

The Changing Face of Early Phase Studies in Oncology Therapeutics: Tensions in a New Era of Immunotherapies

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Outline

Redefining the Objectives

A New Era

A Novel Design for Adoptive T-Cell Therapy

Methods

Stage 1

Stage 2

Simulations

Results

Comparison to '3+3' with standard expansion

Comparison of $N = 25$ vs. $N = 50$ for increasing toxicity

Discussion points

References

Redefining the objectives

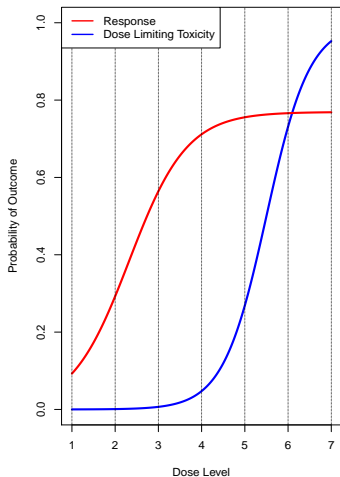
- In traditional cancer treatment, the dogma has always been to administer all drugs at the maximum tolerated dose (MTD)
- The same approach would not be expected to apply to molecularly targeted agents and immunotherapies
- There is a need to redefine the criteria used for defining the recommended phase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

* Ratain, Nature Reviews Clinical Oncology, 2014.

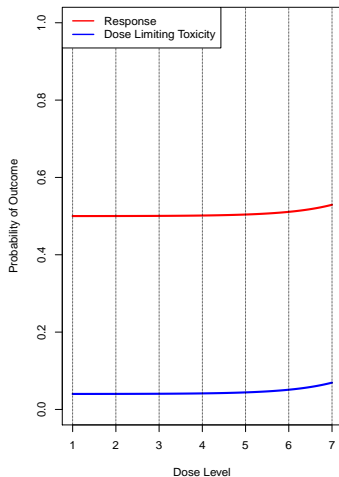


Assumptions of dose finding designs

Classical Assumption



More Recent Observations



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**

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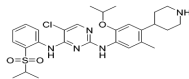
References

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 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.



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.



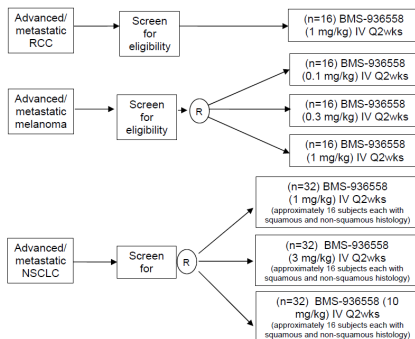
Expansion Cohorts in Nivo Phase I

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

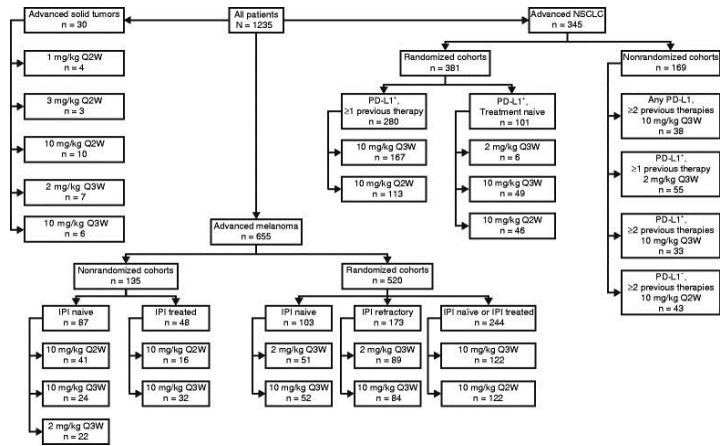


See Pembrolizumab (Keytruda) for a similar story

- Keytruda is a programmed death-1 (PD-1) immune checkpoint inhibitor.
- April 2013: Earns breakthrough designation for advanced melanoma (2nd line)
- September 2014: Approved for 2nd line advanced refractory melanoma
- October 2014: Approved for advanced non-small cell lung cancer (NSCLC)
- November 2015: Earns breakthrough designation for MSI-H metastatic colorectal cancer
- December 2015: Expanded use approval: 1st line advanced melanoma

Pembrolizumab “phase I study”

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, even after hundreds of patients
- Haphazard dose escalation based on MTD paradigm
- **These examples highlight the need for novel dose-finding approaches**
- How could these trials have been better designed, given these characteristics?

