Flexible early-phase design for combination therapies

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Implementation of novel dose-finding methods

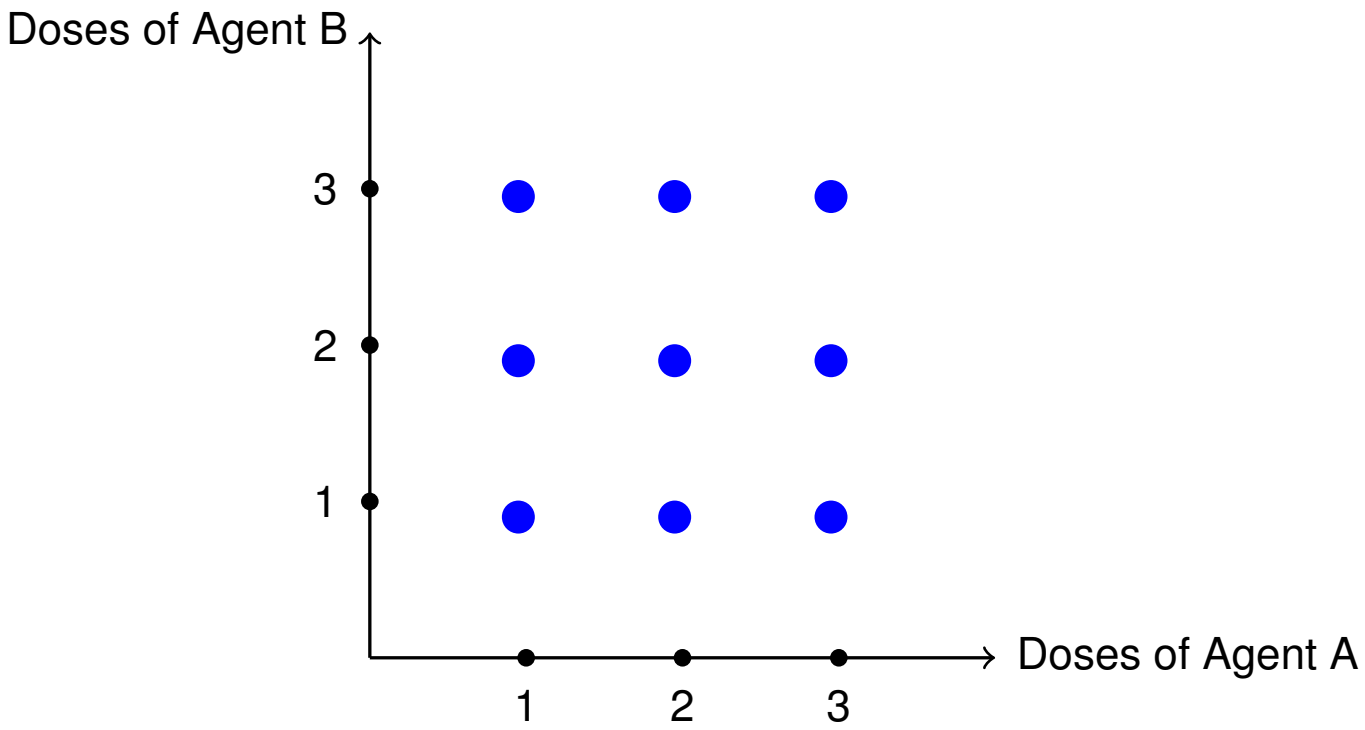
"As research statisticians, it is our responsibility not only to develop new and better designs, but to shepherd new methods into clinical practice."

- Huang B, Bycott P, Talukder E. *J Biopharm Stat* 2017; 27: 44–55.

Design framework

Drug combinations

- Early phase dose finding for combination therapies
  - Structure is to escalate two or more agents



Design objective

Drug combinations

- Initial safety trials
- Goal is to recommend a dose combination for further testing for efficacy in Phase II
- The highest combination with an “acceptable” rate of dose-limiting toxicity (DLT; yes/no), defined by protocol specific adverse events
  - **Maximum tolerated dose combination (MTDC)**
- MTDC is defined as the dose combination with DLT rate closest to a predetermined target DLT rate; i.e. (20%, 25%, 30%, etc.)

