating biomarkers

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Enhancing the Design and Conduct of Phase II Studies
Society for Clinical Trials, May 18, 2014
Disease-based Trials

Register → Experimental Agent → Specific Cancer

Disease-based and Marker-based Trials

Register → Marker Assessment → Exp. Agent targeting a specific pathway → Specific Cancer

Marker-based Trials

Register → Marker Assessment → Exp. Agent targeting a specific pathway

Breast cancer
Colon cancer
Lung cancer
Thyroid cancer
Prognostic and Predictive Markers

• Prognostic
  • Effect Does not Vary with Treatment
    • Main Effect
    • Can Be Concluded from Single Arm Trials

• Predictive
  • Effect Differs by Treatment
    • Interaction
    • Can Only Be Assessed in Multi-Arm Trials
Predictive

Prognostic

- - - Exper Trt
--- Std of Care

Marker +

Marker -

Percent Survival

Time (years)
Drug candidates derailed in case of mistaken identity
PARP inhibitor that wasn’t highlights widespread flaws in preclinical studies.

Iniparib plus Chemotherapy in Metastatic Triple-Negative Breast Cancer
Joyce O’Shaughnessy, M.D., Cynthia Osborne, M.D., John E. Pippen, M.D., Mark Yoffe, M.D., Debra Patt, M.D., Christine Rocha, M.Sc., Ingrid Chou Koo, Ph.D., Barry M. Sherman, M.D., and Charles Bradley, Ph.D.*

Iniparib Phase III failed
We now know it is not a PARPi

Figure 2. Kaplan–Meier Estimates of Progression-free and Overall Survival Rates, According to Treatment Group. Dots represent patients whose data were censored.
False Biomarker Discovery Due to Reactivity of a Commercial ELISA for CUZD1 with Cancer Antigen CA125

Ioannis Prassas,¹,²* Davor Brinc,²* Sofia Farkona,² Felix Leung,² Apostolos Dimitromanolakis,² Caitlin C. Chrystoja,³ Randall Brand,³ Vathany Kulasingam,¹,* Ivan M. Blasutig,¹,* and Eleftherios P. Diamandis¹,³,*

Conclusions: We conclude that poor characterization of commercial ELISA assays is a factor that could lead to false biomarker discovery. To our knowledge, this is the first report documenting that a commercial ELISA marketed for one analyte (CUZD1) may, in fact, recognize a different, nonhomologous antigen (CA125).
Issues to Consider

• Strength of pre-clinical evidence of the marker
  • Restrict patients based on marker status or enroll all patients regardless of the marker status?

• Reproducibility and validity of assays
  • Local versus Central Testing

• Prevalence of the marker
  • Low versus moderate
  • Threshold for cut offs?

• Feasibility and timing of assessments

• Multiple biopsies: serial, paired?

• Key Message: You cannot have many moving parts or unknowns in the design of a trial
Traditional design: All comers strategy

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

Register → Assess Marker → Randomize

Biomarker tested on all patients, but treatment assignment/randomization is not based on marker results. Retrospective marker-subgroup analyses

M+: marker positive pts.; M-: marker negative pts.; T1: Treatment 1; T2: Treatment 2.

In a broad sense, all trials are *selective*, but in the setting of biomarkers, an all-comers design strategy does not restrict eligibility based on molecular features.
Enrichment or targeted trial design

- Randomize marker positive patients only
Enrichment Design example: Vemurafenib in Melanoma with BRAF V600E Mutation

• Compelling evidence: Prior phase I and phase II trials demonstrated response rates of more than 50% in patients with metastatic melanoma with the BRAF V600E mutation.
  • 5 patients with WT did not respond in Phase I to therapeutic doses of Vemurafenib

• Phase III trial: Patients with BRAF V600E mutation were randomized 1:1 to vemurafenib with dacarbazine

• Central testing: At one of five central laboratories in the United States, Germany, and Australia.

• Vemurafenib was associated with a relative reduction of 63% in the risk of death and of 74% in the risk of either death or disease progression, as compared with dacarbazine (P<0.001 for both comparisons).

Chapman et al., NEJM 2011
NCI Precision Medicine Initiatives

MATCH Trial (ECOG-ACRIN)

- REGISTER
- Genetic sequencing
  - Molecular target / marker detected
  - No actionable mutation identified
  - Stable Disease
    - Complete or partial response assessed after every few cycles
  - Targeted Agent matching mutation
    - Disease Progression at any time
      - Check for additional actionable mutations
        - None identified
          - Off study
        - Continue on study agent until disease progression (DP)

- Endpoints: Response Rate and 6-month Progression-free Survival Rate
  - Success: > 25% RR, and/or > 35% 6-month PFS rate

~3000 patients to be screened
~1000 enrolled
~15 drugs to be studied

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Using markers to restrict trial eligibility: beware

Ongoing study of Herceptin in patients with low (1+ or 2+) HER2-positive BC.

Paik et al, NEJM 2008
Hayes et al., NEJM 2011
Marker by treatment interaction design

Randomize all patients, stratified by marker status.

Mostly used in settings with two approved regimens.

