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Toxicity-evaluation designs for cancer immunotherapy trials.

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Presenter Disclosure Information

Karen Messer

The following relationships exist related to this presentation:

No Relationships to Disclose

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Setting

Phase I/II immunotherapy trials

- Agents with low expected toxicity
  - < 10% DLT rate
  - DLT: Dose Limiting Toxicity
- Expect that

Therapeutic dose < Maximum Tolerated Dose

- Goal is to establish safety of therapeutic dose

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Reminder: 3+3 design

- Escalate dose until you see DLT's, then stop
  - Maximum Tolerated Dose (MTD) is one dose below stopping dose
- Commonly used (although inefficient)
- There is a nice theoretical literature
- Rarely compute formal estimates of
  - toxicity rate at MTD
  - Expected sample sizes under high, low toxicity

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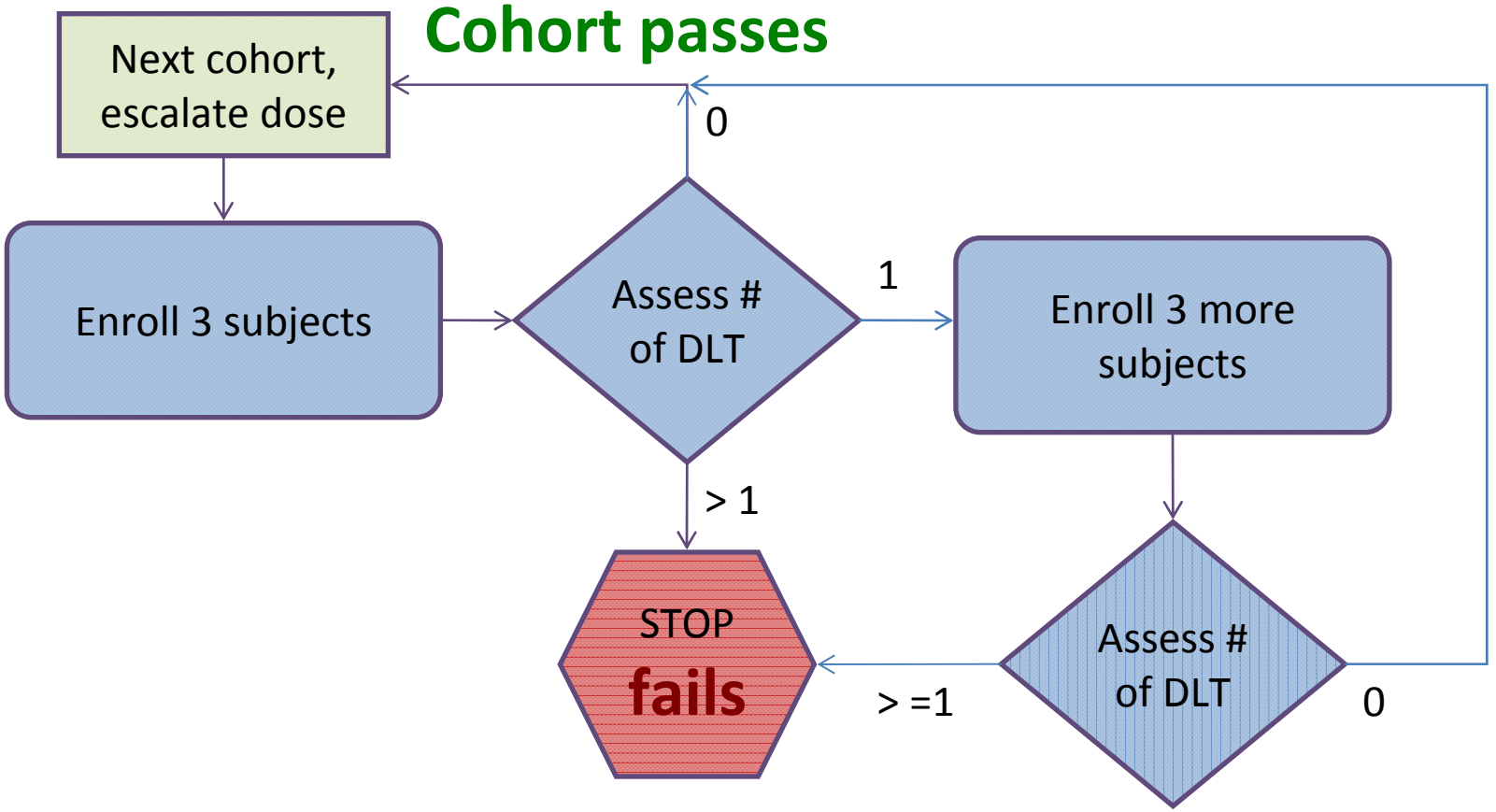
3+3 cohort design



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Quick lit review

Crowley et al (2006) Handbook of Statistics in Clinical Oncology

Durham, Flournoy, Rosenberger, (1997) *Biometrics*

Gemzu and Flournoy (2006) JSPI review.