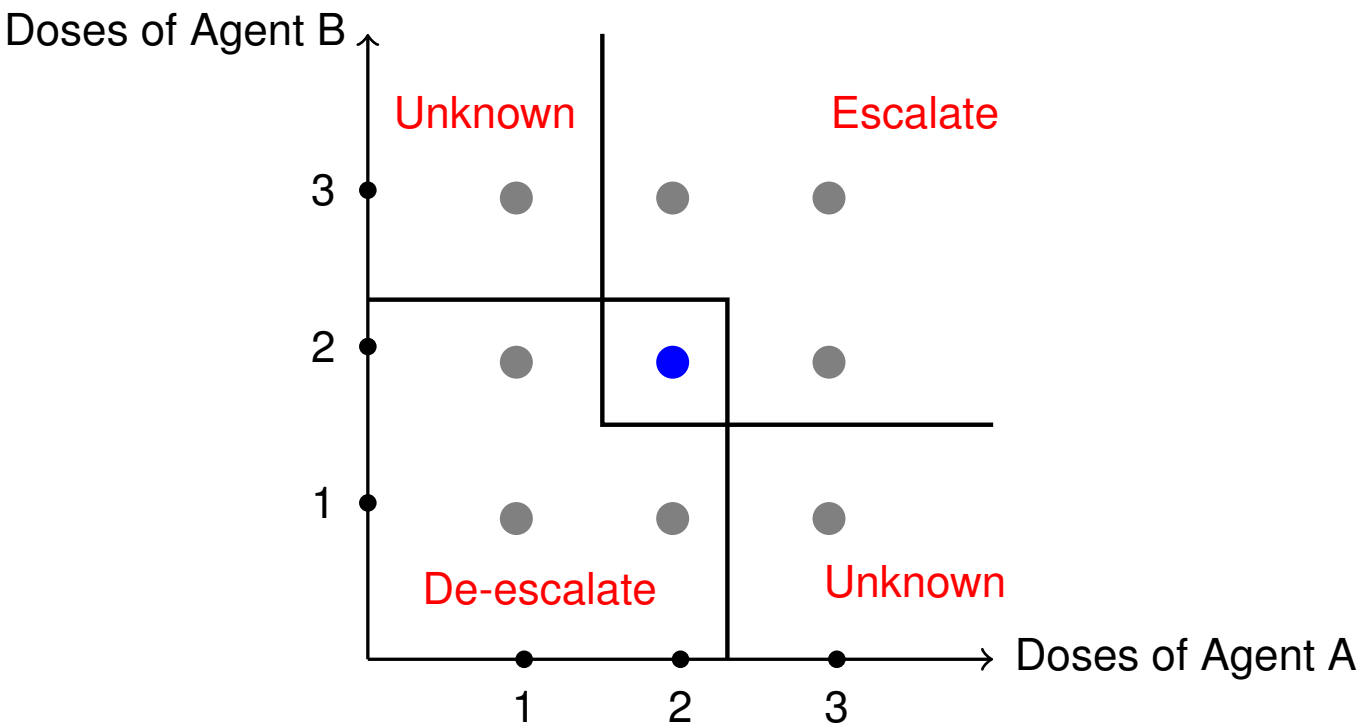
Drug combination studies

Challenges

1. Dose finding methods for single agents assume that doses are ordered from least to most toxic
   - With combinations, this is no longer the case
2. Dimension of the problem may be large
   - Many combinations to consider
3. Multiple MTDCs may exist in the two-dimensional space
   - MTD equivalence contour

