The Changing Landscape of Phase I Trials in Cancer: A Novel Design for Dose Finding in the Era of Non-Cytotoxic Agents

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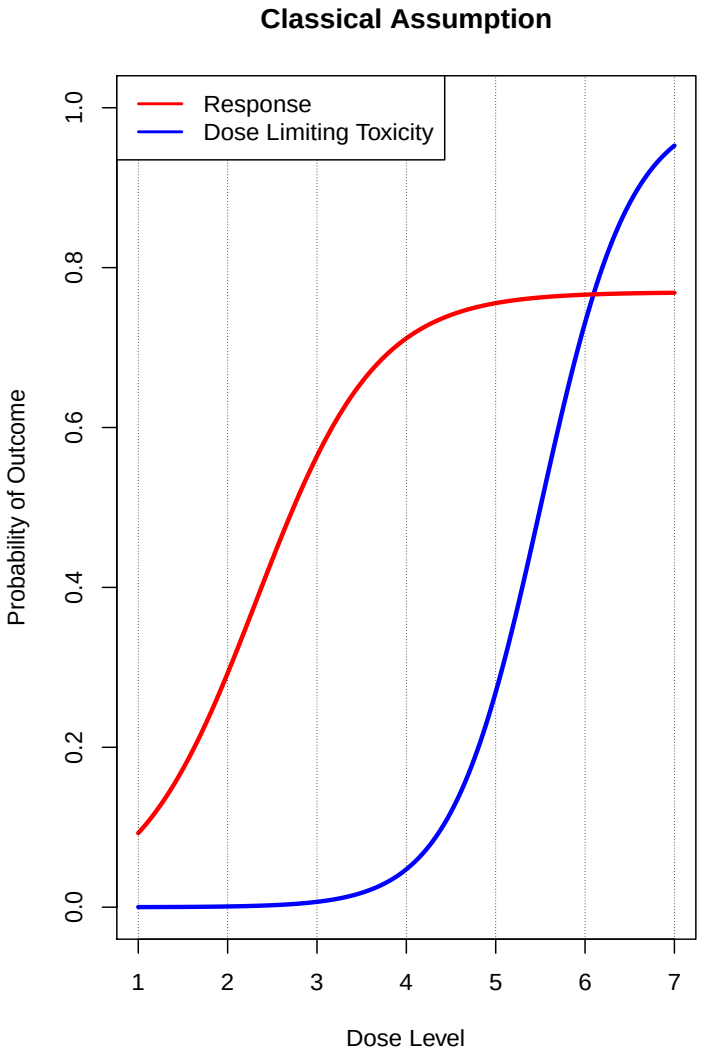
Outline

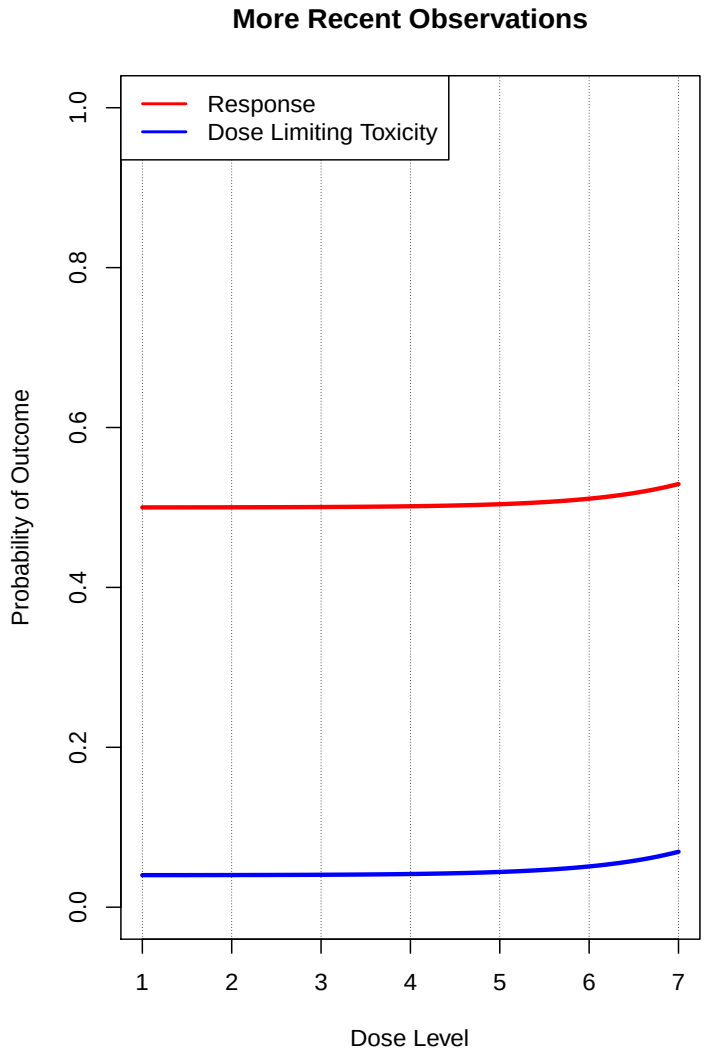
Redefining the objectives

- 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?** *

* Ratain, Nature Reviews Clinical Oncology, 2014.

Assumptions of dose finding designs





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 as 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**
  - **Phase I, II, and III should be blended for a more continuous drug development process**

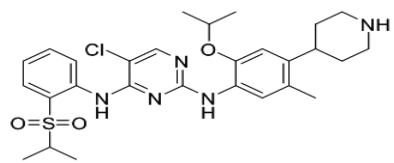
Outline

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 Approval based on 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

- 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).
- Just received "breakthrough designation" for renal cell carcinoma (Sept 2015).

Nivolumab Phase I Study

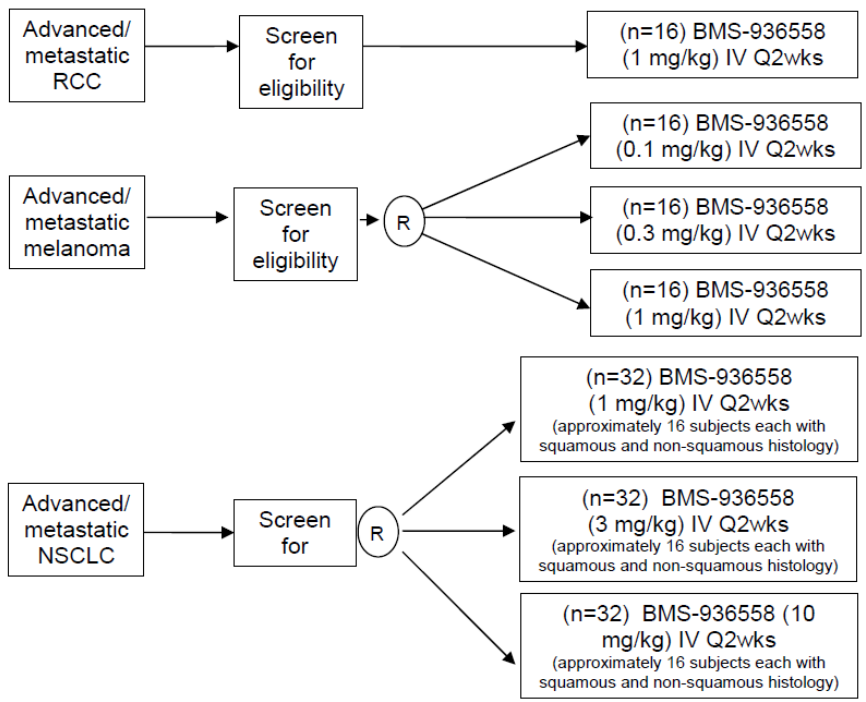
- Protocol version 1: 23 July 2008
  - Three dose levels: 1, 3, 10 mg/kg; '3+3' design (N=12)
  - **Four** dose expansion cohorts (disease-specific) with up to 16 patients per cohort
  - Maximum N=76
- Protocol version 5: 23 Jan 2012
  - Dose 0.1 and 0.3 mg/kg added as part of Amendment 4. "Did not impact 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.