- Isotonic regression estimators Leung and Wang (2001) CCT
  Flournoy et al (2003, 2006) Paul and Rosenberger (2004)

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This paper

Research Article

Statistics in Medicine

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Toxicity-evaluation designs for phase I/II cancer immunotherapy trials

Karen Messer,[a]*† Loki Natarajan,[a] Edward D. Ball[b] and Thomas A. Lane[b]

Adds formal safety estimate to 3+3 design
Can run overlaid on two stage Phase II design

Aims of Tox-Eval design

1. Phase I: formal test of safety hypothesis.
   - The Phase I trial serves as an interim safety analysis.
2. Phase II: confidence interval for DLT rate, at therapeutic dose, combining Phase I/II data
3. Phase I sample size n_1 is the smallest that allows a safety test at 5% significance.
4. Phase II sample size n_2 is the smallest that supports a target margin of error on final conf. interval.
   - Incorporate Phase II efficacy test

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Design characteristics

- Parameters:
  - Expected toxicity rate t_a (≤ 10%)
  - Maximum acceptable safety threshold t_0
- A short run in dose for escalation, then stay at therapeutic dose
- Simple, based on familiar 3+3 design
- Works well at specific toxicity rates t_0 and t_a
  - Somewhat inflexible

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Test of size α

$$H_0 : t \geq t_0 \text{ v.s. } H_a : t < t_0.$$

using *the fewest subjects possible*.

- "Unacceptable toxicity" will stand by default, unless the data compel us to say otherwise.
- Should Phase I succeed, the conclusion will be:
  " Toxicity rate at therapeutic dose $< t_0$, at $(1 - \alpha)100$ confidence."

Test statistic is # of dose cohorts that 'pass' the 3+3 rule

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Group sequential design

- 3+3 dose cohorts
  each at therapeutic dose.
- Assess cohort i prior to enrolling cohort $i + 1$.
- Each cohort *passes* or *fails*

PASS 0 of 3 or 1 of 6 DLT's
FAIL 2 or more DLT's

- Enroll up to $i = m$ cohorts.

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Hypothesis test

$$H_0 : t \geq t_0 \text{ v.s. } H_a : t < t_0.$$

- If m cohorts pass:

  Reject null.
  With 95% confidence, $t < t_0$.

- If fewer than m cohorts pass:

  Fail to reject null.
  There is insufficient evidence to demonstrate safety.

Design properties

- Expected sample size $E[N]$ is determined as the smallest design that will support a test of safety at level (t_0, α)
- Let t_a be actual expected toxicity rate. The design is appropriate only for t_a with adequate power (80%).
- That is, only when the expected toxicity rate t_a is far below the acceptable rate t_0.
- FDA requires ample pre-clinical and clinical evidence that this is the case.

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"Typical" Phase I test:

For

- $t_0 = 33\%$
- and $\alpha = 0.05, \quad m = 4.$

With $m = 4$ cohorts, in a standard 3+3 design, if all 4 pass then with 95 confidence the rate of DLT is less than 33%

We have then established that $p < 0.33$. Go on to Phase II.

Power ≥ 80% if $t_a \leq 6.5\%$

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Operating characteristics

- If toxicity is low, what is probability that you pass Phase I? (power)
- If toxicity is high, what is expected sample size? (safety)
- How many DLT's do you expect to see?

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t_0 determines sample size

Table I. Required number of cohorts and alternative toxicity rates to achieve given size and 80 per cent power, 3+3 toxicity-estimation design.

			$\alpha = 0.05$, Power = 80 per cent				
t_0	$p(t_0)$	m	t_a	$E[N\|t_0]$	$E[\text{DLT}\|t_0]$	$E[N\|t_a]$	$E[\text{DLT}\|t_a]$
0.20	0.71	9	0.048	13.6	2.7	27.7	1.3
0.25	0.60	6	0.059	10.2	2.5	19.0	1.1
0.30	0.49	5	0.065	8.3	2.5	16.1	1.1
0.33	0.43	4	0.074	7.4	2.4	13.15	0.97
0.35	0.40	4	0.074	7.0	2.4	13.15	0.97
0.40	0.31	3	0.086	6.0	2.4	10.7	0.87

As safety test becomes more stringent, sample sizes increase

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t_0 determines feasible $t_a << t_0$

Table I. Required number of cohorts and alternative toxicity rates to achieve given size and 80 per cent power, 3+3 toxicity-estimation design.