Drug combination studies

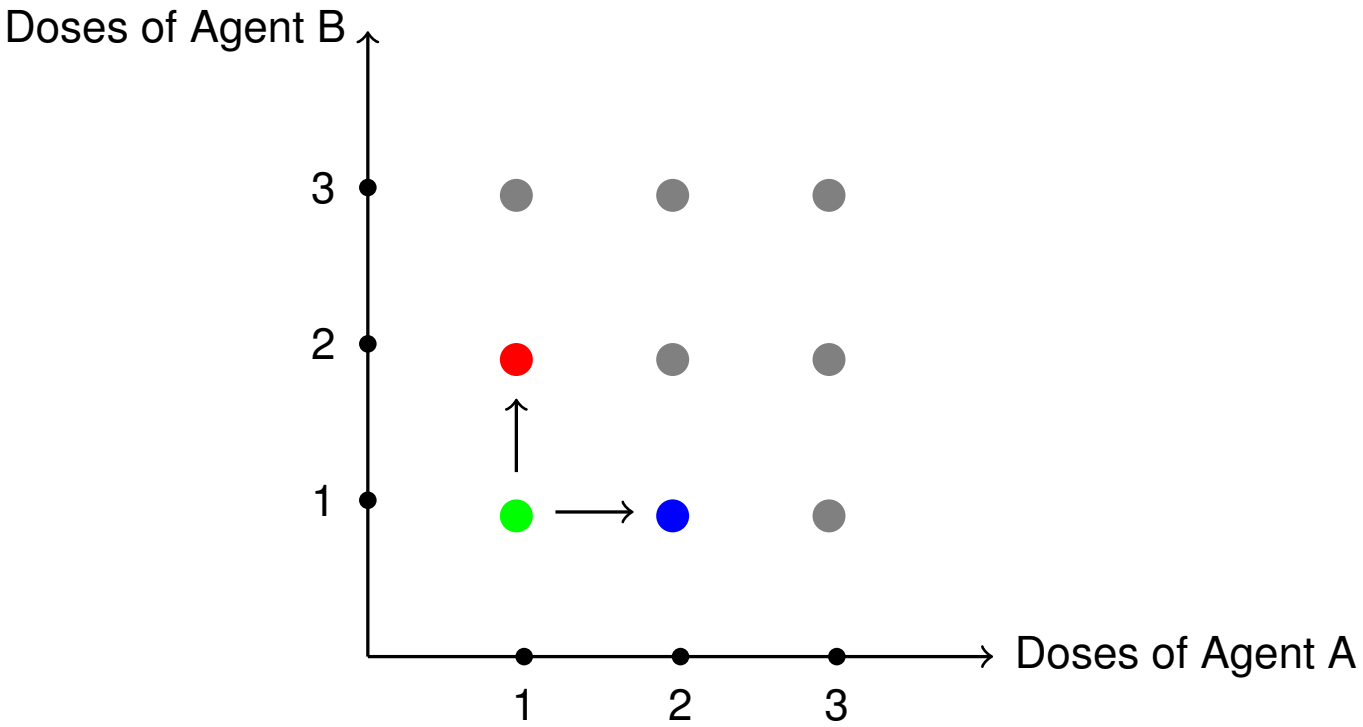
Challenges



Drug combination studies

Challenges

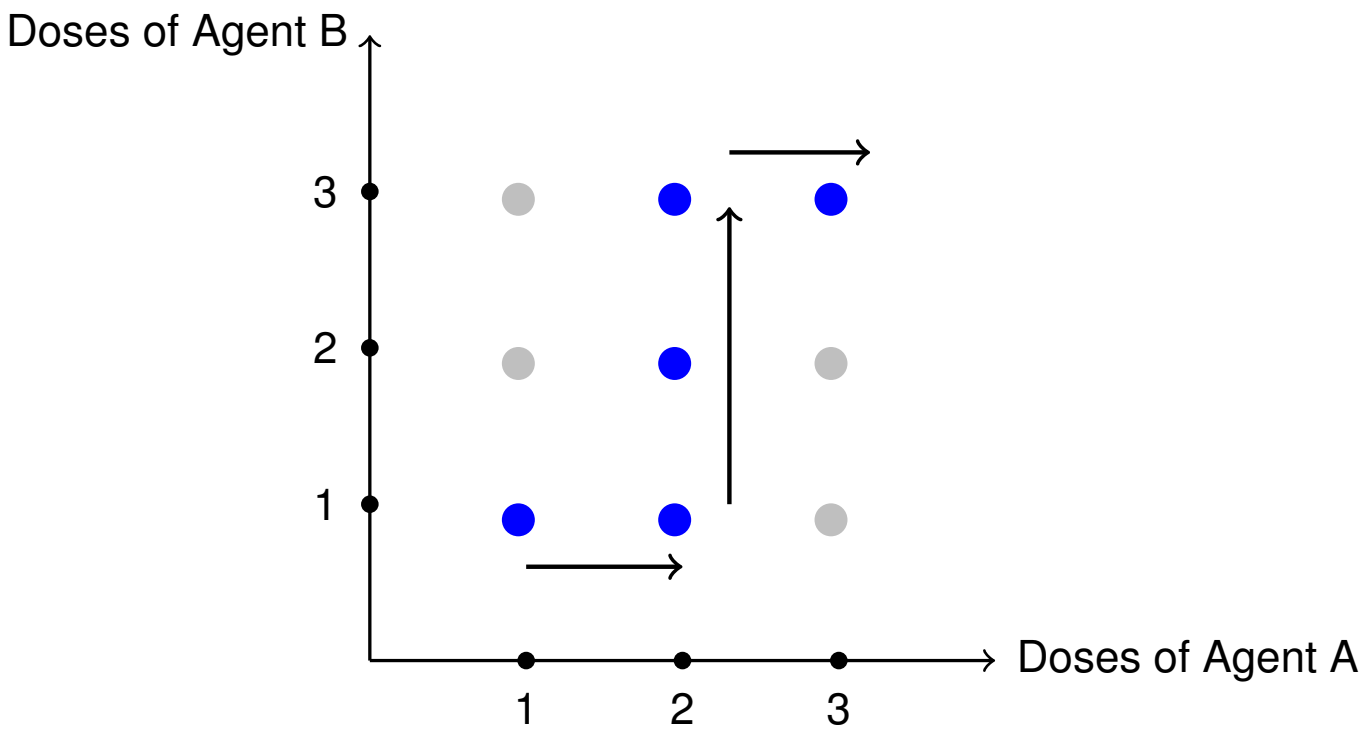
- If ● is safe, where do we go next? ● or ●?



Popular approach to drug combinations

Assume an ordering

- Choose a search path with a known ordering and apply a single agent method



What is commonly used

Drug combination studies

- Literature review over January 2011 and December 2013[1]
  - 847 references retrieved
- 162 papers reported drug-combination in which at least two agents were escalated
  - In 88% a traditional or modified 3+3 dose-escalation design was used
  - All except one trial used a design developed for single-agent evaluation
- Methods for combinations are not commonly used
- Only a small portion of possible combinations are explored