Expansion Cohorts in Nivo Phase I

Table 4: Expansion Cohorts Completed Prior to Amendment 4

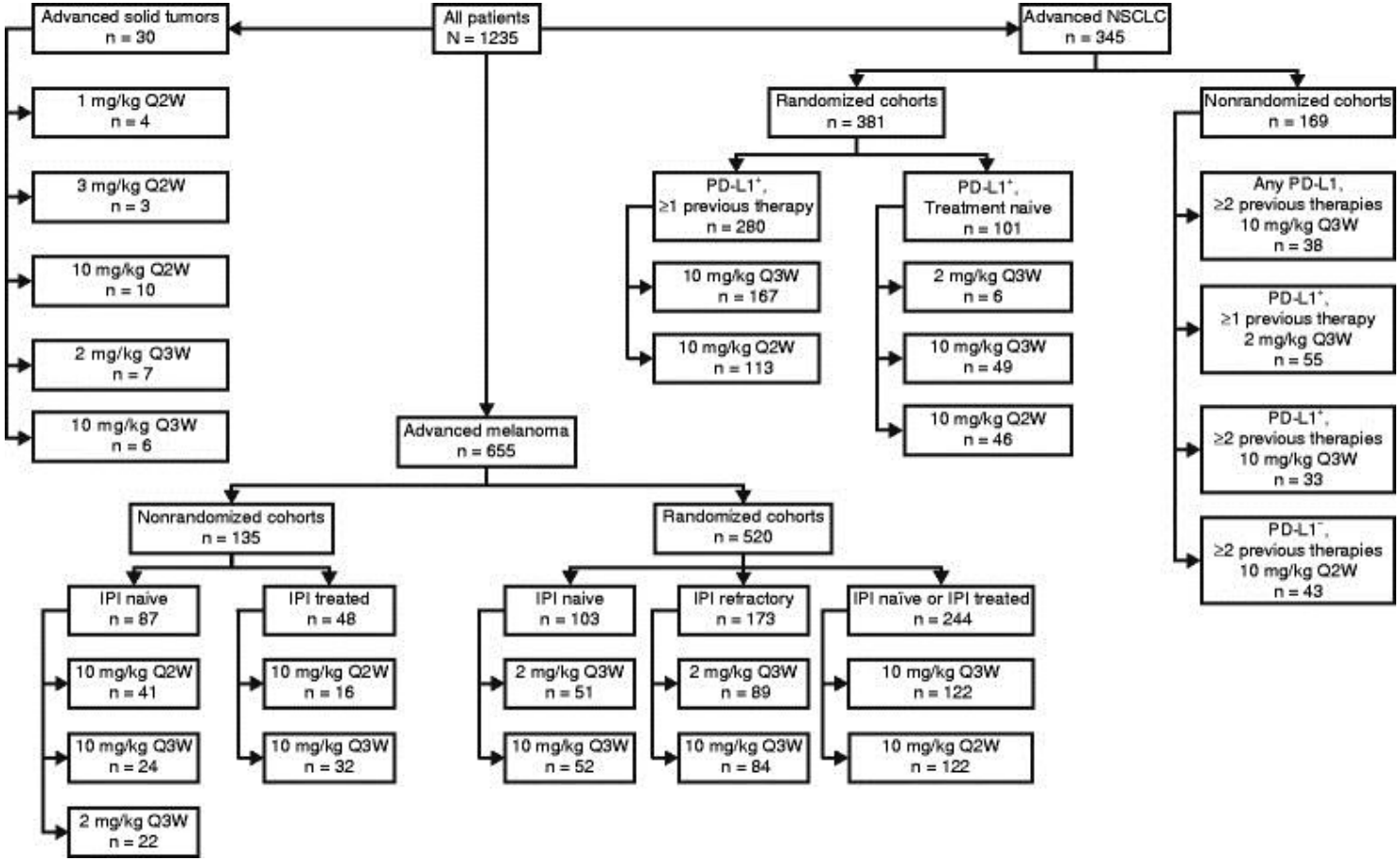
- Melanoma 1 mg/kg
- Melanoma 3 mg/kg
- Melanoma 10 mg/kg
- Renal Cell Carcinoma 10 mg/kg
- Non-small Cell Lung Cancer 10 mg/kg
- Colorectal Cancer 10 mg/kg
- Prostate Cancer 10 mg/kg

Figure 3: Expansion Cohorts Added Under Protocol Amendment 4



See pembrolizumab for a similar story

Figure: Flowchart summarizing the KEYNOTE-001 treatment cohorts in solid tumors, melanoma, and NSCLC that have been reported to date.



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.**

US agencies and associations recognizing need for change

- Panel entitled "Large Phase 1 Studies with Expansion Cohorts: Clinical, Ethical, Regulatory and Patient Perspectives"(Accelerating Anticancer Agent Development and Validation Workshop), May 2015, MD
- Panel entitled "Blurring of Phase 1, 2, and 3 trials in Oncology." Friends of Cancer Research-Brookings panel on Expansion Cohorts, Nov 2015, DC
- FDA Mini-Symposium, "Expansion Cohorts", Sept 2015.

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!
- Informal discussions are leaning towards "flexible" designs
- Stay tuned for "guidance" from FDA and others...

Switching Gears....

- There is a lot of context for what's occurring in Phase I trials
- It's a wide open opportunity for novel dose finding:
  - We have a lot of "MTD" based designs, maybe too many
  - Think of combining escalation and optimization
  - Safety: continuous? binary? ordinal?
  - Efficacy: continuous? binary? ordinal? time-to-event?
- No one knows where we are going and how to get there

Outline

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 as set of potentially optimal doses 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

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 ≥ 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)

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

DLT	'3+3' rule	$L(p_1)/L(p_2)$	$k = 4$
0	acceptable	$LR = 0.35$	weak
1	expand to 6	$LR = 1.33$	weak
2	toxic	$LR = 5.0$	toxic
3	toxic	$LR = 19.0$	toxic

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 mean immunologic parameter 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 :

