New Challenges: Model-based Dose Finding in the Era of Targeted Agents

Elizabeth Garrett-Mayer, PhD
Cody Chiuzan, PhD

1 Hollings Cancer Center
Department of Public Health Sciences
Medical University of South Carolina
2 Department of Biostatistics
The Mailman School of Public Health
Columbia University

April 15, 2015
Outline

Redefining the Objectives
A New Era
A Novel Design for Adoptive T-Cell Therapy

Methods
  Stage 1
  Stage 2

Simulations

Results
  Efficacy
    Stages 1 & 2: Toxicity and Efficacy

Discussion points

References
Redefining the objectives

• In traditional cancer treatment, the dogma has always been to administer all drugs at the maximum tolerated dose (MTD)
• The same approach would not be expected to apply to molecularly targeted agents and immunotherapies
• There is a need to redefine the criteria used for defining the recommended phase II dose
• **Is it critical to define a single recommended phase II dose as part of a phase I trial?** *

Assumptions of dose finding designs

Classical Assumption

- **Response**
- **Dose Limiting Toxicity**

More Recent Observations

- **Response**
- **Dose Limiting Toxicity**
Dose response: a phase I question?

- Dose response should be an integral part of drug development
- The highest dose is not always optimal
- Examples of cancer treatments lacking an increasing dose response relationship: lower doses are efficacious as higher doses
  - Temsirolimus in kidney cancer (Atkins et al., JCO, 2004)
  - Anastrozole in breast cancer (Jonat et al., Eur J Cancer, 1996)
- Proposals for change:
  - Phase I should define a range of doses for phase II instead of one dose based on safety
  - Phase II trials should include two or more doses
  - Phase I and II should be merged using a coherent approach for optimal dosing
Redefining the Objectives

A New Era

A Novel Design for Adoptive T-Cell Therapy

Methods

Stage 1
Stage 2

Simulations

Results

Efficacy

Stages 1 & 2: Toxicity and Efficacy

Discussion points

References
A New Era: “Breakthrough Designation”

• In July 2012, the United States Food and Drug Administration Safety and Innovation Act (FDASIA) was signed.

• A new designation for an experimental treatment was created: Breakthrough Therapy Designation

• A breakthrough therapy is a drug . . .
  • which is intended alone or in combination to treat a serious or life-threatening disease or condition, and
  • for which preliminary clinical evidence indicates the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.

• If designated, **FDA will expedite the development and review of such drug.**

• This may mean that the Phase I trial will evolve with the FDA’s involvement.
Recent Approvals from Phase I Data

- Ceritinib (a tyrosine kinase inhibitor) for the treatment of ALK-rearranged lung cancer: received accelerated approval in April 2014 (Shaw et al, NEJM 2014).

- Approval was based on clinical responses seen in a phase I trial initially designed to include a dose escalation phase followed by a large expansion cohort.

- Approved dose is 750mg based on clinical response rate (44%) in 163 patients and durable responses (7.1 months on average).

- Impressive, but there is substantial uncertainty regarding optimal dose and prandial conditions for administrations.

- FDA has mandated post-market testing which may lead to a different recommended dose.
Recent Approvals from Phase I Data

- Nivolumab (Opdiva) is a fully human IgG4 monoclonal antibody.
- Nivolumab works by blocking a protein called programmed cell death 1 (PD-1). PD-1 blockers free the immune system around the cancer by helping T-cells to attack cancer.
- Approved for lung cancer (March 2015) and advanced melanoma (Dec 2014) via breakthrough designation.
- In advanced melanoma, approval was based on a 32% response rate in 120 trial participants and long duration of response (> 6 months in one-third of responders) with no comparison arm (Topalian, NEJM, 2012)
Nivolumab Phase I Study

- Protocol version 1: 23 July 2008
  - Three dose levels: 1, 3, 10 mg/kg; ‘3+3’ design (N=12)
  - Four dose expansion cohorts (disease-specific) with up to 16 patients per cohort
  - Maximum N=76

- Protocol version 5: 23 Jan 2012
  - Dose 0.1 and 0.3 mg/kg added as part of Amendment 4. “Did not impact dose escalation plan or schedule.”
  - Up to 14 expansion cohorts, enrollment to 7 expansion cohorts already completed.