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

- Meetings, Panels, Symposia
 - 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.
- New publications (among others)
 - Iasonos and O’Quigley. **Design considerations for dose-expansion cohorts in phase I trials.** JCO. November 2013.
 - Boonstra et al. **A statistical evaluation of dose expansion cohorts in phase I clinical trials.** JNCI. February 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
- “Expansion cohorts” are getting bigger and their role is expanding.
- 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
- And what about combination therapies with this profile?

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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 a set of potentially optimal doses to maximize efficacy while maintaining safety.
- Two-stage design:
 - Stage 1: Explore doses for safety and obtain information on immunologic 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 relatively easy to understand

- clinician 'buy-in'
- statistician 'buy-in'

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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)
- Allowable doses: weak evidence, or acceptable dose.

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

<i>DLT</i>	'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 doses.

- 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 :

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

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

Note: can be some other sensible model.

Stage 2: Adaptive randomization

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

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

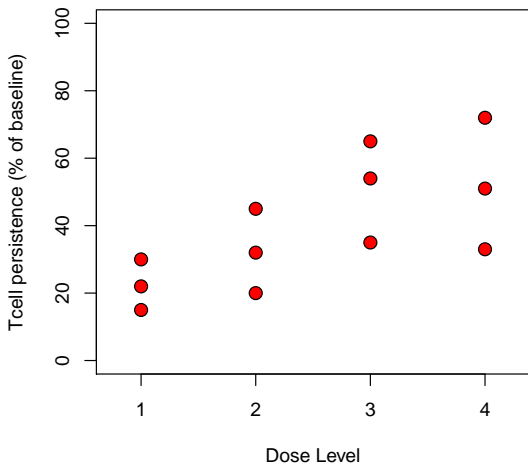
Calculate the randomization probabilities π_j for doses $j = 1, \dots, J$ (Thall & Wathen, Eur J Cancer, 2007):

$$\pi_j = \frac{\hat{p}_j}{\sum_r \hat{p}_r} \quad (\text{better for large } N)$$

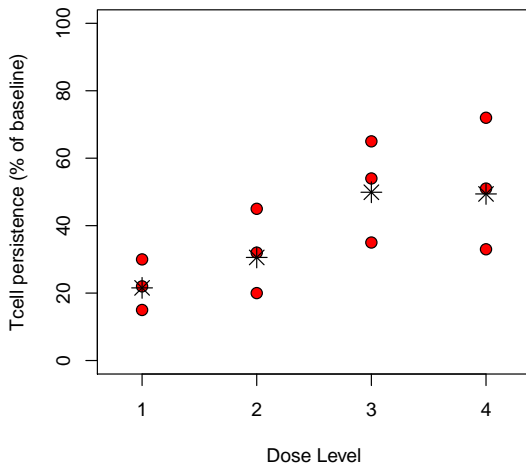
or

$$\pi_j = \frac{\sqrt{\hat{p}_j}}{\sum_r \sqrt{\hat{p}_r}} \quad (\text{better for small } N)$$

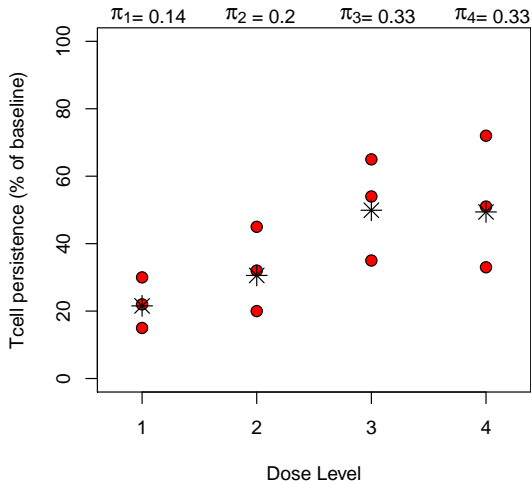
Example 1: shallow slope ($N = 3$ per dose)