[1] Riviere M-K, Le Tourneau CL, Paoletti X, Zohar S. *Ann Onc* 2015; **26**: 669–74.

Breast 49 study

Open to accrual (NCT03473639)

- A Phase I Study of the combination of Entinostat with Capecitabine in breast cancer participants with residual disease.
- **Objective**: identify the combination with DLT rate closest to 25%
- Designed using partial order continual reassessment method (POCRM[1])

Doses of Entinostat	Capecitabine	
	800 mg/m^2	1000 mg/m^2
5 mg	d_3	d_4
3 mg	d_1	d_2

PI: Patrick Dillon, MD

[1] Wages NA, Conaway MR, O'Quigley J. *Biometrics* 2011; **67**: 1555–63.

Breast 49 study

Open to accrual (NCT03473639)

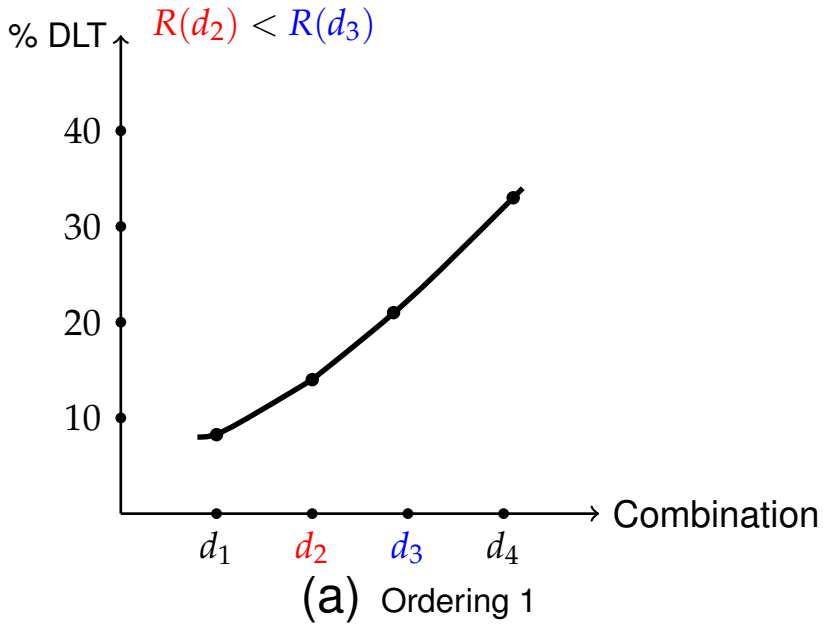
- Let $R(d_j)$ denote the probability of DLT at combination d_j.
- Is $R(d_2) > R(d_3)$ or is $R(d_3) > R(d_2)$?

