Dose-finding in malaria

A combination dose-escalation study using Bayesian logistic regression modeling (BLRM)

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19 May 2016

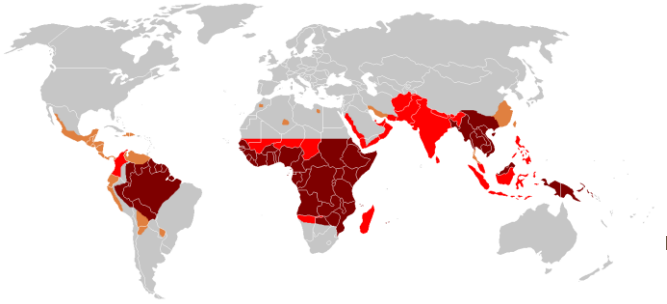
NOVARTIS

Outline

- Malaria – disease overview
- Program overview and context for dose finding
- Candidate phase 2b study design
- Dose escalation – methodology reminder
  - Safety metrics
  - Bayesian logistic regression model for combination modeling
  - Prior specification and derivation
- Implementing the design
  - Planning
  - Communication
  - Simulations
- Summary

Malaria

Disease overview



- Mosquito-borne infectious disease
  - Human cases date back to 2700 BC
  - Historically associated with “bad air” (*mala aria)* around marshes
- Once common in the US and southern Europe
- Now endemic in a “broad band” around the equator
- 2015 facts & figures (WHO)
  - 214 million cases worldwide
  - 438,000 documented deaths
  - 70% of deaths occur in children under 5 years old
- Treatment:
  - In late 19th century: mustard bath, kerosene massage, lots of whiskey
  - Current: artemisinin-based combination regimens (~95% cure rate)

Program overview

Key question for phase 2b

- Setting:
  - Investigational compound (drug A) under development for treatment of malaria
  - Preferred combination partner (drug B) has been identified
- Phase 2a completed – monotherapy only
  - Multiple-dose and single-dose regimens have been investigated
  - Potential for *single dose cure*
- Key question for phase 2b – is single dose cure feasible?
  - Components to answer question: need a combination dose with
    - satisfactory safety profile
    - efficacy comparable with existing multi-day regimens (~95% cure rate)
- In the context of malaria treatment, higher doses are preferable
- Primary purpose of dose-finding: establish the maximum tolerated dose (MTD)

Program overview

Candidate design for phase 2b

- Candidate phase 2b design:
  - Consider dose escalation methodology often used in phase 1 oncology studies
  - Escalate separately for monotherapy and combination therapy
  - Note: partner drug dose kept constant
- Primary endpoint
  - Rate of occurrence of specific dose-limiting toxicities (DLTs)
  - DLTs are pre-defined according to known program and indication risks
- Components of dose escalation
  - Incorporate contextual information from previous studies
  - Quantify dose-toxicity relationship with BLRM
  - Provide model-based recommendation of the next dose level

Interim analysis algorithm

Inference → dose recommendations

- BLRM input – cumulative DLTs and sample size at each studied dose
- Inference:
  - Estimate dose-toxicity relationship
  - Derive safety metrics:
    - Under-dosing DLT probability < 0.05
    - Target dosing DLT probability between 0.05 and 0.20
    - Overdosing DLT probability > 0.20
  - Report interval probability for each candidate dose
- Model-based dose recommendation:
  - Dose with high probability of being in target interval for DLT
  - AND maximal overdose probability of 0.25 (EWOC)
  - Possible recommendations:
    escalate, repeat, de-escalate
    or stop and declare MTD

