Randomized dose-escalation design for drug combination cancer trials with immunotherapy

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Immunotherapy in Phase I clinical trials

Phase I conventional paradigm: the more the better

Important exceptions: molecularly targeted agents (e.g. immunotherapy).

- ⋆ Immune system can regulate/eliminate tumours
- ⋆ Low toxicity profile

Example:

immune-checkpoint proteins blocker anti-programmed-death-receptor-1 (PD1) Pembrolizumab

- ⋆ None of the trials reached MTD
- ⋆ Plateau found. Same toxicity/activity probability for 2 and 10 mg/kg
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Combinations with immunotherapy

Immunotherapy is enough not efficacious in cancer treatment by itself

Current investigations:

- ⋆ the added value of immune checkpoint blockers to backbone therapy
- ⋆ the added value of a new drug to an immune checkpoint blocker.

One drug is administered at **full dose** while the other is **escalated**.

Objectives of the trial:

- ⋆ To find the maximum tolerated combination (MTC)
- ⋆ To detect clinically significant difference between the MTC and standard therapy alone (required by EMA)
- ⋆ To detect a possible dose effect in the combination

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Current approach

Current design: **one parameter CRM design** for single agent trial

Advantages:

- ⋆ Ability to find MTC with high probability
- ⋆ Well-known properties

Disadvantages:

- ⋆ Strong monotonicity assumption
- ⋆ No possibility of a plateau detection
- ⋆ Does not allow a statistical comparison of toxicities

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Proposals

Flexible model:

- ⋆ E_{max} model
- ⋆ A plateau in a dose-toxicity relation
- ⋆ Ability to model the toxicity probability on the single agent alone independently

Randomization between a control and an investigation arm

- ⋆ control is standard therapy
- ⋆ prevents a selection bias
- ⋆ allows statistical comparison of the toxicity
- ⋆ ethical

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Bayesian CRM

Combination of A (fixed) and B: $\tilde{d}_0 = \{a, b_0\}, \tilde{d}_1 = \{a, b_1\}, \ldots, \tilde{d}_m = \{a, b_m\}$

Model $p_i = \psi(d_i, \theta)$; d_i is a unit-less amount of drug

θ is a vector of parameters

Given binary outcomes, the CRM updates the posterior $f_j(\theta)$

$$f_j(\theta) = \frac{f_{j-1}(\theta)\mathcal{L}(d, y, \theta)}{\int_{\mathbb{R}^d} f_{j-1}(u)\mathcal{L}(d, y, u)\mathrm{d}u} \tag{1}$$

The posterior mean **(!)**

$$\hat{p}_k^{(j)} = \mathbb{E}(\psi(d_k, a)|\mathbb{Y}_j) = \int_{\mathbb{R}^d} \psi(d_k, u) f_j(u)\mathrm{d}u \tag{2}$$

Main debate: choice of model $\psi(d_k, a)$

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E_{max} model

$$\psi(d_i, E_0, E_{max}, \lambda, ED_{50}) \equiv \psi(d_i, \theta) = E_0 + \frac{d_i^{\lambda} E_{max}}{d_i^{\lambda} + ED_{50}^{\lambda}} \tag{3}$$

- E_0 is the probability of toxicity on the control
- $E_{max} + E_0$ is the maximum probability of toxicity
- ED_{50} is the combination which produces $E_0 + \frac{E_{max}}{2}$
- $\lambda \geq 0$ is the slope factor

Skeleton construction:

$$d_i = \hat{ED}_{50}^{(0)} \times \left(\frac{\hat{p}_i(0) - \hat{E}_0^{(0)}}{\hat{E}_{max}^{(0)} + \hat{E}_0^{(0)} - \hat{p}_i(0)} \right)^{\frac{1}{\hat{\lambda}^{(0)}}}$$

By definition, $\hat{p}_0(0) \equiv \hat{E}_0^{(0)} \rightarrow d_i = 0$

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Randomization

Assignment cohort-by-cohort

$$c = c_1 + c_2$$

- $\star$ c_1 be the number of patients assigned to the current best combination
- $\star$ c_2 be the number of patients assigned to the control, d_0.

For instance, taking $c_1 = 3$ and $c_2 = 1$, one will end up with 25% of the total sample size being assigned to the control.

CRM with randomization results in the majority of patients on **two** combinations: control and MTC.

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Simulations setting

- ⋆ Sample size $n = 48$
- ⋆ $m = 7$ combinations
- ⋆ Target probability $\gamma = 0.25$;
- ⋆ Clinically significant difference $\tau = 0.05$
- ⋆ Confidence level $\alpha = 0.9$
- ⋆ $c_1 = 3$, $c_2 = 1 \rightarrow 25\%$ on the control treatment.

