Novel PK/PD Model Design and Therapeutic Translation for Targeted Agents in Oncology

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Outline

• Do we need new designs for targeted agents?
  ▸ Why not continue using earlier designs?

• What do we need to measure?
  ▸ What is wrong with past methods?

• What are some proposals?

• Where are we now?
Molecular Targets

• How do cancer cells work?
• ⇒ Identify targets
  ‣ Initiation,
  ‣ Angiogenesis
  ‣ Metastasis

• How best measure PD effect?
  ‣ Radiographically? Biopsies?
Issues

• Newer anticancer agents target molecular pathways or genetic mutations
  - Trastuzumab (Her-2 pos. breast cancer)
  - Tarceva (EGFR inhibitor)
    ‣ Sometimes not as specific
  - Sorafenib
    ‣ Originally Raf-1 inhibitor but found active against B-Raf, VEGF-R1, PDGFR, FLT-3
PD And Clinical Utility

• Assay development is critical
  ‣ Define target pop’n & trt effect
  ‣ Must be
    - Reproducible & meaningful
• PD effect on target ≠ clinical benefit
  ‣ Ultimately need to show clinical benefit
Measures of Clinical Benefit

• Two common measures of efficacy/activity
  ▸ Phase II: tumor response (shrinkage)
    - RECIST
  ▸ Phase III: overall, disease-free, or progression-free survival

• Some targeted agents show survival & clinical benefit despite modest response in phase II

*Suggests need for new designs/endpoints*
Problems W/ Usual Endpoints

• Measurements often difficult
• Response (progression) criteria not uniform
  ‣ WHO vs RECIST 1.0 vs RECIST 1.1
• Anatomic change may not reflect response
  ‣ What is measurable?
• Pseudoresponse and pseudoproggression exist
Tumor Immunotherapy

- Immunotherapy may cause apparent increase
  - Invading lymphocytes - PD by RECIST

- PD by RECIST

\[\text{Immune Response Criteria for Tumor Immunotherapy?}\]
Patterns of Response to Ipilimumab Observed in Advanced Melanoma


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Pseudoprogression

Increased enhancement following surgery, radiation

Pseudoresponse

CT & MRI: reduced permeability to contrast, not tumor response

1 day after cediranib (pan-VEGFR inhibitor)

Dependence on Modality

Dependence on Modality (2)

FLAIR image at baseline

PD: FLAIR image after 7 mos Avastin

Modality-Specific Response Criteria

- **FDG-PET to assess response** (tumor metabolism)
  

- **Criteria for evaluating antitumor responses with immunotherapeutic agents**
  

- **Response criteria for high-grade gliomas**
  

- PERSIST

- Immune-Related Response Criteria (ir-RC)

- RANO Working Group Criteria
Biomarker-Based Designs

• Goal: Find which treatment works for which pts
  ‣ Discovery or validation?
    - Retrospective: Lack of comparability
      ‣ Supportive care differences
      ‣ Assay differences over time
  ‣ Randomization: ensures comparable grps
    - May not be feasible
Retrospective Validation

- Evaluate marker-by-trt interaction
  - Retrospective analysis of completed RCT
- Retrospective study OK if
  - Prospective RCT not possible for ethical or other reasons
  - Prospective RCT not feasible
    - e.g., large sample size or long follow-up

Simon et al JNCI 2009
Needs of Retrospective Study

- Available on all or most pts
- Prospective statement of
  - hypotheses,
  - analysis plan,
  - inclusion/exclusion,
  - algorithms for assay scoring
Prospective Validation

• Designs
  ▸ All-comers or unselected designs
  ▸ Hybrid designs
  ▸ Enrichment designs
  ▸ Adaptive randomization designs
All-Comer (Unselected) Design

- Stratify by marker status, randomize separately
- Within-group sample size & power
  - Trt-by-marker interaction

```
Marker
  +
  Rand
  |
  Rand
  |
  Trt A

  -
  Rand
  |
  Rand
  |
  Trt B
```

Trt A
Trt B
Hybrid Designs

• Randomize marker-positive subgroup
  ▸ Marker neg group gets standard of care
• Collect outcome and specimens for all pts
• Useful if
  ▸ Prior evidence is strong for subgroup efficacy
  ▸ Unethical to randomize pts with marker to other trts
Enrichment Designs

• Screen pts for presence or absence of marker
• Only include pts with (or without) marker
• Want to assess clinical benefit in subgroup defined by marker
• Not controversial if
  ▸ Drug’s mechanism of action is known
  ▸ Reliable & reproducible assay
  ▸ Strong preliminary data
Enrichment Designs

• Enrichment designs
  ‣ Fewer randomized pts but may need to screen more than regular RCT
  ‣ Need real-time marker assessment
  ‣ Assumes marker tells all of who benefits

• Learn which subpop’n to target
  ‣ Who may benefit?
  ‣ Who might not benefit?
Why Different Designs?