		$\alpha = 0.05$, Power = 80 per cent					
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0.33	0.43	4	0.074	7.4	2.4	13.15	0.97
0.35	0.40	4	0.074	7.0	2.4	13.15	0.97
0.40	0.31	3	0.086	6.0	2.4	10.7	0.87

As safety test becomes more stringent, expected tox rate must be smaller

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Phase II sample size

Table II. Standard deviation of $\tilde{t}$, the minimum variance estimator of the toxicity rate using the Phase I and Phase II data, for a range of rates t_a and Phase II sample sizes n.

					$n=10$		$n=15$		$n=20$	
t_0	t_a	m	$E[N\|t_a]$	$SD(\hat{t}_1)$	$SD(\hat{t}_2)$	$SD(\hat{t})$	$SD(\hat{t}_2)$	$SD(\hat{t})$	$SD(\hat{t}_2)$	$SD(\hat{t})$
0.20	0.048	9	27.7	0.025	0.068	0.023	0.055	0.022	0.048	0.022
0.25	0.059	6	19.0	0.036	0.075	0.033	0.061	0.031	0.053	0.030
0.30	0.065	5	16.1	0.043	0.078	0.038	0.064	0.036	0.055	0.034
0.33	0.074	4	13.2	0.054	0.083	0.045	0.068	0.042	0.059	0.040
0.35	0.074	4	13.2	0.054	0.083	0.045	0.068	0.042	0.059	0.040
0.40	0.086	3	10.7	0.072	0.089	0.056	0.072	0.051	0.063	0.047

Phase II sample sizes support reasonable confidence limits estimated DLT rate

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Phase II sample size

Table II. Standard deviation of $\tilde{t}$, the minimum variance estimator of the toxicity rate using the Phase I and Phase II data, for a range of rates t_a and Phase II sample sizes n.

					$n=10$		$n=15$		$n=20$	
t_0	t_a	m	$E[N\|t_a]$	$SD(\hat{t}_1)$	$SD(\hat{t}_2)$	$SD(\hat{t})$	$SD(\hat{t}_2)$	$SD(\hat{t})$	$SD(\hat{t}_2)$	$SD(\hat{t})$
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0.30	0.065	5	16.1	0.043	0.078	0.038	0.064	0.036	0.055	0.034
0.33	0.074	4	13.2	0.054	0.083	0.045	0.068	0.042	0.059	0.040
0.35	0.074	4	13.2	0.054	0.083	0.045	0.068	0.042	0.059	0.040
0.40	0.086	3	10.7	0.072	0.089	0.056	0.072	0.051	0.063	0.047

Expected combined sample at therapeutic dose is E[N] + n

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Summary, Tox-Eval design

For low toxicity agents:

- Phase I formal test of safety
- Confidence intervals on DLT rate at reasonable Phase II n's
- Implementation is familiar and simple
- Computations are not burdensome
  - Tables of sample sizes available

Works well- we are using this design.

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Statistical refinements

- The Tox-Eval design is not based on a sufficient statistic, hence is necessarily inefficient
  - (But not by much!)
- Covers a restricted set of design paramters
  - i.e. If $t_0 = 30\%$ then $t_a \leq 6.5\%$

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Extension: exact group sequential designs