Characteristics

(i) Proportion of correct recommendations

(ii) Proportion of times the clinically significant difference is found

$$\mathcal{P} \equiv \mathbb{P}\left(\mathbb{P}\left(p_{MTC} - p_{control} \geq \tau\right) > \alpha\right) \tag{4}$$

(iii) Goodness of fit measure

$$NMSE = \frac{1}{N}\sum_{j=1}^{N}\sqrt{\frac{\sum_{i=1}^{n}(p_i - \psi(d_i, \hat{\theta}^{(j)}))^2}{\sum_{i=1}^{n}(p_i - \hat{p}_i^{opt})^2}} \tag{5}$$

Prior and comparators

Skeleton

$$\mathbb{P}_0 = [\mathbf{0.08}, 0.25, 0.35, 0.45, 0.55, 0.65, 0.70, 0.75]^{\mathrm{T}}$$

Information to construct prior distributions for model parameters:

(i) Control: upper bound of the 95% credibility interval is 0.25.

(ii) Prior MTC: upper bound of the 95% credibility interval is 0.80.

$$E_0 \sim \mathbb{B}(0.8, 10-0.8);\ \lambda \sim \Gamma(1,1);\quad E_{max}|E_0 \sim \mathbb{U}[0, 1-E_0];\ ED_{50} \sim \Gamma(0.4, 0.4);$$

Comparators

(P1) **One-parameter** power model (**no randomization**):