Sargent et al., JCO 2005; Mandrekar et al. JCO 2009
Randomized Proteomic Stratified Study of Second-Line Erlotinib versus Chemotherapy in Patients with Inoperable Non-Small Cell Lung Cancer

PROSE Trial

VeriStrat is a serum based protein assay.

Initial Registration

2nd line NSCLC with specimen → VeriStrat testing

Strata

VeriStrat Good → Erlotinib (96)

VeriStrat Poor → Pemetrexed or Docetaxel (88)

Randomize

Erlotinib (38)

Pemetrexed or Docetaxel (41)

Primary Endpoint: Overall Survival; Secondary: PFS, RR

Good group: No difference in OS; Poor Group: Chemo better than Erlotinib

Significant interaction between treatment and veriStrat classification (p=0.037)

Gregorc et al., ASCO 2013; WCLC 2013
Marker Strategy design

Randomize to marker-based vs. non-marker-based.

Sargent et al., JCO 2005; Mandrekar et al. JCO 2009
Enrichment followed by “modified” marker strategy design

Patients with refractory cancer (all tumor types) → Informed consent signed → Tumor biopsy → NGS+ Cytoscan HD +IHC → Bioinformatics → Informed consent signed → Specific therapy available

Non eligible patient → Molecular biology board

Eligible patient → Therapy based on molecular profiling - Approved molecularly targeted agent → Conventional therapy based on oncologist’s choice

Cross-over
SHIVA Design Details

• 6 months PFS = 15% in phase I cancer patients treated with cytotoxic agents
  - Hypothesis: 6 months PFS = 30% in the experimental arm (HR = 1.6)

→ 142 events with a type 1 error of 5% and a power of 80% in the bilateral setting
→ 200 patients should be randomized
→ up to 1,000 might have to be included
NCI Precision Medicine Initiatives
Enrichment followed by modified marker strategy design

M-PACT Trial

Tumor biopsy for sequencing

Marker Identified

Randomize

Arm A

Targeted therapy, targeting the identified marker

Disease Progression

Arm B

Conventional Therapy

No Marker Identified

Off-study

Endpoints: response rate and 4-month progression-free survival
Tumor Chemosensitivity Assay in recurrent platinum resistant Ovarian Cancer: Marker Strategy Design

Primary endpoint: compare response rates between the ATP-TCA based arm to that of the non-marker based arm

Design: 90 patients/arm; alpha=10%; power=80%; RR of 30% versus 50% (ATP-TCA arm)

Cree et al., anticancer drugs, 2007
Fig. 1

180 randomized

86 assigned physician’s-choice chemothe
94 assigned assay-directed

28 received \geq 1
50 received < 1
8 treatment ne

72 died
14 alive at analysis

86 assi PFS

Trial profile, showing the completing treatment. PI

**Fig. 3**

**Progression-free survival**

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>TCA</th>
<th>49</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC</td>
<td>38</td>
<td>22</td>
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</table>

**Overall survival**

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>TCA</th>
<th>74</th>
<th>55</th>
<th>36</th>
<th>20</th>
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<tbody>
<tr>
<td>PC</td>
<td>65</td>
<td>51</td>
<td>99</td>
<td>21</td>
<td></td>
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Kaplan–Meier survival curves for (a) progression-free survival and (b) overall survival, showing a trend towards improved progression-free survival (hazard ratio 0.56, 95% confidence interval 0.29–1.10) with no difference between the groups in overall survival (hazard ratio 1.01, 95% confidence interval 0.7–1.3). PC, physician’s choice; TCA, tumour chemosensitivity assay.

<table>
<thead>
<tr>
<th>Patients used during the trial, with the regimens used</th>
<th>Physician’s choice</th>
<th>Assay directed</th>
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</thead>
<tbody>
<tr>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>18</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

50/78 | 72/81
Learning Curve?

- Physician’s choice arm:
  - Oncologists switched to the use of similar combinations in the non-marker based arm as the ATP-TCA directed arm.
  - Late randomization – better PFS!
- ~ 70% Overlap in treatments on both arms – dilutes the treatment effect
- Dilutes the ability to distinguish treatment from marker effect!

![Graph showing progression-free survival](image)
Adaptive Designs

1. Begin Data Collection with Initial Allocation and Sampling Rules
2. Analyze Available Data
3. Revise Allocation and Sampling Rules per Adaptive Algorithm
4. Continue Data Collection
5. Stopping Rule Met?
6. Stop Trial or Begin Next Phase in Seamless Design
Adaptive Designs – Considerations

• Real time data on all aspects
  • Clinical – electronic data capture
  • Biomarkers – rapid testing, and quick turn-around times for patient assignment
  • Reliable short term (surrogate) endpoint

• Bias Issues:
  • Drift in patient population over time?
  • Unblinded trials: Concern that the treating physician noticing an increase in patient accrual to one arm versus the others?
  • Estimation rather than testing?