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

$$e_i \sim N(0, \sigma^2); \qquad \sum_j \beta_j = 0$$

Stage 2: Adaptive randomization

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

$$\hat{p_j} = e^{\hat{\beta}_0 + \hat{\beta}_j}$$

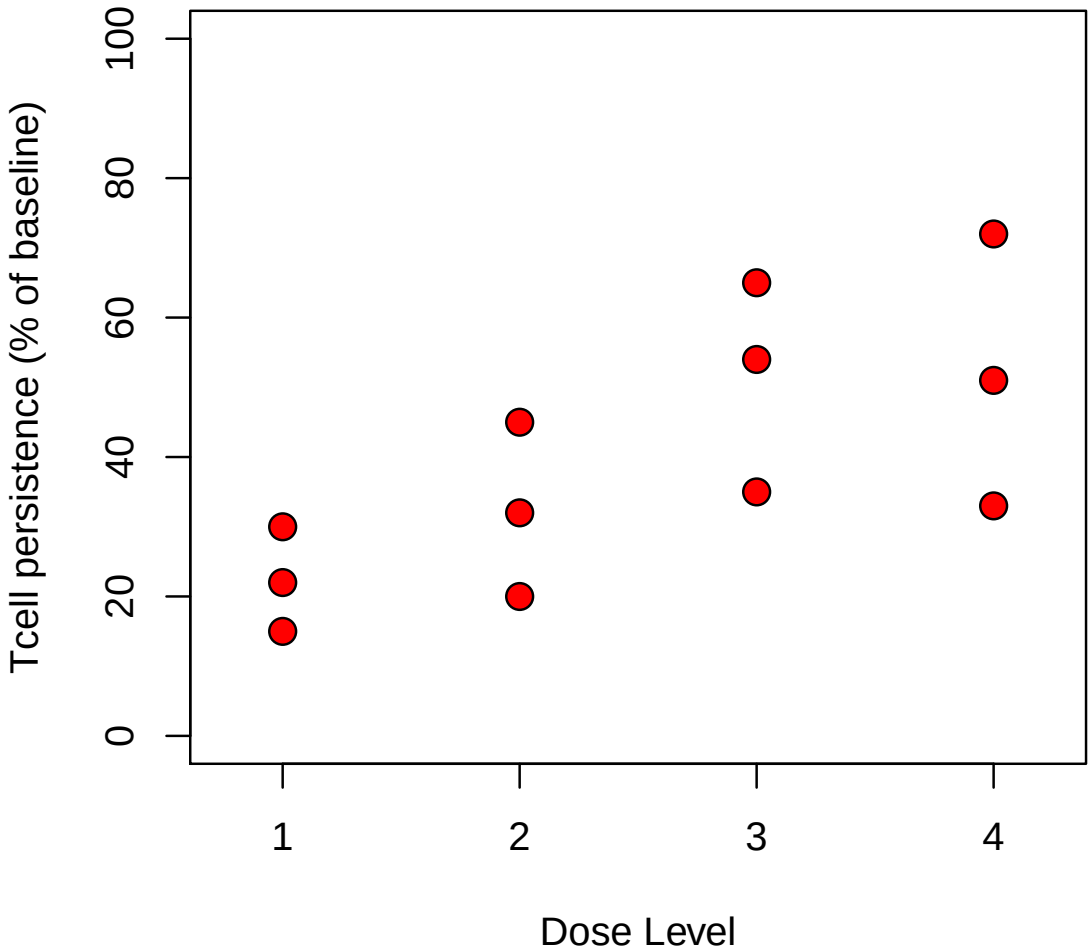
Calculate the randomization probabilities π_j for doses $j = 1, .., J$ (Thall & Wathen, Eur J Cancer, 2007):