Toxicity increases	Doses of Entinostat	Capecitabine	
		800 mg/m^2	1000 mg/m^2
$\uparrow$	5 mg	d_3	d_4
$\uparrow$	3 mg	d_1	d_2
		Toxicity increases $\longrightarrow$	

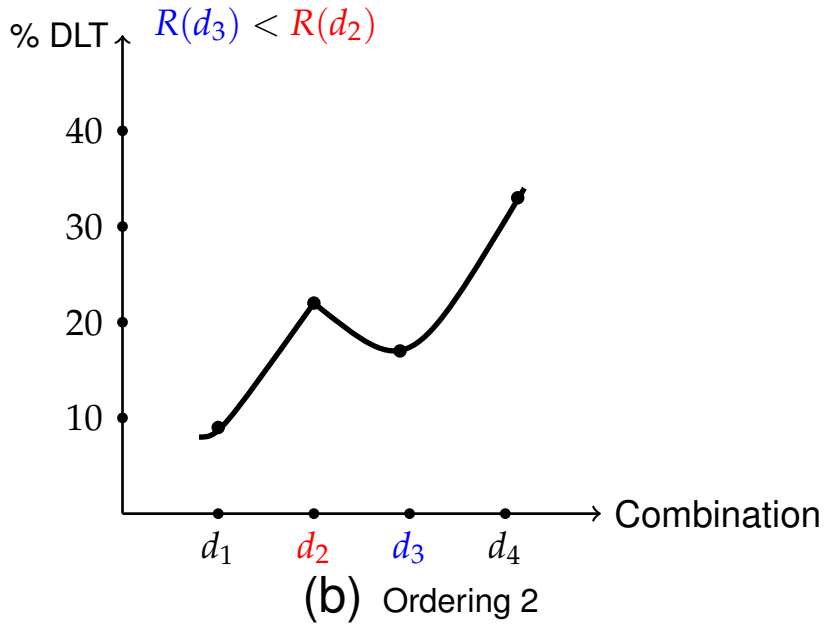
PI: Patrick Dillon, MD

Multiple possible orderings

DLT probabilities



(a) Ordering 1



(b) Ordering 2

Class of Working Models

DLT probabilities

- Let m index the orderings
- Probability of DLT at d_j is

$$R(d_j) = \Pr(\text{DLT at combination } d_j) \approx \alpha_{mj}^{\exp(a_m)}$$

where α_{mj} are pre-specified constants (termed **skeleton**) of the working model m

- Prior on the working models

$$p = \{p(1), \ldots, p(M)\}$$

Working model illustration

Breast 49 study

	Combinations			
Ordering	d_1	d_2	d_3	d_4
$m = 1$	$0.25^{\exp(a_1)}$	$0.35^{\exp(a_1)}$	$0.46^{\exp(a_1)}$	$0.56^{\exp(a_1)}$
$m = 2$	$0.25^{\exp(a_2)}$	$0.46^{\exp(a_2)}$	$0.35^{\exp(a_2)}$	$0.56^{\exp(a_2)}$

Likelihood and prior

POCRM

- Data: $\mathcal{D} = \{y_j, n_j\}$, # DLT's and participants at each combo
- Likelihood under model m

$$\mathcal{L}_m(\mathcal{D} \mid a_m) \propto \prod_{j=1}^{J} \Big(\psi_m(d_j, a_m)\Big)^{y_j} \Big(1 - \psi_m(d_j, a_m)\Big)^{n_j - y_j}$$

- Prior $g_m(a_m)$ on a_m

$$a_m \sim \mathcal{N}(0, \sigma^2_{a_m})$$

with σ_{a_m} calibrated via simulation studies.