Combination BLRM

Modeling the dose-toxicity relationship

$$\log(\text{odds}(\pi_{1,d_1})) = \log(\alpha_1) + \beta_1 \log(d_1)$$

$$\log(\text{odds}(\pi_{2,d_2})) = \log(\alpha_2) + \beta_2 \log(d_2)$$

$$\pi^0_{12,d_1,d_2} = \pi_{1,d_1} + \pi_{1,d_2} - \pi_{1,d_1}\pi_{2,d_2}$$

$$\text{odds}(\pi_{12,d_1,d_2}) = \text{odds}(\pi^0_{12,d_1,d_2})\exp(\eta d_1 d_2)$$

$$(\alpha_1, \beta_1, \alpha_2, \beta_2 > 0)$$

Dose-toxicity relationship for each individual drug

DLT probability under no interaction

Dose-dependent interaction term on odds scale

- (note: reference/scaling doses dropped in formulas)
- if no dose-dependent interaction desired: simply use *exp(η)*
- no interaction $\Leftrightarrow \eta = 0$
- typically $\eta > 0$, but not necessarily

Combination BLRM

Specifying the priors

MAP* prior for α^*, β^* obtained from hierarchical model

$$
\begin{aligned}
r_{d,h} &\sim \text{Bin}(\pi_{d,h}, n_{d,h}) \\
\log(\pi_{d,h}/(1-\pi_{d,h})) &= \log(\alpha_h) + \beta_h \log(d/d^*) \\
(\log(\alpha_h), \log(\beta_h)) &\sim \text{BVN}((\mu_1, \mu_2), \psi) \\
(\log(\alpha^*), \log(\beta^*)) &\sim \text{BVN}((\mu_1, \mu_2), \psi)
\end{aligned}
$$

Priors

$$
\psi = \begin{pmatrix} \tau_1^2 & \tau_1\tau_2\rho \\ \tau_1\tau_2\rho & \tau_2^2 \end{pmatrix}
$$

$$
\mu_1 \sim \text{N}(m_{\mu_1}, s_{\mu_1}^2), \mu_2 \sim \text{N}(m_{\mu_2}, s_{\mu_2}^2)
$$

$$
\tau_1 \sim \text{LN}(m_{\tau_1}, s_{\tau_1}^2), \tau_2 \sim \text{LN}(m_{\tau_2}, s_{\tau_2}^2), \rho \sim \text{Unif}(-1,1)
$$

Interaction prior – normal prior on η

$$
\boxed{\text{odds}(\pi_{12,d_1,d_2}) = \text{odds}(\pi^0_{12,d_1,d_2})\exp(\eta d_1 d_2)}
$$