$$\pi_j = \frac{\hat{p_j}}{\sum_r \hat{p_r}}$$

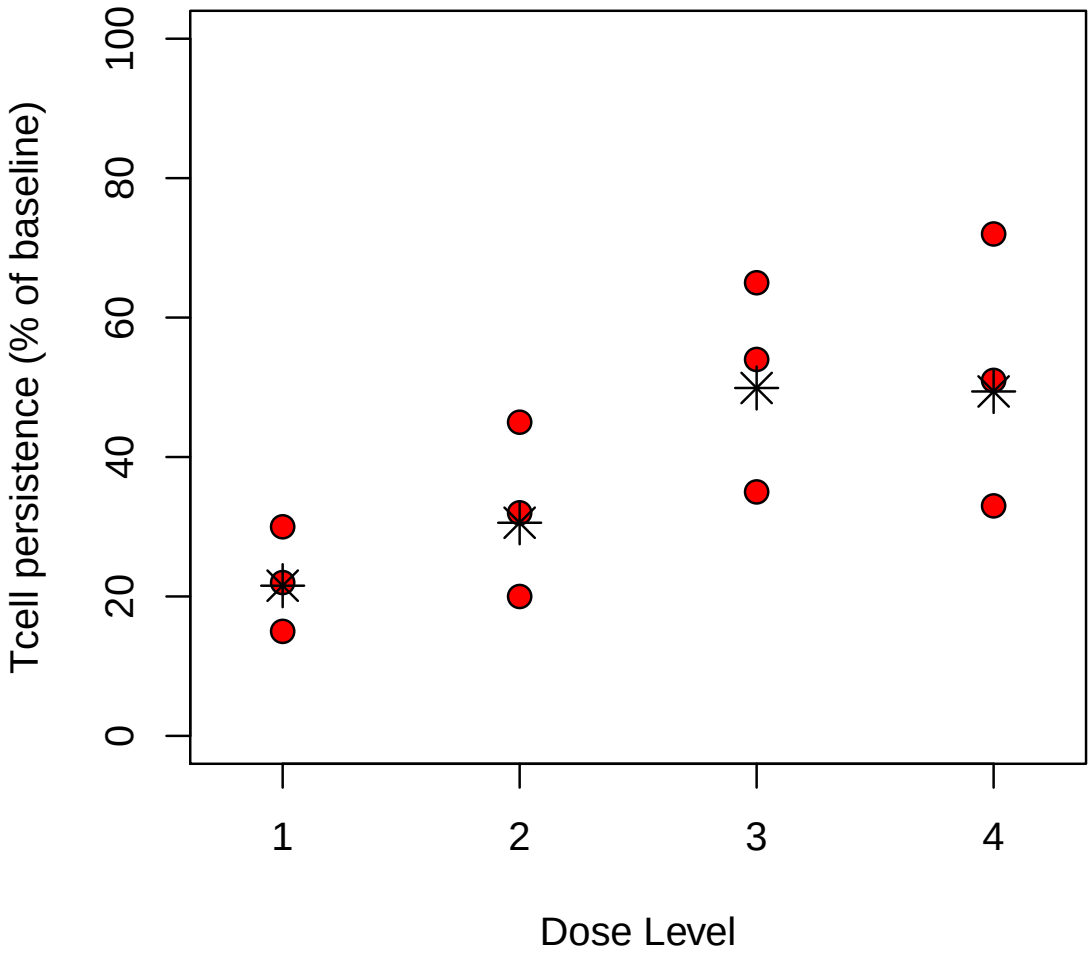
$$or$$

$$\pi_j = \frac{\sqrt{\hat{p_j}}}{\sum_r \sqrt{\hat{p_r}}}$$

Example 1: shallow slope



Example 1: shallow slope



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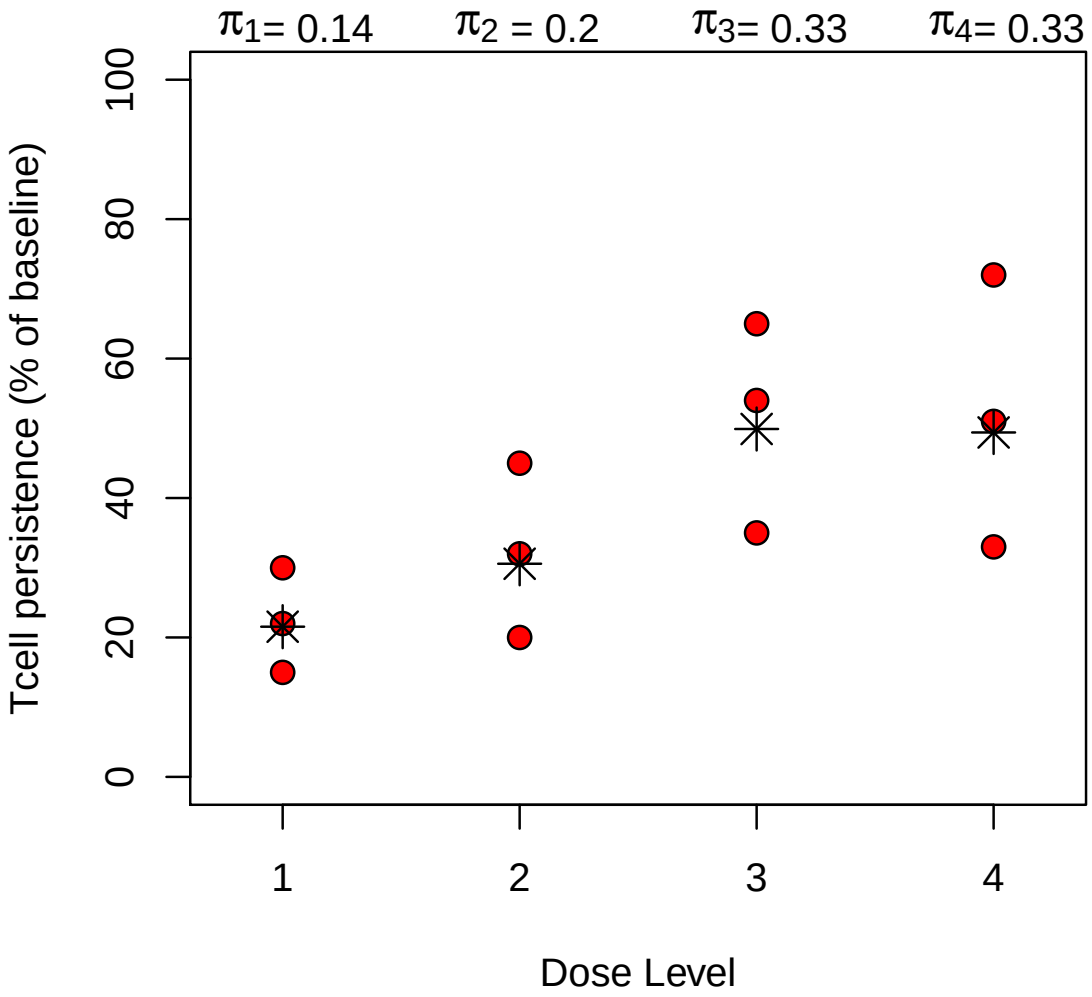
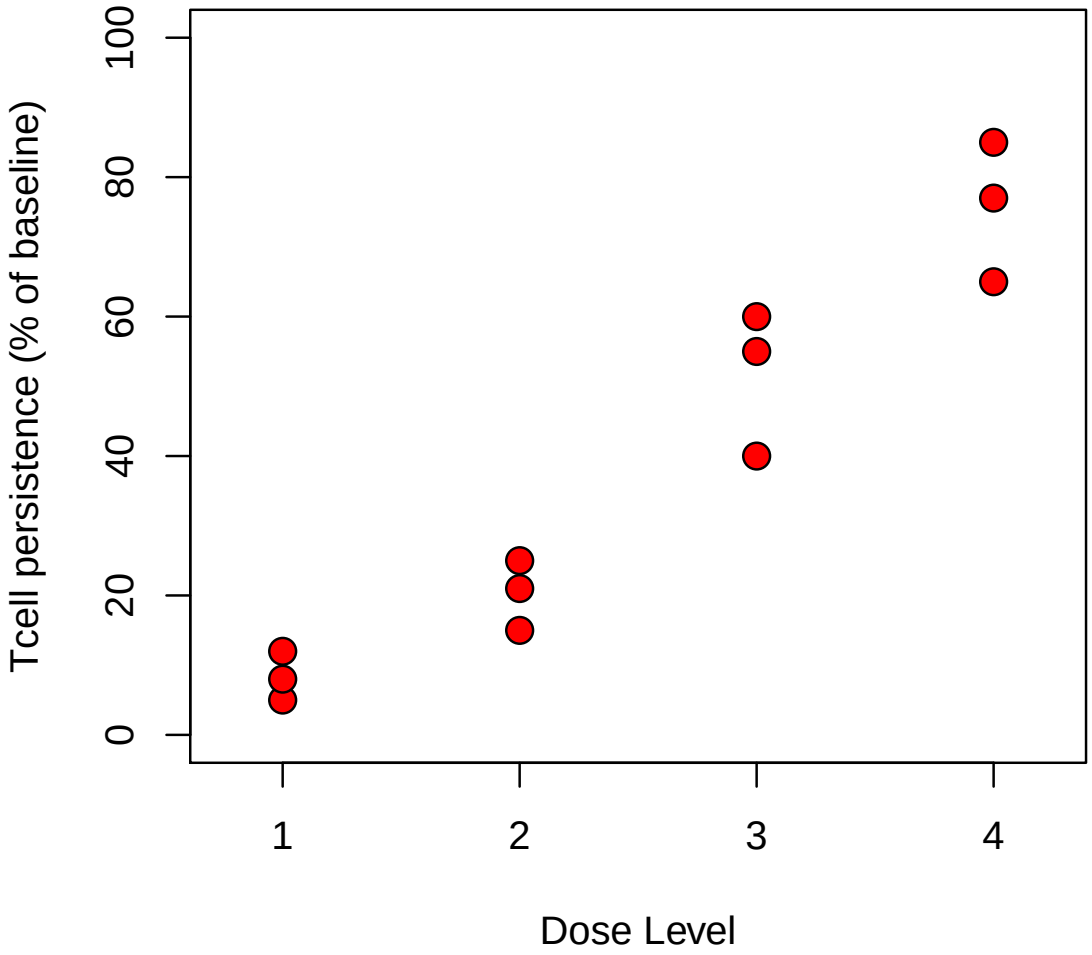


Example 2: steep slope



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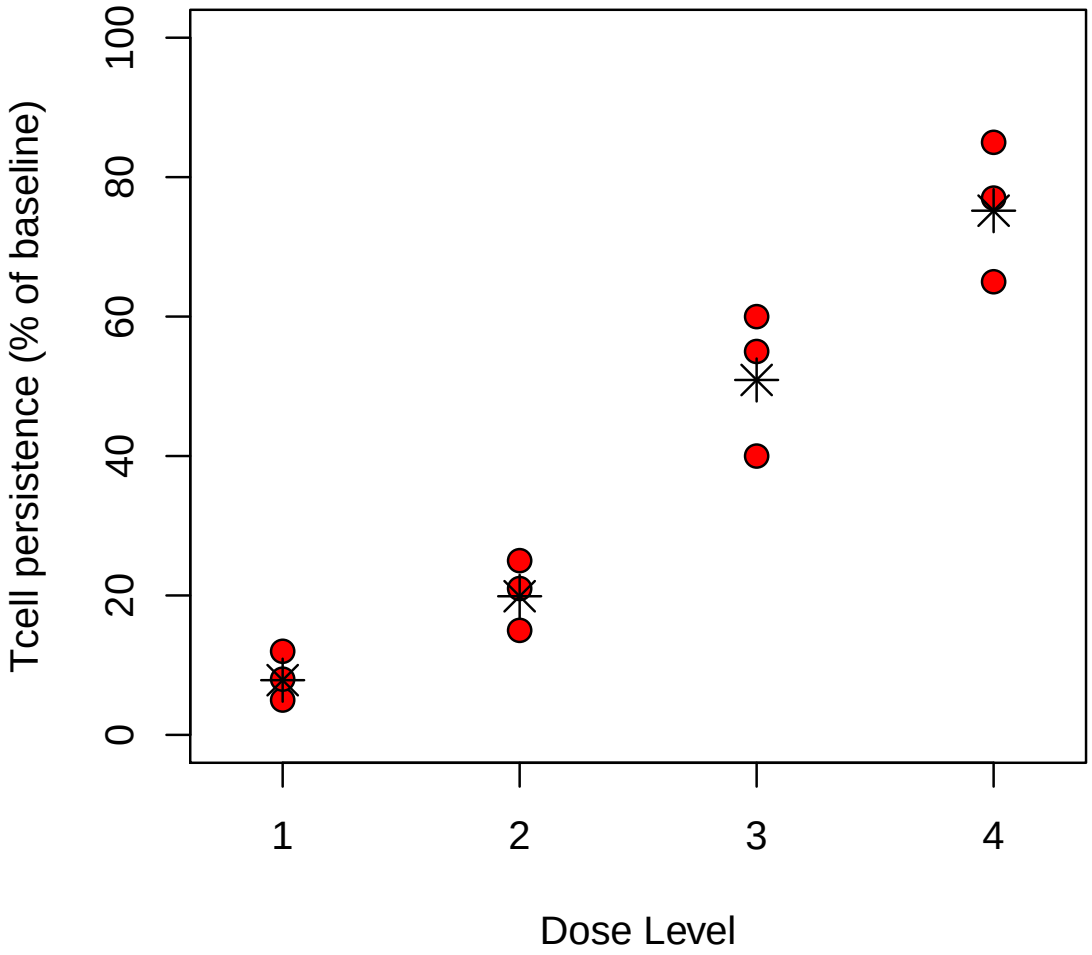