- At the trial’s end, 296 patients had been enrolled in five cancer subtypes.
Table 4: Expansion Cohorts Completed Prior to Amendment 4
- Melanoma 1 mg/kg
- Melanoma 3 mg/kg
- Melanoma 10 mg/kg
- Renal Cell Carcinoma 10 mg/kg
- Non-small Cell Lung Cancer 10 mg/kg
- Colorectal Cancer 10 mg/kg
- Prostate Cancer 10 mg/kg
Recent Approvals from Phase I Data

- See pembrolizumab for a similar story (Robert et al, Lancet, 2014)
- Common themes?
  - Lack of dose-response relationship
  - Low toxicity (in most cases)
  - Rapid pace to approval
  - Uncertainty about optimal dose
  - Haphazard dose escalation based on MTD paradigm
- **These examples highlight the need for novel dose-finding approaches**
- How could these trials been have better designed?
US agencies and associations recognizing need for change

- ASCO’s new policy statement on phase I trials in cancer (Weber et al., JCO, Jan 2015)
- First update since 1997
- Key conclusions:
  - Marked increase in molecularly targeted agents and immunotherapies
  - Increase in the number of new agents
  - Need for innovative trial designs to reduce exposure to ineffective treatments and reduce exposure to toxic levels of treatment.
  - Phase I trials have greater potential as a treatment option than they did in 1997 and there should be an emphasis to increase enrollment to phase I trials.
US agencies and associations recognizing need for change

Dose-finding of Small Molecule Oncology Drugs
May 18-19, 2015
Washington Court Hotel, Washington, DC

Online Registration for this workshop is open.

The purpose is to provide an interdisciplinary forum to discuss the best practices of dose finding and dose selection for small molecule kinase inhibitors developed in oncology. The goal is to promote a movement away from conventional dose escalation trial design and move toward innovative designs that can incorporate key clinical, pharmacologic, pharmacometric data, and when appropriate, non-clinical information to guide dose selection.
Outline

Redefining the Objectives

A New Era

A Novel Design for Adoptive T-Cell Therapy

Methods

Stage 1
Stage 2

Simulations

Results

Efficacy

Stages 1 & 2: Toxicity and Efficacy

Discussion points

References
Heterogeneity of immunotherapy in cancer

- Adoptive T-Cell transfer therapy (June, JCI, 2007)
- Immunologic outcomes are usually treated as continuous.
  - Example: T cell persistence (% of T-cells at follow-up)
  - Target levels not always known or well-defined
  - Patient-level heterogeneity

- Immunotherapies are expected to have lower toxicity compared to cytotoxic agents
  - Monotonicity of dose-response is not necessarily implied
  - The highest tolerated dose might not have the most substantial immunologic response

- More relevant to use efficacy-driven dose finding designs with safety boundaries.
**Goal:** Develop an adaptive early phase design for assessing toxicity and efficacy outcomes in cancer immunotherapy trials.

- Identify the optimal dose to maximize efficacy while maintaining safety.
- **Two-stage design:**
  - Stage 1: Explore doses for safety and obtain information on immunotherapy outcomes
  - Stage 2: Allocate patients to allowable doses with emphasis towards doses with higher efficacy
- Uses both:
  - continuous (immunologic) outcomes
  - binary toxicity information
- Optimize efficacy while setting a threshold on acceptable toxicity
Practical Goals

Make it easy to implement

- relatively few assumptions
- estimation can be done using standard software
- flexibility to different outcomes:
  - fold-change (e.g. genetic marker)
  - % persistence (e.g. immunology)
  - absolute count (e.g. pharmacokinetics; CTCs)

Make it easy to understand

- clinician ‘buy-in’
- statistician ‘buy-in’
Outline

Redefining the Objectives
A New Era
A Novel Design for Adoptive T-Cell Therapy

Methods
  Stage 1
  Stage 2

Simulations

Results
  Efficacy
    Stages 1 & 2: Toxicity and Efficacy

Discussion points

References
Stage 1: Confirm Safety

- Define $p_1$ and $p_2$ as unacceptable and acceptable DLT rates
- Use cohorts of size $m$ to explore selected dose levels
- Likelihood inference used to declare dose levels “allowable” based on $p_1$ and $p_2$ and observed data.
- Define $k$ as the threshold of evidence required for declaring a dose to be toxic
- At end of Stage 1, there will be a set of doses for Stage 2.
- Continue to Stage 2 if two or more allowable doses.
- Details in Chiuzan et al., Clin Trials, 2015
Likelihood method with cohorts of size 3

Example:

- $p_1 = 0.40; \ p_2 = 0.15; \ m = 3$
- Require likelihood ratio $\geq 4$ (in favor of $p_1$) to declare toxic.
- 0 or 1 DLT in 3 pts: allowable dose
- 2 or 3 DLTs in 3 pts: unacceptable dose (and all higher doses unacceptable)

$$H_1 : p_1 = 0.40 \quad H_2 : p_2 = 0.15$$

<table>
<thead>
<tr>
<th>DLT</th>
<th>‘3+3’ rule</th>
<th>$L(p_1)/L(p_2)$</th>
<th>$k = 4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>acceptable</td>
<td>$LR = 0.35$</td>
<td>weak</td>
</tr>
<tr>
<td>1</td>
<td>expand to 6</td>
<td>$LR = 1.33$</td>
<td>weak</td>
</tr>
<tr>
<td>2</td>
<td>toxic</td>
<td>$LR = 5.0$</td>
<td>toxic</td>
</tr>
<tr>
<td>3</td>
<td>toxic</td>
<td>$LR = 19.0$</td>
<td>toxic</td>
</tr>
</tbody>
</table>

toxic: $LR \geq k$; acceptable: $LR \leq \frac{1}{k}$; weak: $\frac{1}{k} < LR < k$
Stage 2: Adaptive randomization

Using data from Stage 1, estimate immunologic parameter estimate at each of $J$ allowable dose.

- Example: T cell persistence at 14 days.
- $y_i = \%$ CD3 cells of patient $i$ at 14 days compared to baseline
- $d_i =$ dose level for patient $i$
- Estimation is based on a standard linear regression model using a log transformation of $y_i$:

$$
\log(y_i) = \beta_0 + \sum_{j=1}^{J} \beta_j I(d_i = j) + e_i
$$

$$
e_i \sim N(0, \sigma^2); \quad \sum_j \beta_j = 0
$$
Stage 2: Adaptive randomization

Define \( p_j \) as the estimated persistence (\%) at dose \( j \):

\[
\hat{p}_j = e^{\hat{\beta}_0 + \hat{\beta}_j}
\]

Calculate the randomization probabilities \( \pi_j \) for doses \( j = 1, \ldots, J \) (Thall & Wathen, Eur J Cancer, 2007):

\[
\pi_j = \frac{\hat{p}_j}{\sum_r \hat{p}_r}
\]

or

\[
\pi_j = \frac{\sqrt{\hat{p}_j}}{\sum_r \sqrt{\hat{p}_r}}
\]
Example 1: shallow slope

![Graph showing T-cell persistence (% of baseline) vs Dose Level]

- T-cell persistence (% of baseline)
- Dose Level

0 20 40 60 80 100

1 2 3 4
Example 1: shallow slope

![Graph showing Tcell persistence (% of baseline) vs Dose Level. The graph displays a scattered plot with data points at dose levels 1, 2, 3, and 4. The y-axis represents Tcell persistence (% of baseline) ranging from 0 to 100, and the x-axis represents Dose Level from 1 to 4. The data points indicate a shallow slope, suggesting a consistent level of Tcell persistence across different dose levels.](image-url)
Example 1: shallow slope
Example 2: steep slope
Example 2: steep slope
Example 2: steep slope
Stage 2

- For the first patient in Stage 2, randomize to allowable doses $j = 1, \ldots, J$ based on $\pi_j$.
- As data becomes available, update randomization probabilities for accruing patients.
- Repeat until total sample size is achieved, or some other stopping criteria is met.
- When DLTs are observed, utilize likelihood inference to determine if dose is “toxic”.

Example: cohort of size 5, 2 DLTs observed.

Example:

- $p_1 = 0.40; p_2 = 0.15$
- Require likelihood ratio $\geq 4$ (in favor of $p_1$) to declare toxic.
- 0 or 1 DLT in 5 pts: allowable dose
- $\geq 2$ DLTs in 5 pts: unacceptable dose (and all higher doses unacceptable)

$$H_1 : p_1 = 0.40 \quad H_2 : p_2 = 0.15$$

<table>
<thead>
<tr>
<th>DLT</th>
<th>$L(p_1)/L(p_2)$</th>
<th>$k = 4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>$LR = 0.18$</td>
<td>acceptable</td>
</tr>
<tr>
<td>1</td>
<td>$LR = 0.66$</td>
<td>weak</td>
</tr>
<tr>
<td>2</td>
<td>$LR = 5.0$</td>
<td>toxic</td>
</tr>
<tr>
<td>3</td>
<td>$LR = 19.0$</td>
<td>toxic</td>
</tr>
</tbody>
</table>

toxic: $LR \geq k$; acceptable: $LR \leq \frac{1}{k}$; weak: $\frac{1}{k} < LR < k$
Redefining the Objectives