*Meta-analytic predictive

Combination BLRM

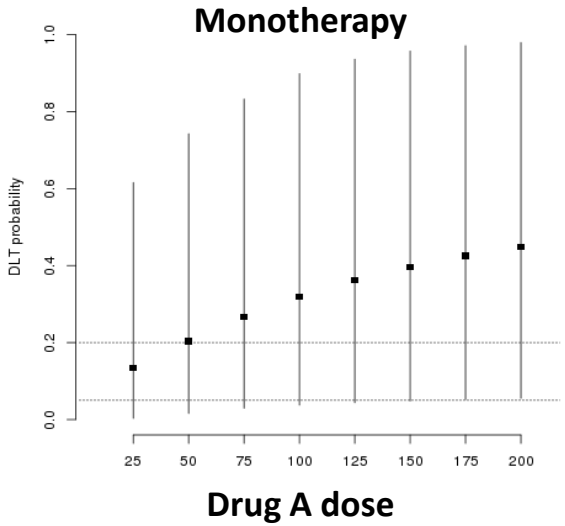
Deriving the MAP prior

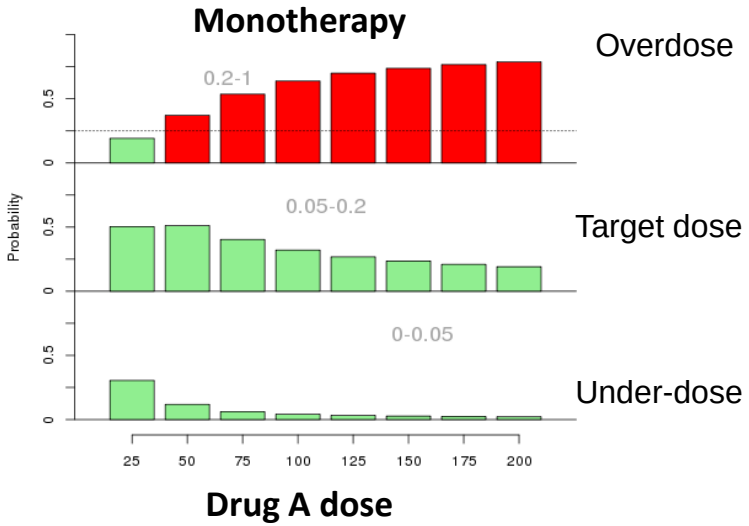
- Contextual information from patient studies of drug A:
  - Two single-dose studies – several dose levels
  - One multiple-dose study – one dose level
    - Summed and treated as single dose in meta-analysis
- Differential discounting of historical information:
  - Assumption of multi-dose = single-dose x days is crude, needs attention!
  - Approach: Split prior data into strata (single vs. multiple-dose)
  - ...and assume larger prior variability in multiple-dose stratum
- Deriving the MAP prior:
  - The described model can be easily fit with BUGS/JAGS/Stan...
  - Approximate MAP prior with bivariate normal mixture
  - Mixture components can be written directly in the protocol

Summary of contextual information

Prior distributions for dose-toxicity

- MAP prior fitted to the available dose-DLT data and robustified
- A priori: 25mg is MTD, 50m too toxic, but *substantial uncertainty*





- Main source of information for drug B: drug label
  - Single dose of drug B at recommended dose expected to be relatively safe
- No dose-response data, so two assumptions for dose of interest:
  - Pr(DLT < 0.2) = 0.95 and Pr(DLT < 0.05) = 0.5
  - Converted into a bivariate normal prior to fit with the combination BLRM setup

Implementing the design

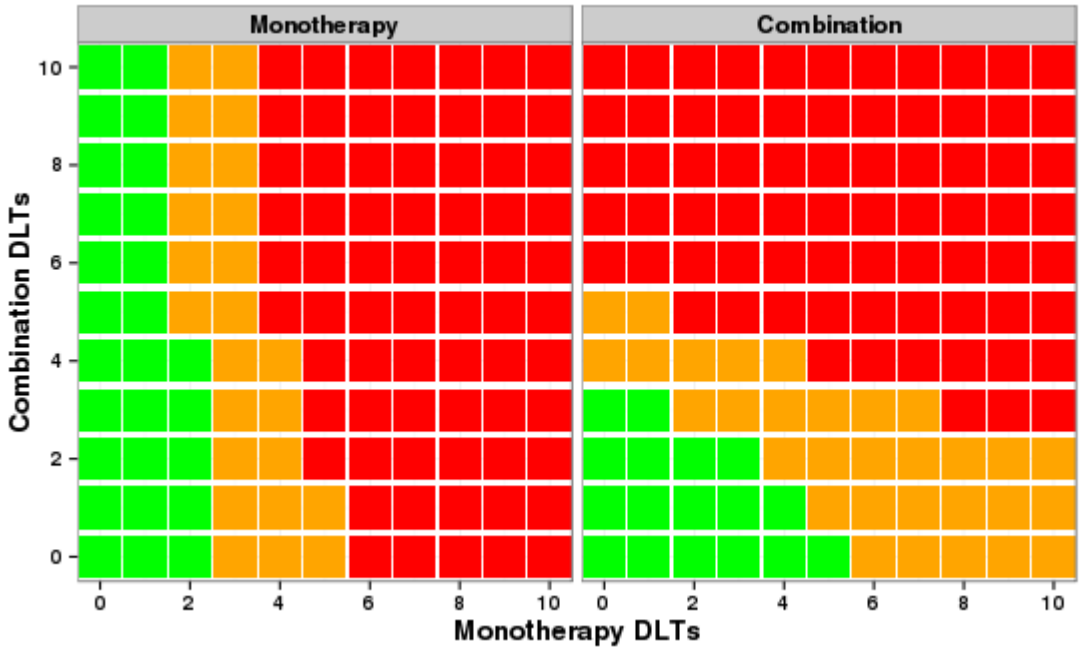
Planning, simulating, communicating!