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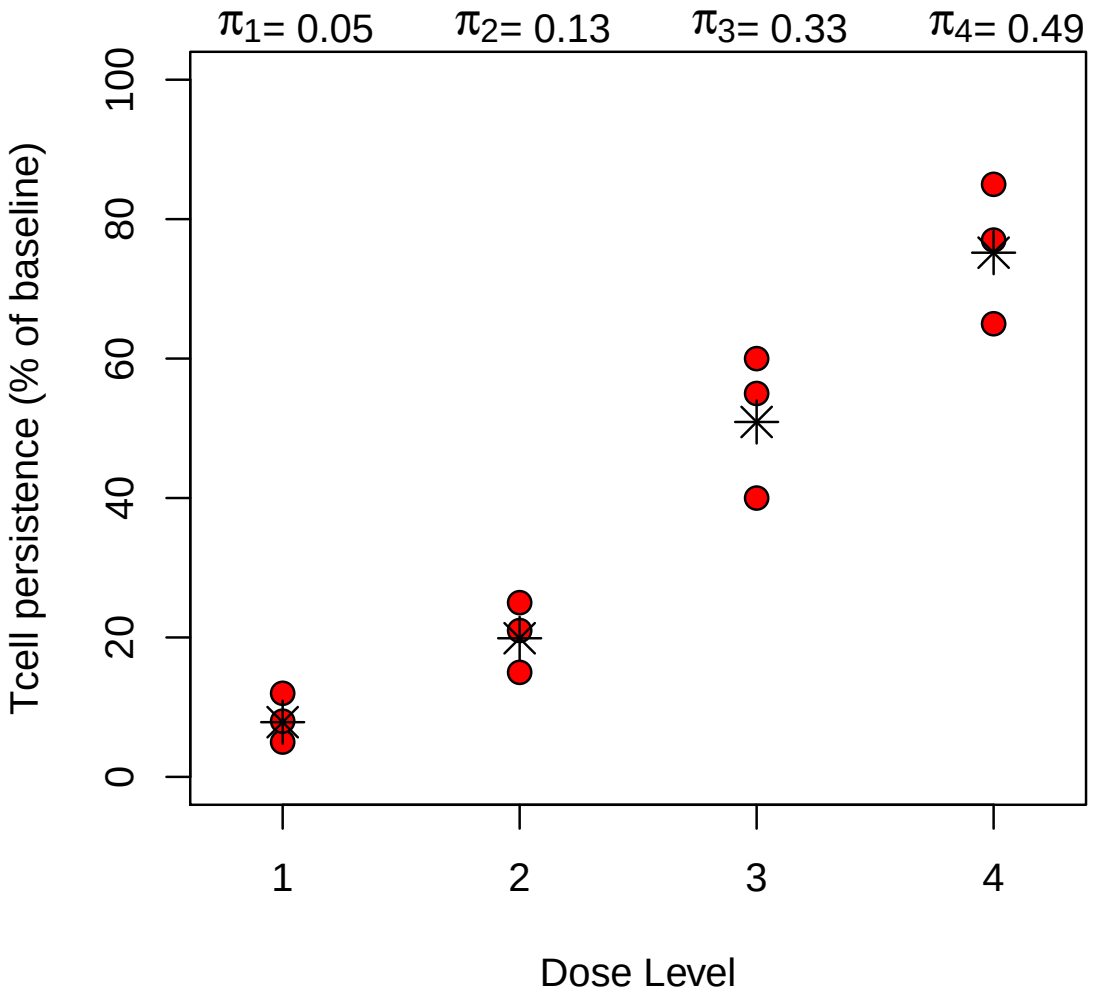

Stage 2

- For the first patient in Stage 2, randomize to allowable doses $j = 1, .., J$ based on π_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 ≥ 4 (in favor of p_1) to declare toxic.
- 0 or 1 DLT in 5 pts: allowable dose
- ≥ 2 DLTs in 5 pts: unacceptable dose (and all higher doses unacceptable)

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

DLT	$L(p_1)/L(p_2)$	$k = 4$
0	$LR = 0.18$	acceptable
1	$LR = 0.66$	weak
2	$LR = 5.0$	toxic
3	$LR = 19.0$	toxic

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

Outline

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.
Safety constraint was implemented based on $H_1 : p_1 = 0.40$;
$H_2 : p_2 = 0.15$; $k = 4$