• Traditional designs based on tumor shrinkage
  ‣ Response versus non-response
  ‣ Highest dose assumed best
    - Efficacy vs. toxicity

• Targeted agents may not shrink tumors
  ‣ May stall or slow growth
  ‣ Stable disease may be goal
Principal Objective of Phase II

• Determine if a drug has sufficient activity to warrant further investigation

  ‣ Not clinical efficacy analysis
    - Clinical Efficacy \(\rightarrow\) Activity
    - Activity \(\leftrightarrow\) Clinical Efficacy

  ‣ Not estimating size of trt effect in larger pop’n
    - Explanatory vs. pragmatic
End Points Proposed in Literature

• Multinomial (incl progression and response)

• Progression-free survival & time to progression

• Biomarker-based
  McShane LM, Hunsberger S, Adjei AA. *Clin Cancer Res* 15:1898-1905, 2009

• Tumor size as continuous variable
Example of Enrichment Design

• Challenge for phase II studies of putative cytostatic agents

• Randomized discontinuation design
  ‣ What is it?
  ‣ Is it good? bad?

Randomized Discontinuation Design

- **Two-phases**
  - Open treatment phase
    - Find best dose, remove noncompliers, etc.
  - Randomize pts with SD in our version
    - Those who tolerate drug or
    - Those whose disease may be slowing
  - Double-blind RCT
Randomized Discontinuation Design

Open label

Response?  
Tolerate?  
Adhere?

Continue if CR/PR

Y

Continue therapy

Placebo*

* Switch back to therapy if PD

Out

T1

T2
Optimal RDD

- Apply decision theory to help choose design
  - Length of open-label phase
  - Length of follow-up after randomization
  - Number of patients to enroll
    - Function of number enrolled, durations of two phases, difference to detect, etc.

Trippa, Rosner, & Müller (to appear) Biometrics
Tumor Growth Model

• Gompertzian tumor growth

\[ \frac{dX_t}{dt} = a \cdot X_t - b \cdot X_t \cdot \log(X_t), \quad X_0 = x_0 \]

• Stochastic differential equation

  ‣ Allow for between-patient heterogeneity
  ‣ Allow for deviation from expected trajectory

\[ dX_{it} = \{ a_i \cdot X_{it} - b_i \cdot X_{it} \cdot \log(X_{it}) \} dt + \sigma_i X_{it} dW_{it} \]

\[ X_{i0} = x_{i0}, \quad t \in [0, T] \]
Steps to Proposed Construction

• Generate future pts’ tumor growth curves via model-based interpolation of historical data
  ‣ Gompertz diffusion process defined earlier
    - 3 parameters
  ‣ Interpolation makes it robust against possible deviations from model assumptions
  ‣ Construction easily interpreted & implemented
  ‣ Add treatment effect parameter
Using Historical Information for Prior

• Elicitation of expert opinion on tumor growth process across heterogeneous pop’n difficult

• Expert judgement about the three pivotal probabilities is available
  ‣ $p_e = \text{prob pt is eligible for randomization}$
  ‣ $p_0$ & $p_1 = \text{prob response for trt 0 & trt 1, resp.}$

• We only need elicitation for trt effect $\psi_i$
  ‣ $\psi_i$ is a function of 3 model parameters
Prior Elicitation & Specification

**Figure 3.**

Panel (i): The upper trajectory shows observed historical tumor growth data \( t_i \) under the control regimen. The lower trajectory shows imputed measurements and trajectory under the treatment regimen.

Panels (ii) and (iii): Median trajectories, 80% & 50% confidence bands of \( X_{1i,t} \sim \text{GP}(\tilde{\alpha}_j - \tilde{\psi}_j \tilde{\beta}_j, \tilde{\beta}_j, \tilde{\sigma}_j | X_{1i,t}^0, \ldots, X_{1i,t}^k = \tilde{X}_{1j,t}^0, \ldots, \tilde{X}_{1j,t}^k) \) under two alternative prior distributions for \( \{\tilde{\psi}_j\}_{M_j=1} \).

**Upper:** Obs historical tumor growth data (cntl)

**Lower:** Imputed meas & trajectory (new trt)

Median trajectories, 80% & 50% confidence band under two alternative priors for trt effect \( \psi_i \).
Formulate as Decision Problem

• Have dist’n of data (tumor growth)
• Have dist’n of model parameters
• Action space: alternative designs
  ‣ Total no. of pts enrolled: $N$
  ‣ Duration of open-label phase: $T_1$
  ‣ Duration of follow-up post-randomization: $T_2$
Utility Function

• Balance

  ‣ Costs of the study:
  \[ C(d, \phi, X) = c_1 N + c_2 n + c_3 (T_1 N + T_2 n) \]