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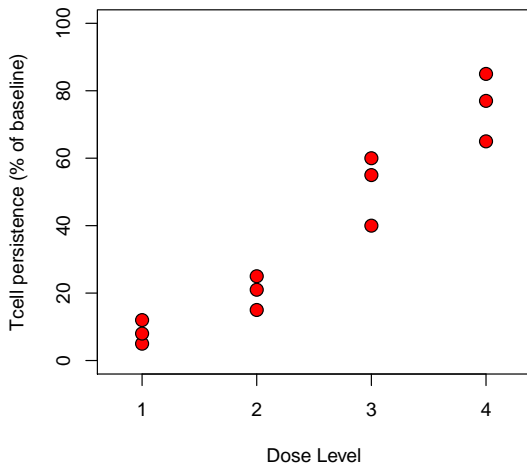


Example 1: shallow slope ($N = 3$ per dose)

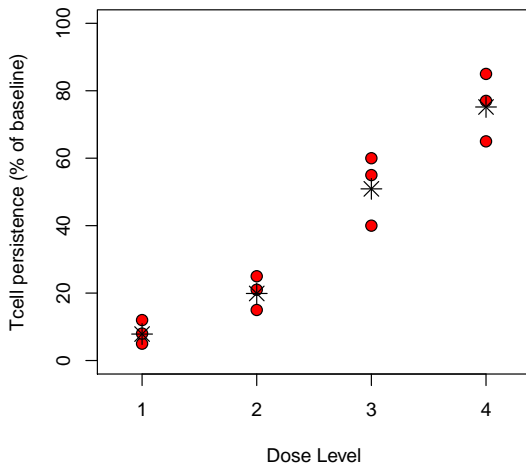




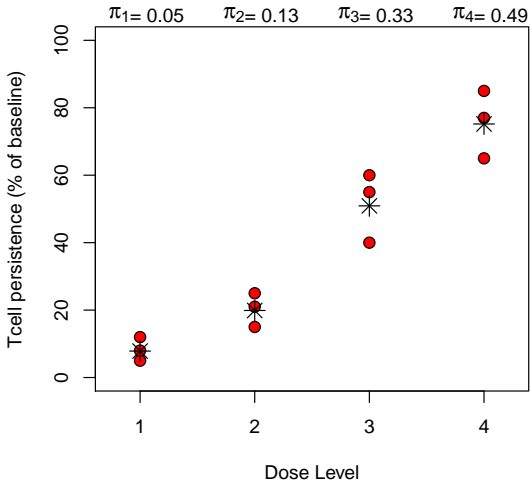
Example 2: steep slope ($N = 3$ per dose)



Example 2: steep slope ($N = 3$ per dose)



Example 2: steep slope ($N = 3$ per dose)





Stage 2

- For the first patient in Stage 2, randomize to allowable doses $j = 1, \dots, J$ 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.
- ≤ 2 DLTs in 5 pts: allowable dose
- ≥ 3 DLTs in 5 pts: unacceptable dose (and all higher doses unacceptable)

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

<i>DLT</i>	$L(p_1)/L(p_2)$	$k = 4$
0	$LR = 0.18$	acceptable
1	$LR = 0.66$	weak
2	$LR = 2.50$	weak
3	$LR = 9.45$	toxic
4	$LR = 35.7$	toxic

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

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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