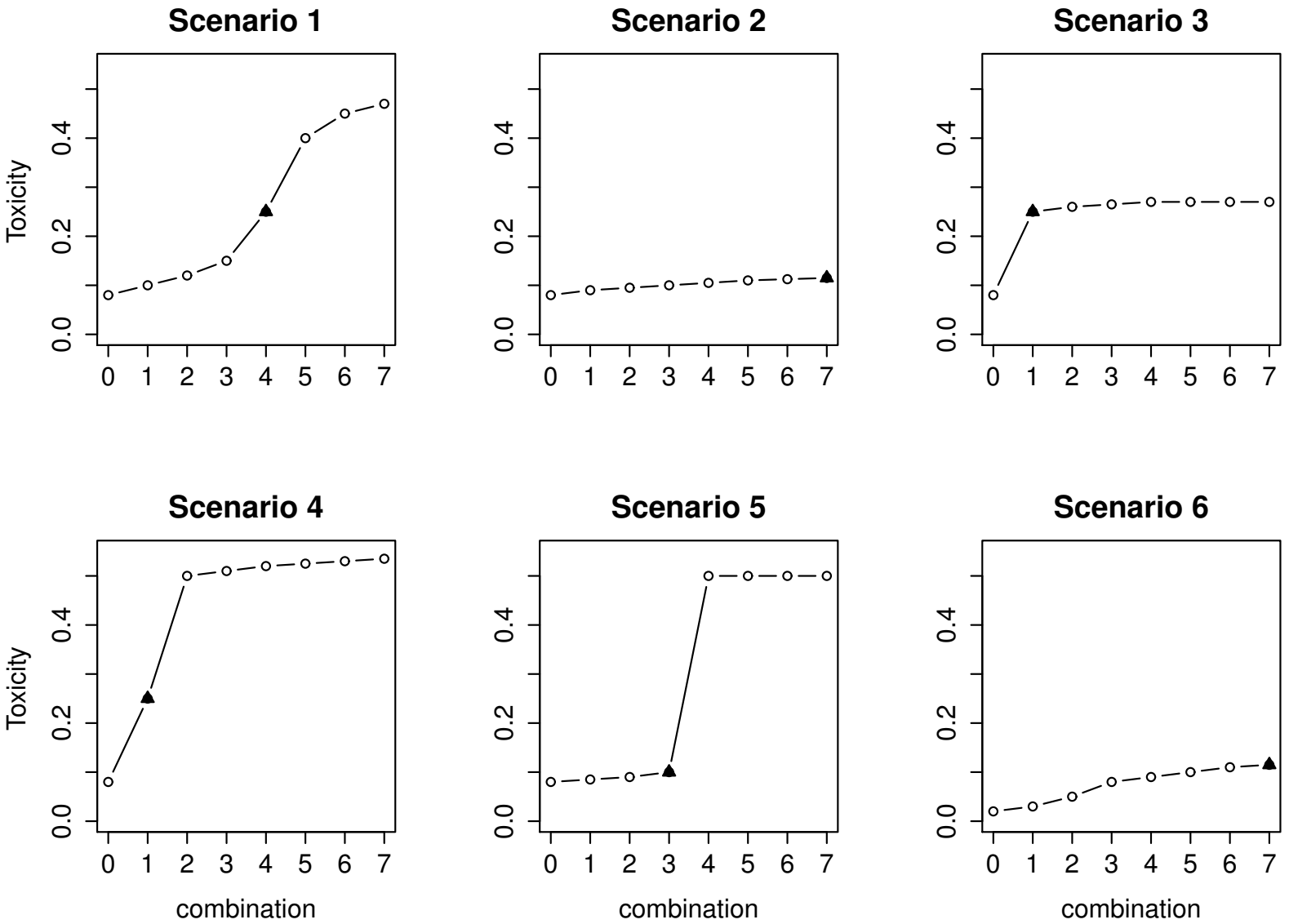
$$\psi(d_i, z) = d_i^z.$$

(L2) **Two-parameter** logistic models

$$\psi(d_i, \beta_1, \beta_2) = \frac{\exp(\log(\beta_1) + \beta_2 d_i)}{1 + \exp(\log(\beta_1) + \beta_2 d_i)}$$

with (R) and without randomization.

Scenarios


Scenario 1
Scenario 2
Scenario 3
Scenario 4
Scenario 5
Scenario 6
Toxicity
combination
0.0
0.2
0.4
0 1 2 3 4 5 6 7

Results (I)

	d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7	TR
Sc 1	0.08	0.10	0.12	0.15	0.25	0.40	0.45	0.47	
$E_{max}(R)$	0.0	2.1	8.7	22.9	**45.1**	13.6	3.8	3.7	19.1
$L2(R)$	0.0	1.8	8.3	26.5	**44.6**	13.8	3.1	2.0	19.2
$L2$	0.4	0.1	3.3	24.9	**52.6**	16.4	2.1	1.3	25.1
$P1$	0.0	1.0	4.2	16.5	**51.4**	20.4	5.5	1.0	29.2
Sc 2	0.08	0.09	0.095	0.10	0.10	0.11	0.11	0.11	
$E_{max}(R)$	0.0	0.3	0.5	0.9	0.5	1.6	1.9	**94.4**	10.2
$L2(R)$	0.0	0.62	0.75	1.50	3.00	2.13	1.75	**90.2**	10.6
$L2$	0.3	0.1	0.3	0.5	1.8	1.0	0.5	**95.6**	11.4
$P1$	0.0	0.0	0.0	0.0	0.0	0.6	0.8	**98.7**	11.3

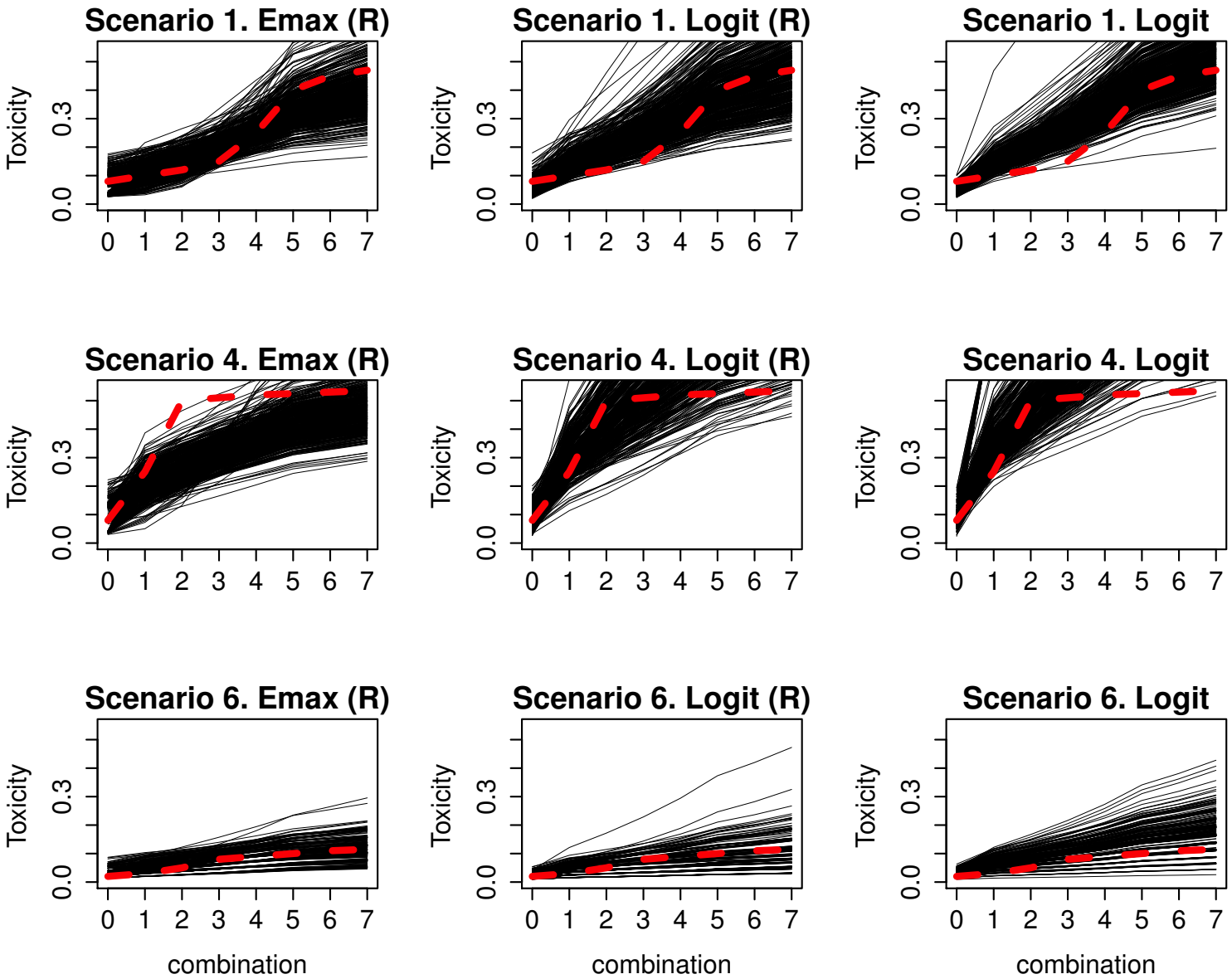
Results (II)