- Many (though not all) members of clinical team were unfamiliar with this type of design
- Clear visual communication essential to ensure clarity regarding
  - Methodology – quantification of uncertainty in DLT rates
  - Credibility – sanity checks that reasonable recommendations will be made
  - End-to-end understanding – illustration of a hypothetical trial
- Robustness assessment – does the design perform as desired?
- Simulation plan written to
  - Define dose-toxicity scenarios for evaluation
  - Define metrics for comparison of competing design options
  - Agree on key design parameters such as sample size
    - In a cohort/overall

First interim analysis

Dose recommendation

- Question:
  - “Given all the assumptions for the prior...”
  - “...and given the agreed-upon limits for dose toxicity categories...”
  - “...does the design make reasonable recommendations in light of actual data?”
- Address by showing grid of outcomes for first IA



Assumptions:

- 25 patients per cohort
- Mono starting dose: 50mg
- Combo starting dose: 25mg

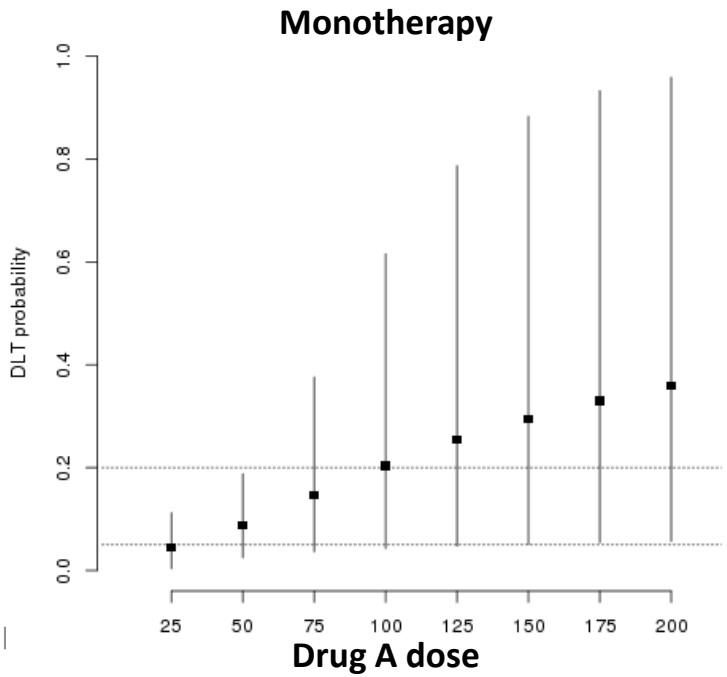
Example – Complete study

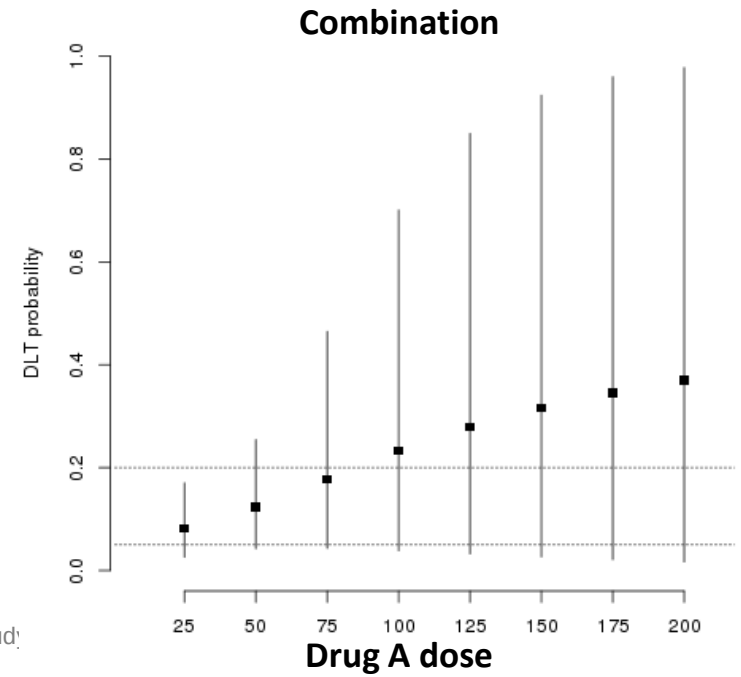
Using maximal escalation rule

Cohort 1

Monotherapy 2/25; Combination 1/25

	Dose	25	50	75	100	125
Mono	# Patients	0	25	0	0	0
	# DLT		2			
Comb	# Patients	25	0	0	0	0
	# DLT	1				