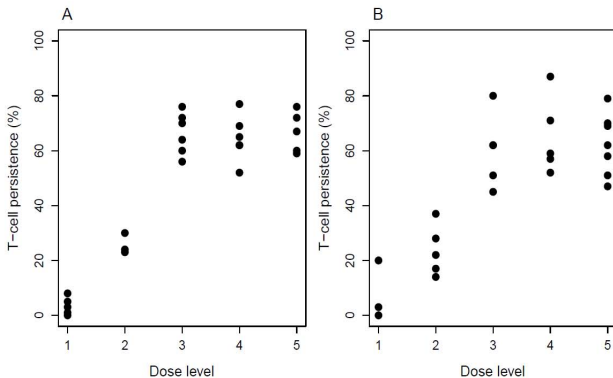


Figure 1. Illustration of variability among doses using a beta-distribution variance of 0.002 (A) versus 0.01 (B). A plateau trend for T-cell persistence as function of dose (0.05, 0.25, 0.65, 0.65, 0.65) and a total sample size of 25 patients are used in both cases.

Simulating Toxicity and Efficacy Outcomes

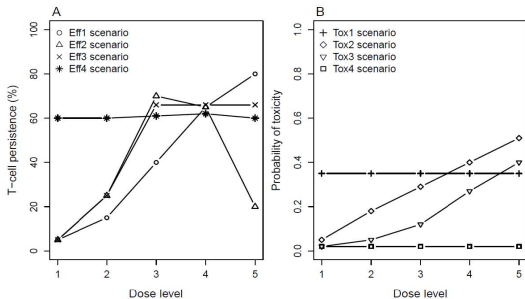


Figure 2. Simulated efficacy (A) and toxicity (B) scenarios as a function of dose level. The efficacy outcome is defined as persistence (%) of transduced T-cells at follow-up compared to baseline.

- 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.

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 to compare to traditional design
- Comparison of $N = 25$ vs. $N = 50$ given increase in sample sizes in recent trials

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“Pretty toxic at all levels” scenario

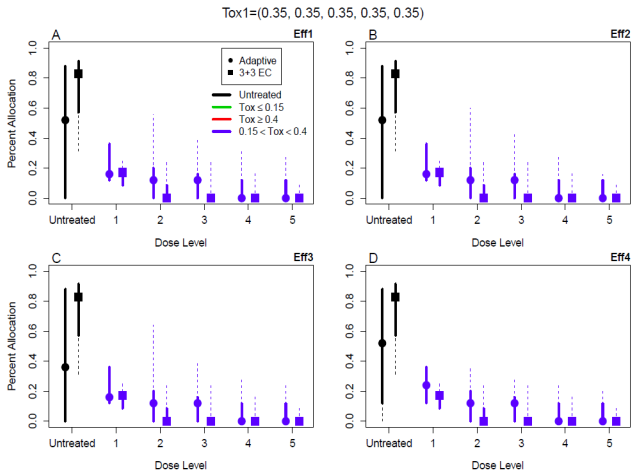


Figure 3. Percent allocation per dose for the two-stage adaptive design versus ‘3+3’ EC. Results of 5,000 simulated trials for each combination of toxicity 1 scenario with all four efficacy scenarios are summarized as: median (filled circle/square), 25th - 75th percentiles (solid line), and 2.5th - 97.5th 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 [].

“Increasing toxicity, more toxic” scenario

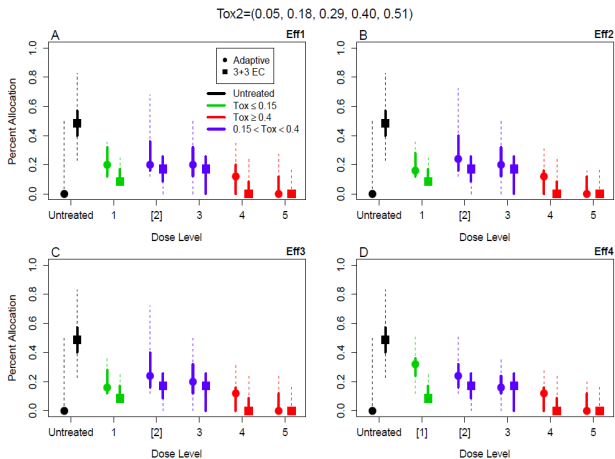


Figure 4. Percent allocation per dose for the two-stage adaptive design versus “3+3” EC. Results of 5,000 simulated trials for each combination of toxicity 2 scenario with all four efficacy scenarios are summarized as: median (filled circle/square), 25th - 75th percentiles (solid line), and 2.5th - 97.5th 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 [].