Variance Assumptions

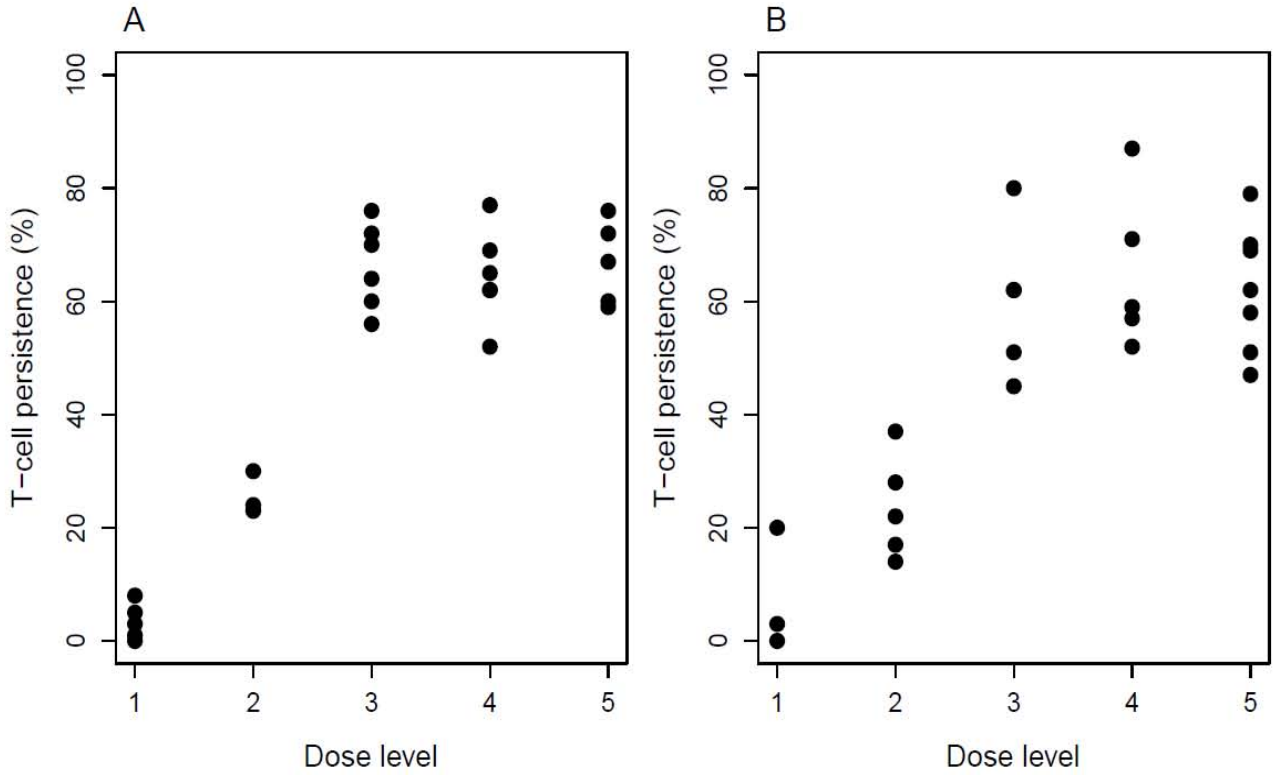

Figure 1. Illustration of variability among doses using a beta-distribution variance of 0.002 (A) versus 0.01 (B). A plateau trend for T-cell persistence as function of dose (0.05, 0.25, 0.65, 0.65, 0.65) and a total sample size of 25 patients are used in both cases.

Simulating Toxicity and Efficacy Outcomes

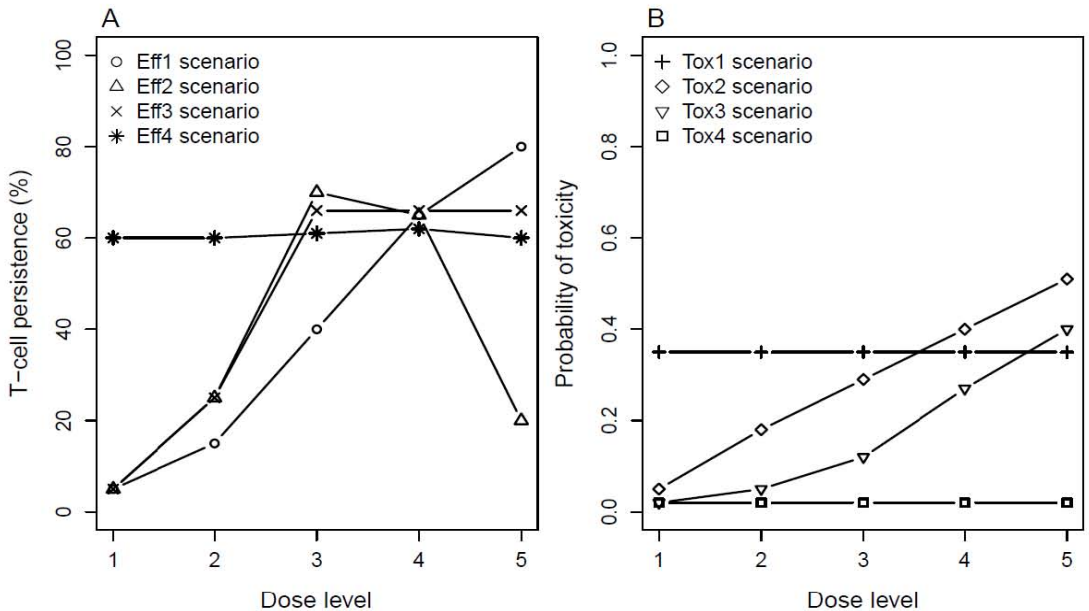

Figure 2. Simulated efficacy (A) and toxicity (B) scenarios as a function of dose level. The efficacy outcome is defined as persistence (%) of transduced T-cells at follow-up compared to baseline.

- 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.

Comparisons

Comparisons made between:

- '3+3' design with an expansion cohort of up to 9 patients
- Our Adaptive Design

Criteria compared: Fraction of patients treated per dose
Focus on:

- Larger variance scenario
- Maximum $N = 25$ for the adaptive design

Outline

Results: Pretty toxic at all levels

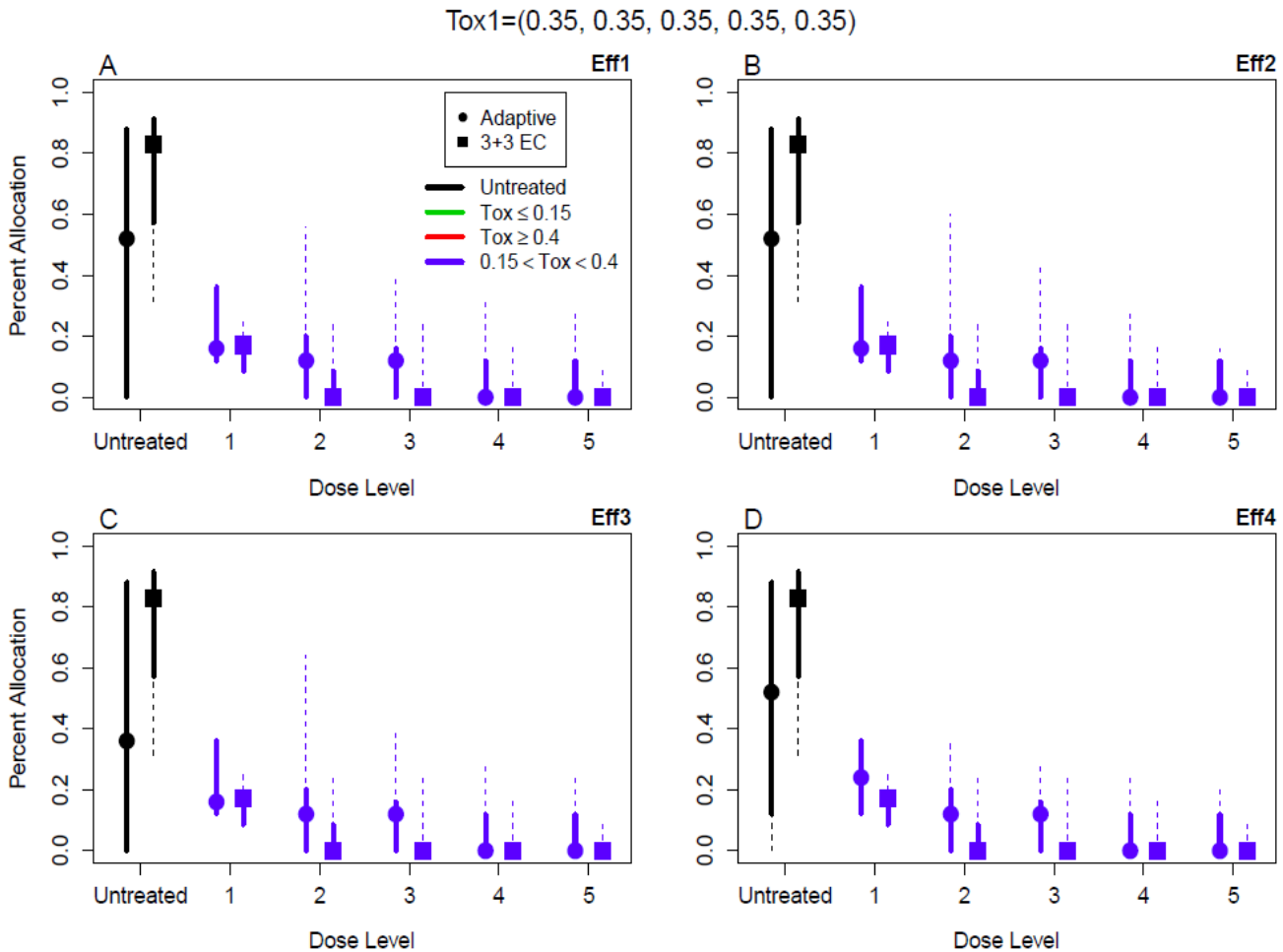

Figure 3. Percent allocation per dose for the two-stage adaptive design versus '3+3' EC. Results of 5,000 simulated trials for each combination of toxicity 1 scenario with all four efficacy scenarios are summarized as: median (filled circle/square), 25^{th} - 75^{th} percentiles (solid line), and 2.5^{th} - 97.5^{th} percentiles (dashed line).
Eff1=(0.05, 0.15, 0.40, 0.65, 0.80), Eff2=(0.05, 0.25, 0.70, 0.65, 0.20), Eff3=(0.05, 0.25, 0.65, 0.65, 0.65), Eff4=(0.60, 0.60, 0.61, 0.62, 0.60).
The best doses having a probability of toxicity less than or equal to 25% and the highest T-cell percent persistence are marked by [].

Results: Increasing toxicity, more toxic

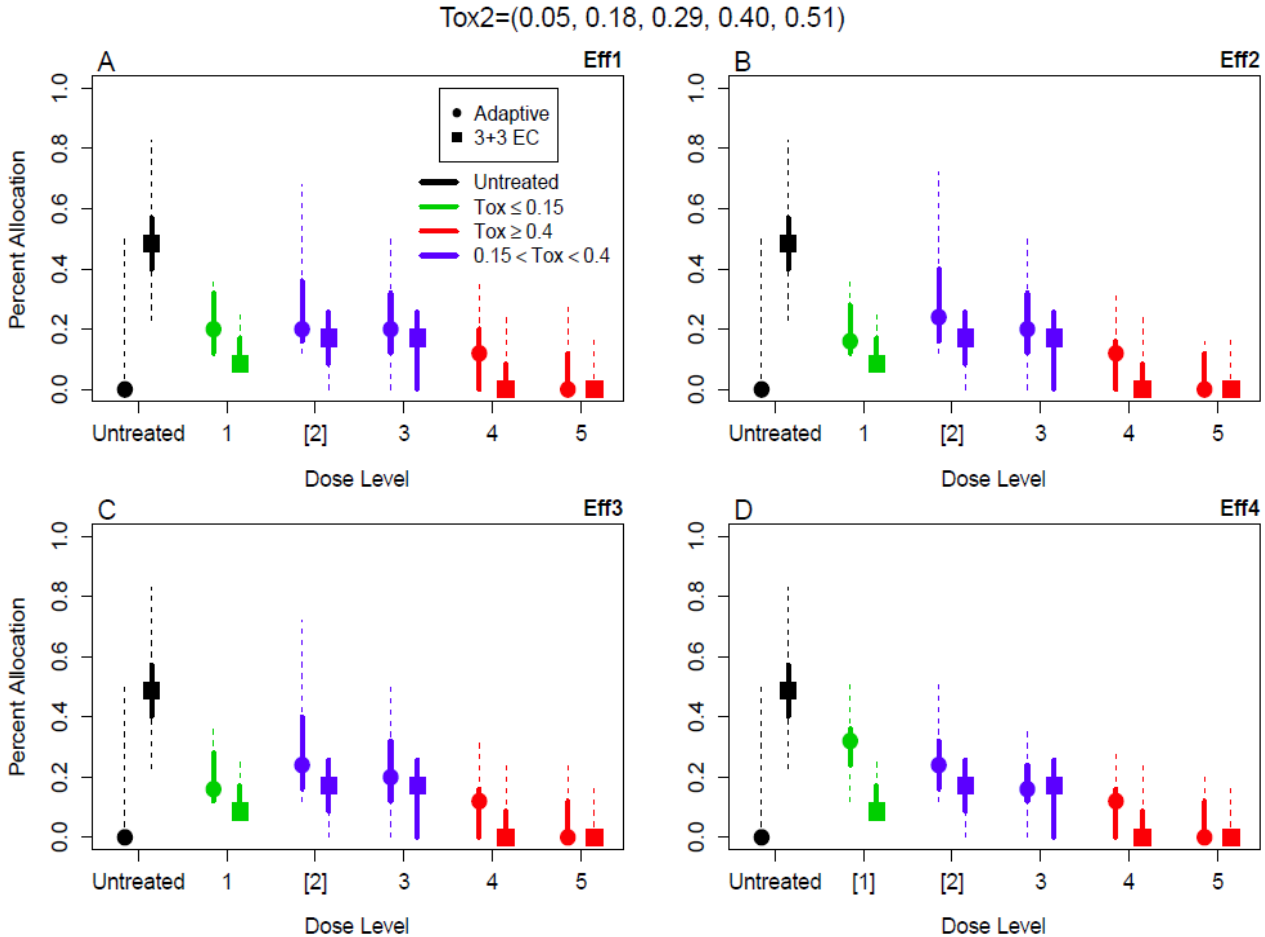

Figure 4. Percent allocation per dose for the two-stage adaptive design versus '3+3' EC. Results of 5,000 simulated trials for each combination of toxicity 2 scenario with all four efficacy scenarios are summarized as: median (filled circle/square), 25^{th} - 75^{th} percentiles (solid line), and 2.5^{th} - 97.5^{th} percentiles (dashed line).
Eff1=(0.05, 0.15, 0.40, 0.65, 0.80), Eff2=(0.05, 0.25, 0.70, 0.65, 0.20), Eff3=(0.05, 0.25, 0.65, 0.65, 0.65), Eff4=(0.60, 0.60, 0.61, 0.62, 0.60).
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Results: Increasing toxicity, less toxic