Sequential Bayesian model choice

POCRM

- Posterior model probability for m is

$$\pi(m \mid \mathcal{D}) = \frac{p(m) \int \mathcal{L}_m(\mathcal{D} \mid a_m) g_m(a_m) da_m}{\sum_{m=1}^{M} p(m) \int \mathcal{L}_m(\mathcal{D} \mid a_m) g_m(a_m) da_m}$$

- After each inclusion, choose model h such that

$$h = \arg\max_m \pi(m \mid \mathcal{D})$$

Trial conduct

POCRM

- Estimated DLT probability at each combination

$$\widetilde{R}(d_j) = \int \psi_h(d_j, a_h) \frac{\mathcal{L}_h(\mathcal{D} \mid a_h) g_h(a_h)}{\int \mathcal{L}_h(\mathcal{D} \mid a_h) g_h(a_h) da_h} da_h$$

- Recommend combination closest to the target DLT rate θ

$$\widetilde{\nu} = \arg\min_j |\widetilde{R}(d_j) - \theta|$$

- Assign the next cohort to $\widetilde{\nu}$
- Observe DLT outcome(s) of new cohort and repeat model selection / estimation

Trial conclusion

Maximum sample size N participants

- Stop the trial for safety if the lowest combination is deemed too toxic, as evaluated by
  - whether the lower bound of a binomial confidence interval exceeds θ
- Continual accrual until n_s participants have been treated on a combination or to maximum accrual
- MTDC is the recommended combination...
  - that has already been given to n_s participants **or**
  - that would have been given to participant $N + 1$

Design specifications

Skeleton choice and prior distribution

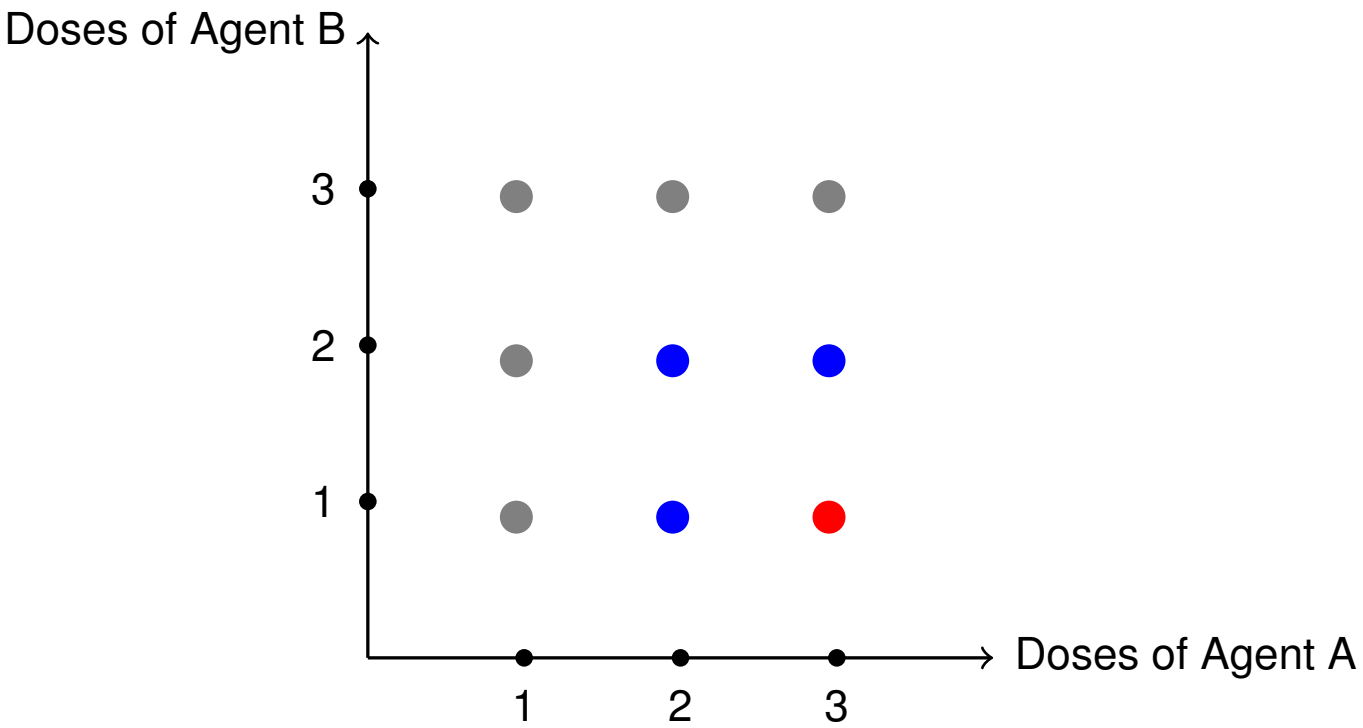
- For skeleton, we can lean on the algorithm of Lee and Cheung[1]
  1. Use **getprior** function in **R** package **dfcrm**
  2. Arrange skeleton values to correspond to possible orderings
- Prior variance $\sigma^2_{a_m}$ can calibrated using Lee and Cheung[2]
  - Algorithm yields least informative normal prior
  - Vague in terms of which dose is the MTD