A New Era

A Novel Design for Adoptive T-Cell Therapy

Methods

Stage 1
Stage 2

Simulations

Results

Efficacy

Stages 1 & 2: Toxicity and Efficacy

Discussion points

References
Simulations

To evaluate the model behavior we varied (or fixed) the following:

- Total sample size: $N = 25, N = 50$
- Number of dose levels: 3 to 5
- Dose-toxicity model (binary toxicity)
- Dose-persistence model (continuous persistence)
- Two levels of variance of persistence within dose level

For each combination, 5000 trials were simulated.
Simulating Toxicity and Efficacy Outcomes

- **Toxicity**: simulated from a binomial model, given dose
- **Persistence**: simulated from a beta-binomial model, given dose
  - Variance across patients is controlled by the beta distribution
  - Assumptions: small vs. large variance in beta distribution
  - Assumptions: constant vs. varying variance across dose
- Reasonable assumptions and not completely consistent with the fitted model.
- Allows robustness to misfit to be evaluated.
- No dependence included between toxicity and efficacy.
Outline

Redefining the Objectives

A New Era

A Novel Design for Adoptive T-Cell Therapy

Methods

Stage 1
Stage 2

Simulations

Results

Efficacy

Stages 1 & 2: Toxicity and Efficacy

Discussion points

References
Results: Stage 2

Comparisons made between:

- Balanced Design
- Doubly Biased Coin Design
- Our Adaptive Design

Criteria compared:

- Number of patients treated per dose
- Estimation of Persistence
Characteristics: Large variance, \( N = 25 \), plateau increase.
Including Toxicity Constraints

- Six toxicity models, five efficacy models, two variance structures, two sample sizes
- Safety constraints implemented using $H_1 : p_1 = 0.40$; $H_2 : p_2 = 0.15$; $k = 4$
- Subset presented:
  - Three toxicity scenarios
  - “Plateau” efficacy model
  - Large variance across patients
  - Smaller sample size ($N = 25$)
Results: Stage 1 & 2

DLT rates: 0.25, 0.25, 0.25, 0.25, 0.25
Results: Stage 1 & 2

DLT rates: 0.05, 0.18, 0.29, 0.40, 0.51
Results: Stage 1 & 2

DLT rates: 0.02, 0.02, 0.02, 0.02, 0.02
Inferences from the Trial

Choosing the best dose?

- The goal is to identify a set of doses for further study
- Adaptive randomization emphasizes treating patients at doses that are more likely to be efficacious
- Additional information, such as pharmacokinetic profiles and clinical outcomes, can also be used to help select promising doses for next study.
Redefining the Objectives

A New Era

A Novel Design for Adoptive T-Cell Therapy

Methods
  Stage 1
  Stage 2

Simulations

Results
  Efficacy
    Stages 1 & 2: Toxicity and Efficacy

Discussion points

References
Additional Considerations

- **Lag time:**
  - 14 days (or 30 days) to measure persistence in this situation.
  - if relatively rapid accrual (compared to the time to evaluate the efficacy endpoint), randomization probability will not be updated frequently and design will lean more towards balanced.

- **Transformation for efficacy outcome:**
  - choice of transformation will be context specific
  - dose selection will have a similar issue
  - Should we consider using ranks?

- **Drop-outs/inevaluables:** patients who drop out or whose follow-up measures are inevaluable

- **Accounting for uncertainty and small \( N \) in the model:**
  - quite a few ways to go.
  - additional constraints to “balance” at doses with similar randomization probabilities?
A New Era for Early Phase Cancer Trials

- There is a huge change occurring in dose-finding and early phase clinical trials in cancer
- This is an excellent time to pay attention to what the changes are:
  - Phase I trials are answering new questions
  - MTD is no longer recognized as the optimal dose
- Statisticians have been pushing CRM and other model-based design for 25 years
- The clinical oncology research community might finally be ready!
Outline

Redefining the Objectives
A New Era
A Novel Design for Adoptive T-Cell Therapy

Methods
Stage 1
Stage 2

Simulations

Results
Efficacy
Stages 1 & 2: Toxicity and Efficacy

Discussion points

References
References