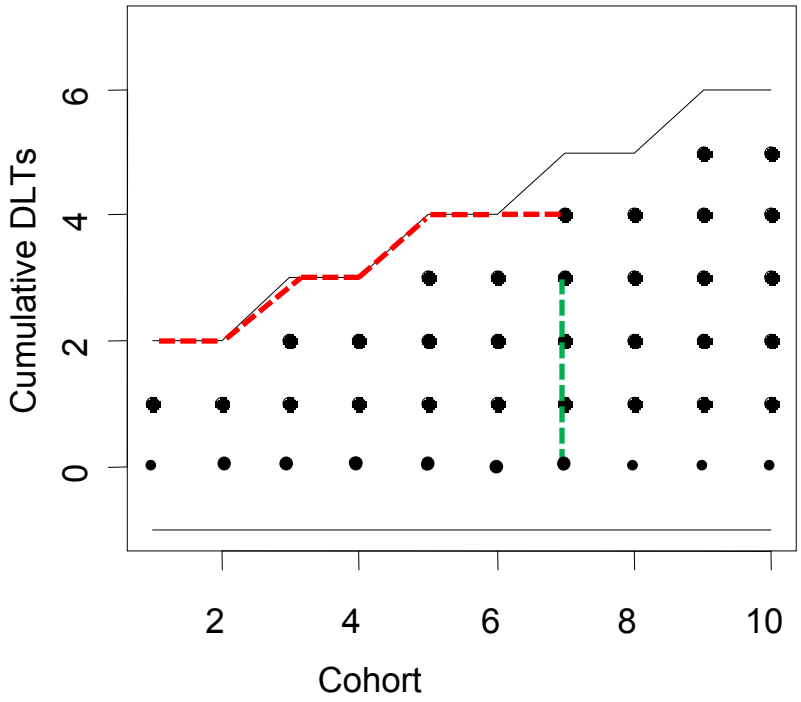
Example: a trial of stem cell therapy in stroke

- t_0 = 30% and t_a = 10%
- test of size α = 10%

The corresponding 3+3 design :

- M=4 cohorts
- Expected sample sizes
  - Null (toxic): 8 subjects
  - Alternative (safe) : 13 subjects
- *Power* 82% at t_a = 7% ; only 67 % at t_a = 10%

An exact group sequential design



One sided:

- Stop early for toxicity
- Declare 'safe" (t < 30%)

Moral: the GS design with comparable size and power is very similar, given feasible t_0 and t_a

M=4 cohorts

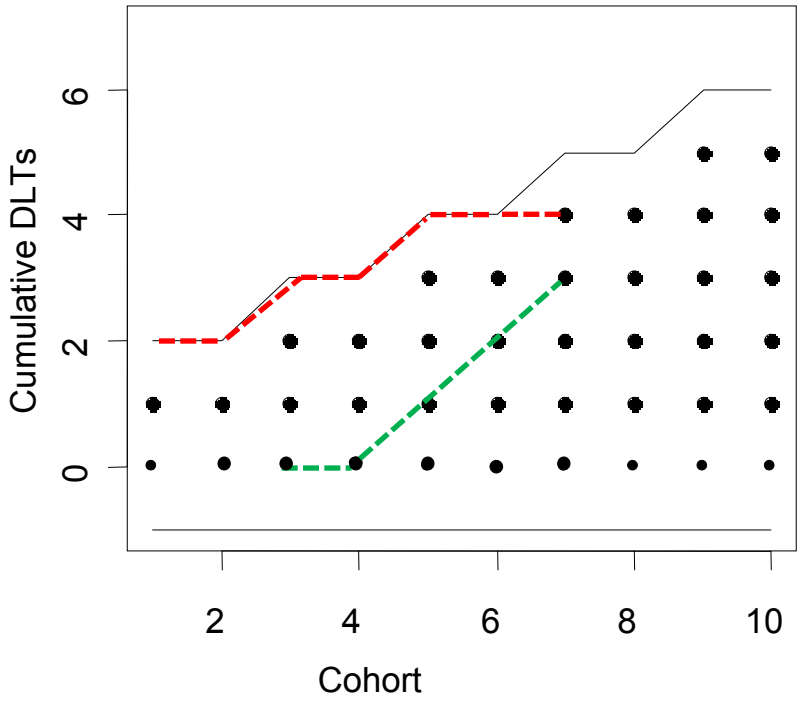
Expected sample sizes

Null (toxic): ~~8~~ 7.2 subjects

Alternative (safe) : ~~13~~ xx subjects

Power ~~82%~~ 80 % at t_a = 7% ; only ~~67 %~~ 66% at t_a = 10%

An exact group sequential design



Two sided:

- Stop early for toxicity
- Declare 'safe" (t < 30%)

Moral: Exact GS designs are more complex,
but also more flexible in terms of feasible t_0 and t_a

M=7 cohorts

Expected sample sizes

Null (toxic): ~~8~~ 8.6 subjects

Alternative (safe) : ~~13~~ xx subjects

Power ~~82%~~ at t_a = 7% ; only ~~67 %~~ 79% at t_a = 10%

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Exact GS designs

- Are more complex
- Do not add much, if there is a Tox-Eval design that fits
- However, cover a wider range of possible t_0, t_a
  - We have code to implement these, but it is not yet published.

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Thank you!

Collaborators:

- Loki Natarajan
- Colleen Kelly
- Ted Ball
- Tom Lane