[1] Lee SM, Cheung YK. *Clin Trials* 2009; 6: 227–38

[2] Lee SM, Cheung YK. *Stat Med* 2011; 30: 2081–9

Allocation restrictions

- For each combination being studied, specify a set of admissible combinations for allocation of the next cohort
  - i.e., if current combo is ●, may only consider ●.



Safety stopping bounds

- Compute safety stopping bounds for the lowest combination based on Agresti-Coull binomial confidence interval estimation
  - More practical behavior than a model-based stopping rule
- Stop the study for safety if the observed DLT rate at lowest combination $\geq$ #DLTs out of #pts treated

#DLTs	2	2	3	3	4	$\cdots$	t
#pts	2	3	4	5	6	$\cdots$	N

Design behavior early in the trial

- DLTs on patients 1 and 2

patient	combo	DLT	CI lower bound	Rec for next pt
1	1	Yes	0.22	Combo 1
2	1	Yes	0.37	STOP STUDY

- DLT on patient 1, followed by non-DLTs

patient	combo	DLT	Rec for next pt
1	1	Yes	Combo 1
2	1	No	Combo 1
3	1	No	Combo 1
4	1	No	Combo 1
5	1	No	Combo 1
6	1	No	Combo 2

Simulation results checklist

Wide range of possible scenarios

1. Percentage of trials each combination is recommended as the MTDC
2. Average number of participants treated on each combination
3. Average (and percentiles) overall trial size
4. Percentage of trials stopped for safety
5. Percentage of participants with a DLT

Adaptation to Breast 49

Open to accrual (NCT03473639)

- Review of the study protocol by the FDA:

  "You should conduct your Phase 1 dose escalation trial in the metastatic setting. Once the safe dose for the combination is found, then the combination can be evaluated in the early breast cancer setting."

- Created the need to adapt the trial design in order to accommodate a shift in patient populations[1]
  - Find MTDC metastatic population $\rightarrow$ use accumulated data in finding MTDC in residual disease.

[1] Wages NA, Millard T, Dillon PM, Brenin CM, Petroni GR. *JNCI: Cancer Spectrum* 2018; in review.

Mel 58

Completed (NCT01585350)

- Phase I trial of a toll-like receptor (TLR) agonists, lipopolysaccharide (LPS), with or without a form of incomplete Freund's adjuvant (IFA).
- IFA subgroups
  - V0 IFA is not administered with any of the 6 vaccines
  - V1 IFA is administered just with the first vaccine
  - V6 IFA is administered with all 6 vaccines
- 4 doses of LPS (25, 100, 400, 1600 EU)
- **Objective:** determine MTDC of LPS and IFA

PI: Craig Slingluff, MD

Mel 58

Completed (NCT01585350)

- Phase I trial of a toll-like receptor (TLR) agonists, lipopolysaccharide (LPS), with or without a form of incomplete Freund's adjuvant (IFA).