  ‣ Benefits from subsequent phase III trial:
  \[ B(d, \theta, Y) = I \{ S_d(Y) \in R_d \} E \{ \log(1 + \psi_{N+1}) \mid \theta \} \]

\[ u(d, \theta, Y) = B(d, \theta, Y) - C(d, \theta, Y) \]
Implementation

• Simulate clinical trial for various values of 3 parameters: \((N, T_1, T_2)\)
  
  ‣ \(n\) is a function of \(T_1\) and dist’n of tumor growth across pop’n
    - Pt continues if SD (tumor within bounds)

• Monte Carlo optimization
  
  ‣ Approximate expected utility by smoothing simulation results across various \((N, T_1, T_2)\)
Monte Carlo Approximation

Sims yield \((d_h, u_h), h = 1, \ldots, H\) for different \((N, T_1, T_2)\)

\[
u(d, \theta, Y)
\]

\[
T_2
\]

\[
T_1
\]

\[
u(d, \theta, Y)
\]

\[
N^N
\]
Example Solutions

c_1 = c_2 = 0.001, c_3 = 3.3 \times 10^{-5}

d^* = (216, 60, 102)

\[ u(d, \theta, Y) \]

\[ N = 246 \]

Decision maker favors RDD over 2-arm RCT \( T_1 = 0 \)
and over no study \( N = 0 \)

c_1 = 0.004, c_2 = c_3 = 0

d^* = (204, 62, 108)

\[ c_1 = c_2 = 0.002, c_3 = 6.6 \times 10^{-5} \]

d^* = (152, 56, 105)

\[ c_1 = 0.004, c_2 = c_3 = 0 \]
Provide Table of Operating Chars

- Use historical information from CALGB 69901
- Costs are $c_1 = c_2 = 0.001, c_3 = 3.3 \times 10^{-5}$
- Action space: $D = \{d = (N, T_1, T_2) \in (0, 1, \ldots, 300)^3\}$
- Expected growth at 4 months:
  - 12% (trt) vs 24% (control)
    - Optimal design: $d^* = (N^* = 221, T_1^* = 72, T_2^* = 145)$
Response Adaptive Examples

**BATTLE & BATTLE 2**
- Prospective study to identify biomarkers to predict tumor response (NSCLC)
- Predefined targets
- Adaptive rand to 4 trts
- 8-wk disease control
- Enrolled 255 pts in 3 yrs
- “Step toward personalized medicine”

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**Plenary Session**

**Innovations in Translational Cancer Medicine**

**Sunday, April 18, 2010 • 9:30 a.m.-12:15 p.m.**

**Exhibit Hall D, Washington Convention Center**

**Chairperson:** Frank McCormick, UCSF Comprehensive Cancer Center, San Francisco, CA

**LB-1**

The BATTLE trial (Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination): Personalizing therapy for lung cancer.


**Background:** Patients (pts) with chemotherapy-resistant non-small cell lung cancer (NSCLC) have few options for effective treatment. BATTLE is a hypothesis-driven prospective study that identifies biomarkers (BMs) to predict tumor response and thus may help select personalized therapy for lung cancer pts.

33%, 244 pts were evaluable for 8 wk DC. All 11 BMs were evaluable in 215 pts. Biopsy sites were lung 55%, liver/adrenal 19%, other 26%. Pneumothorax incidence was 11.5%, and 6.5% of pts had treatment-related grade 3-4 toxicity. *EGFR* status included M in 15%, FISH amplification (A) in 16% and high polysomy in 28%; Other BMs were KRAS M in 20%; VEGF/R2 staining in 40%; RXR alpha nuclear staining in 80%; Cyclin D1 staining in 54%. Overall DCR at 8 weeks was 48%, median overall survival (OS) was 9 months, 1 year survival was 39%, and progression-free survival (PFS) was 1.9 months. Better DCR was seen with *EGFR* M for E (p=0.04); Cyclin D1 IHC positivity (IHC+) (p=0.011) and *EGFR* FISH A (p=0.008) for E + B; VEGF/R2 IHC+ for V (p=0.05); and absence of *EGFR* M (p=0.012) or high polysomy (p=0.048) for S. Pts with both *EGFR* M and FISH A had 100% DC (n=6) with E or EB and 0% DC (n=8) with B. Pts with KRAS M tended to respond better with S.
BATTLE

- **Biomarker-based Approaches of Targeted Therapy for Lung Cancer Elimination**

  - Match pathway with targeted agent
    - 4 pathways & 4 drug regimens
    - Progression-free survival at 8 weeks
    - Adaptive randomization
Response Adaptive Example 2

- I-SPY & I-SPY 2
- Neoadjuvant breast cancer
- Path CR endpoint
- Adaptive rand by group
- Validate MRI markers

“I-SPY 2 will provide a path to personalized medicine,” said Dr. Esserman.
Summary

- Targeted agents may need newer designs with new endpoints
- Endpoint evaluation can be tricky
- Many new designs appearing in literature
  - Randomized discontinuation design feasible
  - Enrichment designs
  - Adaptive designs
Thank You!