“Increasing toxicity, less toxic” scenario

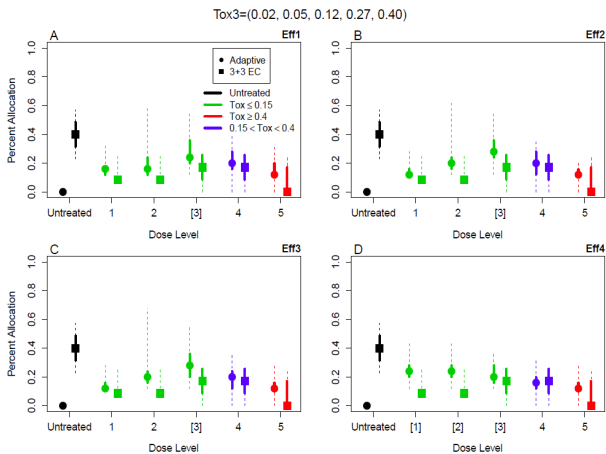


Figure 5. Percent allocation per dose for the two-stage adaptive design versus ‘3+3’ EC. Results of 5,000 simulated trials for each combination of toxicity 3 scenario with all four efficacy scenarios are summarized as: median (filled circle/square), 25th - 75th percentiles (solid line), and 2.5th - 97.5th 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 [].

“Non-toxic ($P(DLT = 0.02)$)” scenario

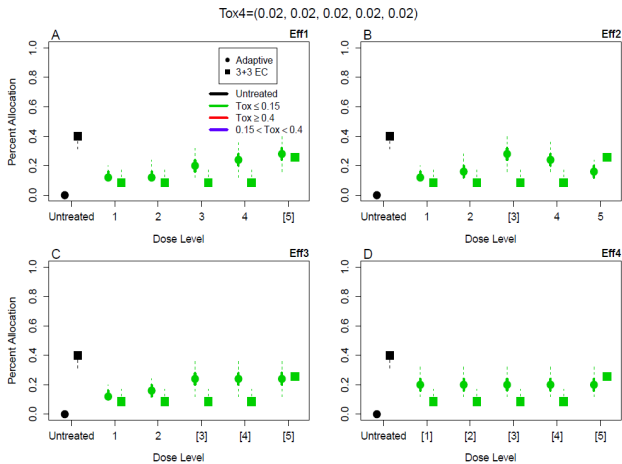
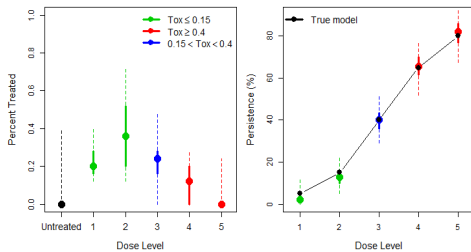


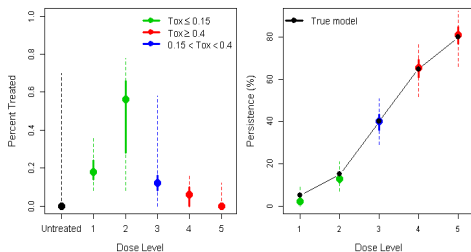
Figure 6. Percent allocation per dose for the two-stage adaptive design versus ‘3+3’ EC. Results of 5,000 simulated trials for each combination of toxicity 4 scenario with all four efficacy scenarios are summarized as: median (filled circle/square), 25th - 75th percentiles (solid line), and 2.5th - 97.5th 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, 0.60, 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 [].