Doses of LPS	IFA		
	V0	V1	V6
1600			
400			
100			
25			

PI: Craig Slingluff, MD

Melssen MM, Petroni GR, Wages NA, Grosh WW, et al (2018). *in preparation*

Mel 60

Completed (NCT02126579)

- Early phase trial evaluating safety and immunogenicity of a Long Peptide Vaccine (LPV7) plus TLR Agonists

Zone	Regimen	LPV7+
1	d_1	Resiquimod
1	d_2	IFA
1	d_3	PolyICLC
2	d_4	IFA + Resq.
2	d_5	PolyICLC + Resq.
2	d_6	IFA + PolyICLC
3	d_7	IFA + PolyiCLC + Resq.

PI: Craig Slingluff, MD

Wages NA, Slingluff CL, Petroni GR (2015). *Contemp Clin Trials*; 41: 172-9.

Mel 63

Completed (NCT02425306)

- Early-phase study evaluating safety and immunogenicity of a mixture of 6 melanoma helper peptides (6MHP) administered with one of 2 local adjuvant combinations (IFA or IFA + PolyICLC), alone or with low-dose cyclophosphamide (mCy)

Zone	Regimen	6MHP+
1	d_1	IFA
2	d_2	IFA+mCy
2	d_3	IFA+PolyICLC
3	d_4	IFA+PolyICLC+mCy

PI: Craig Slingluff, MD

Wages NA, Slingluff CL, Petroni GR. *Ann Oncol* 2017; 35: 696-701.

Combination of two oral targeted inhibitors

Current accrual 22 participants (NCT02419560)

- Multi-institution (4 sites) Phase I/Ib study of ibrutinib with ABT-199 in relapsed/refractory mantle cell lymphoma
- **Objective**: identify an optimal treatment combination defined by low toxicity and high efficacy
- Efficacy: response (CR+PR) at 2 months from start of treatment

		Ibrutinib (mg/day)		
		280	420	560
ABT-199 (mg/day)	400	d_3	d_5	d_6
	200	d_1	d_2	d_4

PI: Craig Portell, MD

Wages NA, Portell CA, et al. *Clin Cancer Res* 2017; 23: 7158-64.

Flexibility in which combinations to explore

Recently submitted to FDA

- Phase I Study of C6 Ceramide NanoLiposome and Vinblastine in Patients with Relapsed/Refractory Acute Myeloid Leukemia and Patients with Untreated Acute Myeloid Leukemia Who Are Not Candidates for Intensive Induction Chemotherapy

Combination and Zone Designation				
CNL Twice Weekly dosing mg/m^2	215	Combination 6	Zone 5 / Combination 13	Zone 6 / Combination 16
	183	Combination 5	Zone 4 / Combination 12	Zone 5 / Combination 15
	122	Combination 4	Zone 3 / Combination 10	Zone 4 / Combination 13
	81	Combination 3	Zone 2 / Combination 8	Zone 3 / Combination 11
	54	Combination 2	Zone 1 / Combination 7 (*start*)	Zone 2 / Combination 9
	36	Combination 1		
Possible dose combinations		0.375	0.75	1.5
		Vinblastine Twice Weekly dosing mg/m^2		

PI: Michael Keng, MD

Implementation of more novel approaches[1]

- Novel statistical methods are being developed but not used.
- Single-agent design structure should not limit goals of the study.
- Requirements:
  - time, effort, and personnel
  - attention to detail up-front
  - strong communication, team effort
  - statistical expertise throughout
  - available software
  - flexible clinical research management system

[1] Petroni GR, Wages NA, et al (2017). *Stat Med*; 36: 215–24.

Concluding remarks

- Number of working models increases as dimension/complexity of problem grows
- Design has good operating characteristics
  - extension of CRM
- Can be adapted for application in a broad class of partial order problems
- **R** code for simulation, implementation, and generating stopping bounds available at `http://faculty.virginia.edu/model-based_dose-finding/`

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  - Trish Millard, MD
  - Michael Keng, MD