	d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7	TR
Scenario 4	0.08	0.25	0.50	0.51	0.52	0.52	0.53	0.54	
$E_{max}(R)$	5.1	**82.1**	11.5	0.9	0.3	0.1	0.0	0.0	24.4
$L2(R)$	4.1	**86.4**	8.4	0.9	0.3	0.0	0.0	0.0	24.6
$L2$	20.9	**75.0**	4.0	0.1	0.0	0.0	0.0	0.0	26.9
$P1$	20.2	**71.7**	7.4	0.7	0.0	0.0	0.0	0.0	31.0
Scenario 5	0.08	0.09	0.09	0.10	0.5	0.5	0.5	0.5	
$E_{max}(R)$	0.0	1.9	7.7	**57.1**	31.2	1.6	0.1	0.4	18.8
$L2(R)$	0.0	1.5	9.5	**56.4**	30.2	1.4	0.8	0.3	18.2
$L2$	0.1	0.1	1.4	**62.7**	35.5	0.2	0.1	0.0	25.1
$P1$	0.0	0.0	0.0	**54.9**	36.4	7.0	1.2	0.5	33.2

Results (III)

		Sc 1	*Sc 2*	Sc 3	Sc 4	*Sc 5*	Sc 6
$E_{(R)}$	$\mathcal{P}$	**74.7%**	**16.3%**	**66.7%**	**71.5%**	**67.9%**	**24.2%**
	NMSE	1.7	*2.0*	2.2	3.5	*3.1*	1.5
$L2_{(R)}$	$\mathcal{P}$	71.8%	**14.4%**	59.7%	64.1%	*74.9%*	20.9%
	NMSE	1.9	*2.2*	7.2	4.4	*3.4*	1.5
$L2$	$\mathcal{P}$	61.5%	**15.7%**	50.1%	50.2%	**64.7 %**	18.1%
	NMSE	2.0	*2.5*	7.7	5.8	*3.6*	1.6
$P1$	$\mathcal{P}$	**99.9%**	*93.7%*	**99.7%**	**99.7%**	*99.4%*	**95.3%**
	NMSE	2.1	*2.6*	7.8	6.1	*3.8*	2.1

Fitted curves



Sensitivity analysis

Prior distributions:

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- ⋆ Recommendation: An informative for λ and an uninformative for ED_{50}

Randomization proportion

- ⋆ Recommendation: 20%-25% on the control arm

Conclusions

- ⋆ Randomization and E_{max} model allow to identify clinically significant differences **with higher probability** than alternatives.
- ⋆ The cost of randomization: **a small reduction** in the proportion of correct recommendations in some scenarios.
- ⋆ The randomization helps to **overcome problems with fitting**
- ⋆ This design should be considered if **not only MTC identification** is of interest

Further work

- ⋆ Large variance of number of patients on the MTC.
- ⋆ Further investigation on the fitting problem
- ⋆ Phase II trials: a statistical comparison of the optimal combination and control effectivenesses