Linear trend in Persistence scenario

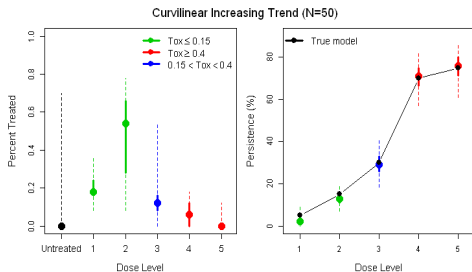
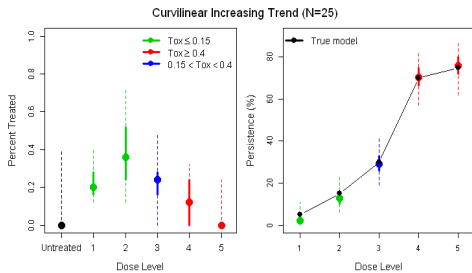
Linear Increasing Trend (N=25)



Linear Increasing Trend (N=50)



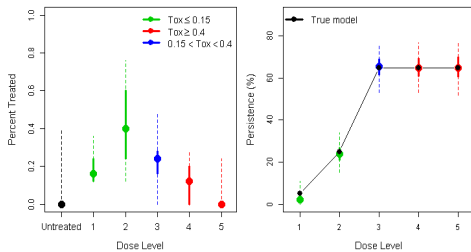
Curvilinear trend in Persistence scenario



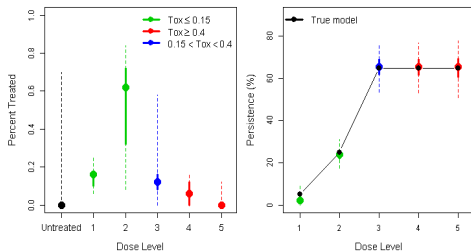


Plateau trend in Persistence scenario

Plateau Trend (N=25)

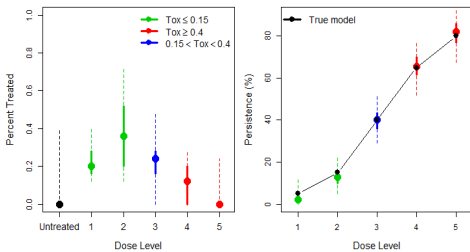


Plateau Trend (N=50)

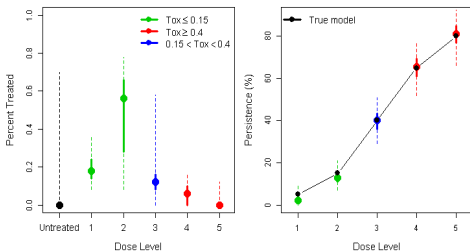


Flat trend in Persistence scenario

Linear Increasing Trend (N=25)



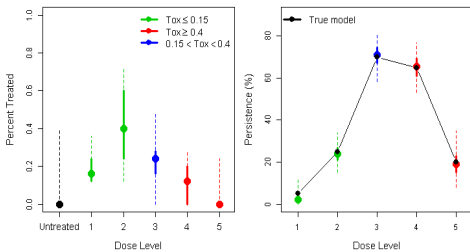
Linear Increasing Trend (N=50)



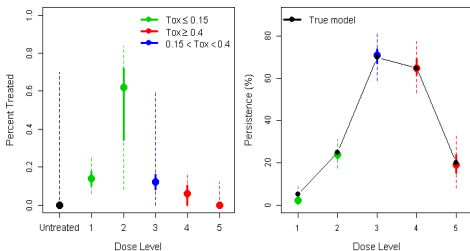


Quadratic trend in Persistence scenario

Quadratic Trend (N=25)



Quadratic Trend (N=50)



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Inferences from Results

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.

Inferences from Results

- $N = 50$ seemed large when we started looking into this; now it does not!
 - Comparison of the modern approaches with large expansions cannot be made to '3+3'
 - Designing dose-finding studies with 50-100 patients (or more) is totally reasonable in this new paradigm.
 - There is a shift towards on a drug development program in one protocol (for better or worse).

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

Redefining the Objectives

A New Era

A Novel Design for Adoptive T-Cell Therapy

Methods

Stage 1

Stage 2

Simulations

Results

Comparison to '3+3' with standard expansion

Comparison of $N = 25$ vs. $N = 50$ for increasing toxicity

Discussion points

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