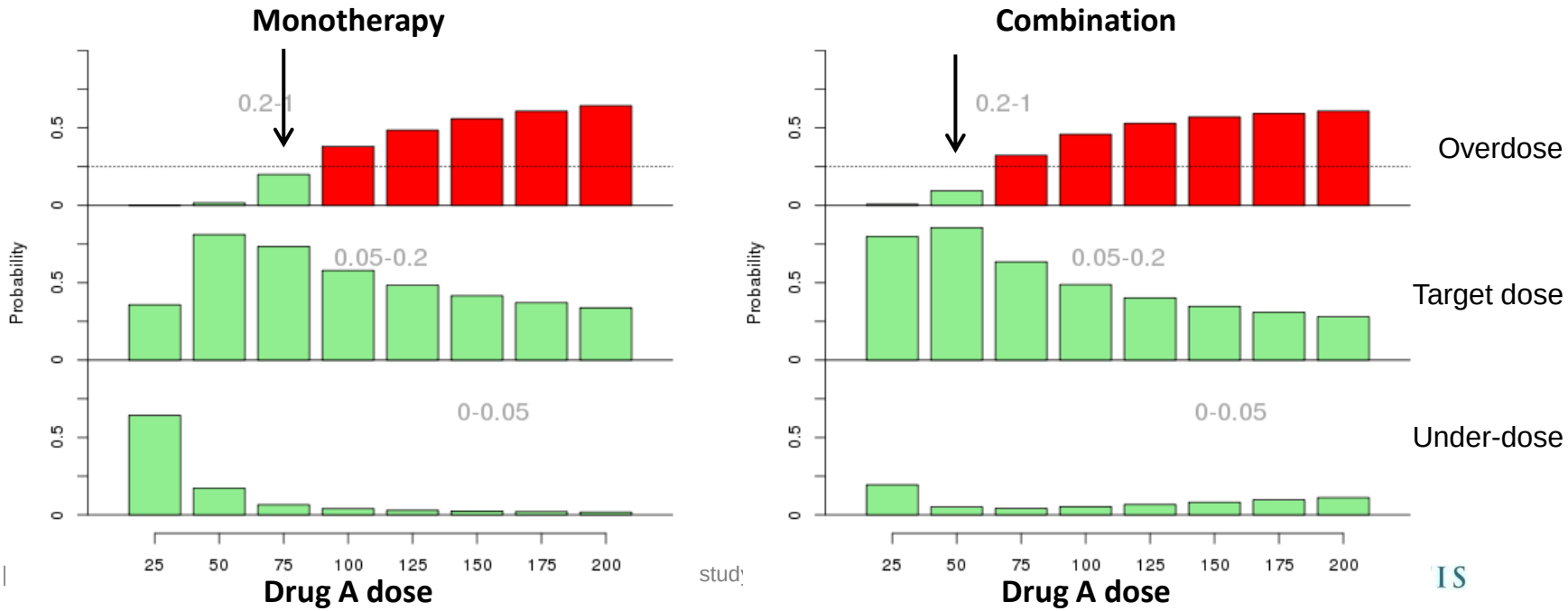


Cohort 1

Monotherapy 2/25; Combination 1/25

Both mono and comb may escalate, 75mg and 50mg respectively

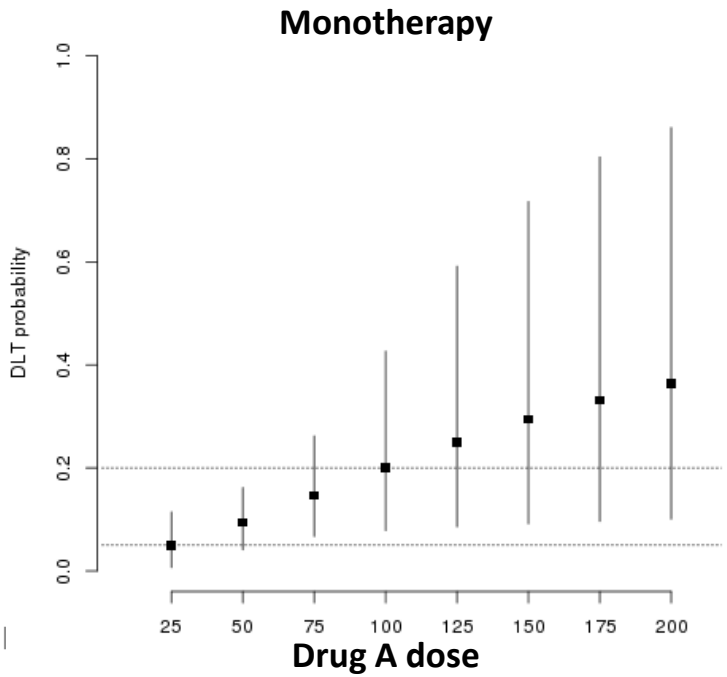
	Dose	25	50	75	100	125
Mono	# Patients	0	25	0	0	0