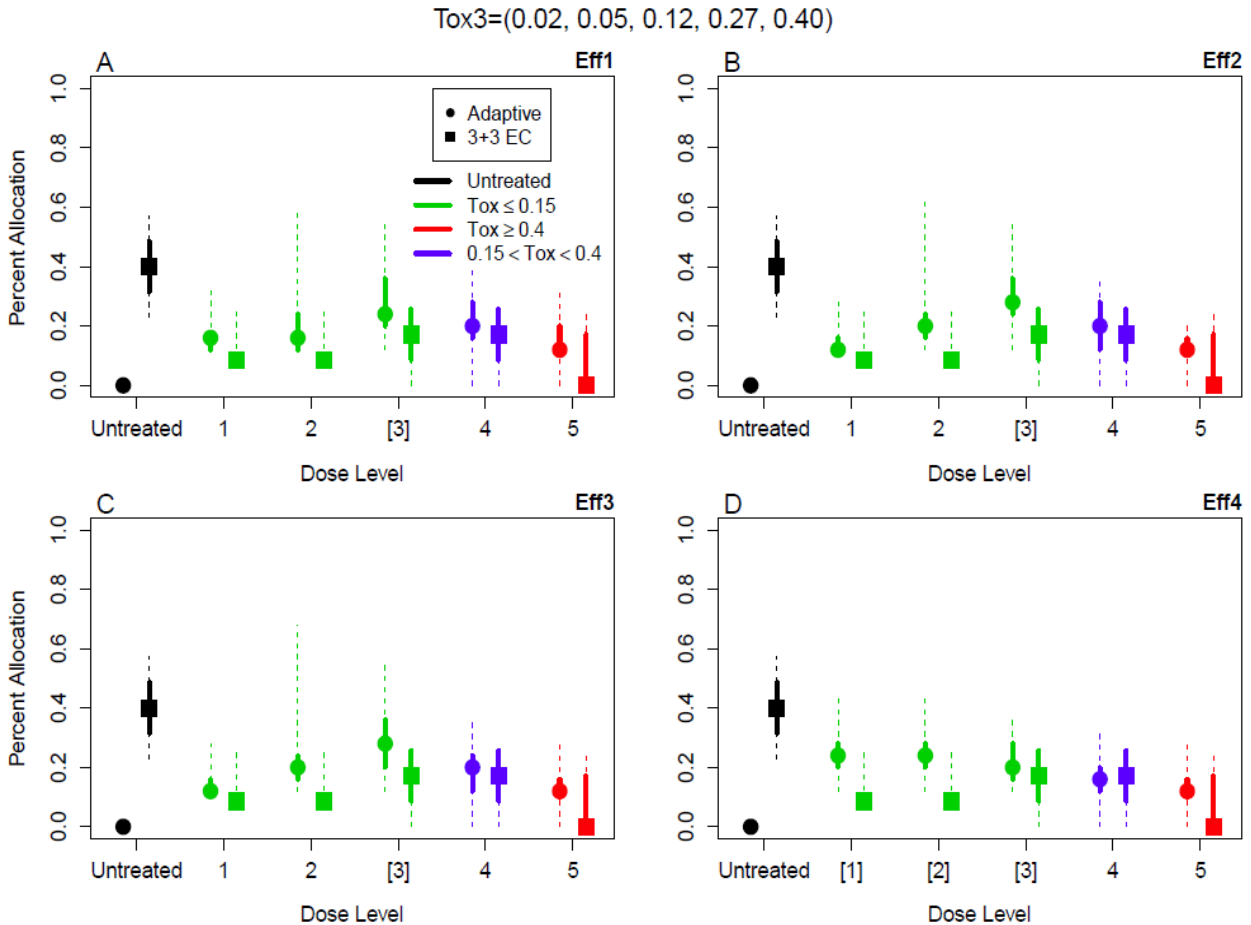

Figure 5. Percent allocation per dose for the two-stage adaptive design versus '3+3' EC. Results of 5,000 simulated trials for each combination of toxicity 3 scenario with all four efficacy scenarios are summarized as: median (filled circle/square), 25^{th} - 75^{th} percentiles (solid line), and 2.5^{th} - 97.5^{th} percentiles (dashed line).
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The best doses having a probability of toxicity less than or equal to 25% and the highest T-cell percent persistence are marked by [].

Results: Non-toxic ($P(DLT = 0.02)$)

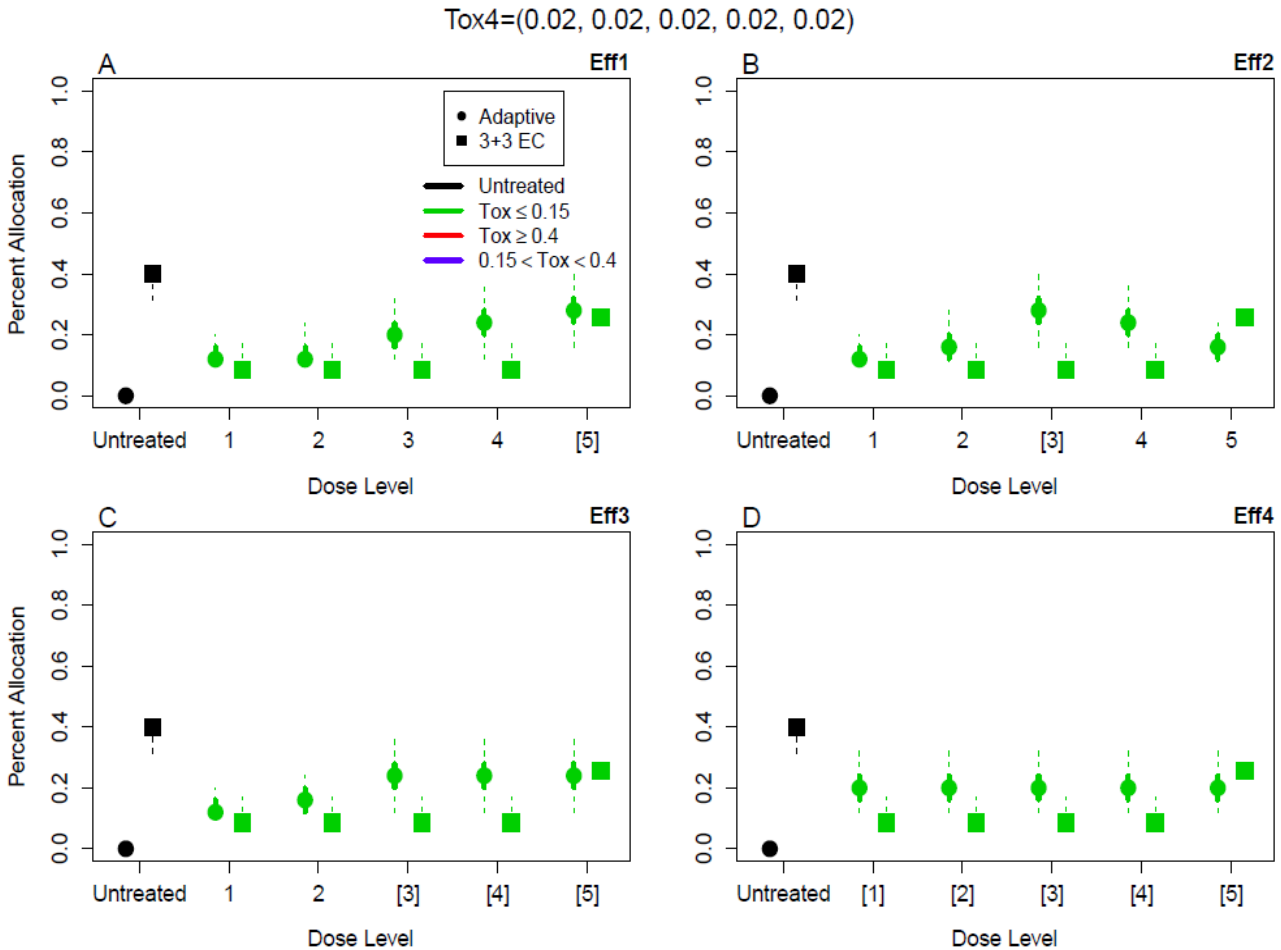

Figure 6. Percent allocation per dose for the two-stage adaptive design versus '3+3' EC. Results of 5,000 simulated trials for each combination of toxicity 4 scenario with all four efficacy scenarios are summarized as: median (filled circle/square), 25^{th} - 75^{th} percentiles (solid line), and 2.5^{th} - 97.5^{th} percentiles (dashed line).
Eff1=(0.05, 0.15, 0.40, 0.65, 0.80), Eff2=(0.05, 0.25, 0.70, 0.65, 0.20), Eff3=(0.05, 0.25, 0.65, 0.65, 0.65), Eff4=(0.60, 0.60, 0.61, 0.62, 0.60).
The best doses having a probability of toxicity less than or equal to 25% and the highest T-cell percent persistence are marked by [].

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.
- When doses are toxic, behaves more like a traditional dose escalation design led via toxicity.
- When there is no or low toxicity, "better" doses are sampled more frequently.

Outline

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?

Outline

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