• What if the marker or assessment itself changes over time?
Direct Assignment Option Design

Randomize (1:1)

- Stop, efficacy
- Continue, Direct
- Continue, Randomize
- Stop, futility

No Interim Analysis-2 (direct design in Stages II/III)

- Stop, efficacy
- Continue, Direct
- Continue, Randomize
- Stop, futility

Null (PFS3 rate = 50%)

<table>
<thead>
<tr>
<th>IA-1 Decisions</th>
<th>IA-2 Decisions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Continue from first IA, randomize (58.7%)</td>
</tr>
<tr>
<td>Stop at first IA, efficacy</td>
<td>Stop at first IA, efficacy</td>
</tr>
<tr>
<td>Stop at first IA, futility</td>
<td>Stop at first IA, futility</td>
</tr>
</tbody>
</table>

With direct at both IA: 0.5% 26.1% 4.7% 3.1% 44% 3% 18.5%

Alternate (PFS3 rate = 75%)

<table>
<thead>
<tr>
<th>IA-1 Decisions</th>
<th>IA-2 Decisions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Continue from first IA, randomize (64%)</td>
</tr>
<tr>
<td>Stop at first IA, efficacy</td>
<td>Stop at first IA, efficacy</td>
</tr>
<tr>
<td>Stop at first IA, futility</td>
<td>Stop at first IA, futility</td>
</tr>
</tbody>
</table>

With direct at both IA: 8.1% 3.5% 24% 25.0% 8.8% 11.1% 19.4%
Tandem 2-step design

All-comers, with early stopping rule

Stage I

Too few responses in Stage I

Assess within Marker subset A

Continue with Marker A only

Stop

Too few responses

Promising results

Complete 2nd stage accrual

Stage II

Assess within Marker subset B

Continue with Marker B only

Stop

Too few responses

Promising results

Complete 2nd stage accrual

Promising results

Continue with All-comers

Marker subset A

Marker Stage I

Marker subset B

Marker Stage II

McShane et al., CCR 2009
SWOG S1400 Master Lung Protocol Schema

**Common Broad Platform**
**CLIA Biomarker Profiling**

- **Biomarker A**: Sub-study A
  - Drug A: SoC*
- **Biomarker B**: Sub-study B
  - Drug B: SoC*
- **Biomarker C**: Sub-study C
  - Drug C: SoC*
- **Biomarker D**: Sub-study D
  - Drug D: SoC*
- **Non-match Study**: Non-match drug
  - SoC*

*Experimental drug/regimen could be single agent or a combination with SoC
SoC can vary by biomarker. SoC = Standard of Care*
Phase II/III Design: SWOG S1400

- Phase II Interim Analysis: 55 PFS events
- Phase III Interim Analyses
- Complete Accrual
- Final Analysis: 256 OS events

Futility established → Stop

PFS: Primary endpoint for Phase II
OS: Primary endpoint for Phase III

Follow-up period
Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing


Intratumor heterogeneity may foster tumor evolution and adaptation and hinder personalized-medicine strategies that depend on results from single tumor-biopsy samples.
PROstate cancer Medically Optimized genome enhanced ThErapy – I (PROMOTE)

1. CRPC stage patients initiating treatment with abiraterone acetate (n=200)
   - 1st biopsy of metastatic tumor tissue and obtain germline DNA

2. 12-week PFS Composite response assessment endpoint OR treatment failure prior to 12 weeks
   - 2nd biopsy of metastatic tissue

3. Change of treatments in disease progressors

4. Abiraterone continued in responders

5. Continued monitoring as per standard of care – and follow-up for overall survival (OS) for the entire cohort

- Therapeutic options for treating advanced stage castrate resistant prostate cancer (CRPC) patients currently based solely on patient characteristics.

- Understanding the genomics of individual tumors to identify novel mutations in “druggable” genes or pathways might greatly improve outcomes.
PROMOTE-1 features:

- Activated May 28, 2013 (~200 patients)
  - Identification of molecular signatures associated with response/resistance to abiraterone
  - Perform whole genome sequencing of tumor DNA and RNA-sequencing
  - Germline DNA prior to abiraterone therapy

- Design strategies for PROMOTE-II:
  - Compelling evidence from PROMOTE-1: Enrichment design
  - Fairly strong, but not compelling evidence from PROMOTE-I: Stratified design with treatment and biomarker interaction to validate the genomic signature as a predictive biomarker
  - PROMOTE-1 evidence preliminary and exploratory: adaptive design
Overall Design Strategy Recommendations

• Phase I: No restrictions
  • Use expansion cohorts to further understand marker-subgroup effects, endpoints etc.

• Phase IIa (optional): Single arm, enriched
  • Proof of concept

• Phase IIb: Randomized phase II unselected
  • Primary comparison: Marker (+)
  • Randomize enough Marker (-) to demonstrate lack of benefit
  • Consider adaptive designs

• Phase III: Based on randomized phase II
Closing Comments

• An optimal design can help to predict which patient is likely to benefit from a treatment and/or requires intensive treatment. This helps to:
  • Improve the success rate of clinical drug development
  • Bring down trial costs in terms of patients and resources
  • Prevent patients from being exposed to toxic treatments that may not benefit them.

• Choice of trial design depends on
  • Biological rationale
  • Marker prevalence
  • Assay performance
  • Strength of preliminary evidence
  • Incremental benefit of marker-based selection
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