	# DLT		2			
Comb	# Patients	25	0	0	0	0
	# DLT	1				

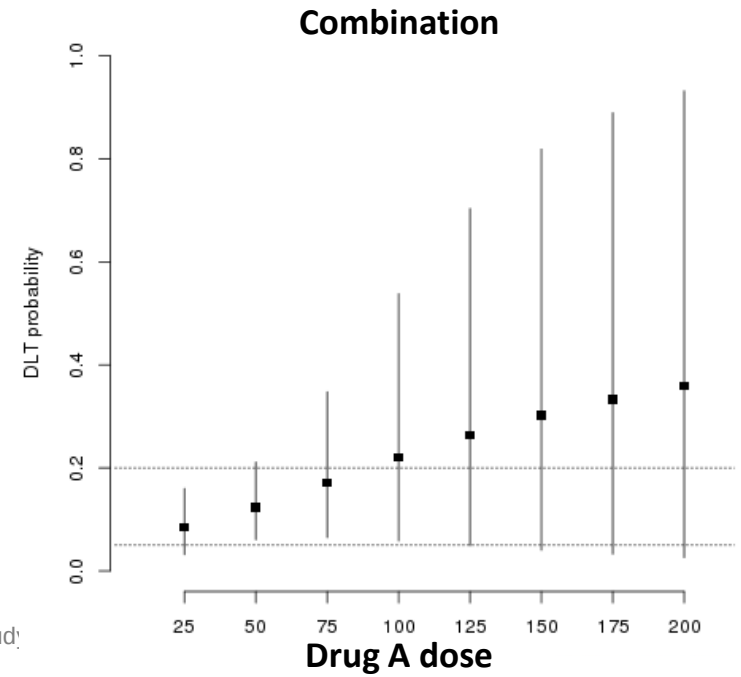


Cohort 2

Monotherapy 4/25; Combination 3/25

	Dose	25	50	75	100	125
Mono	# Patients	0	25	25	0	0
	# DLT		2	4		
Comb	# Patients	25	25	0	0	0
	# DLT	1	3			



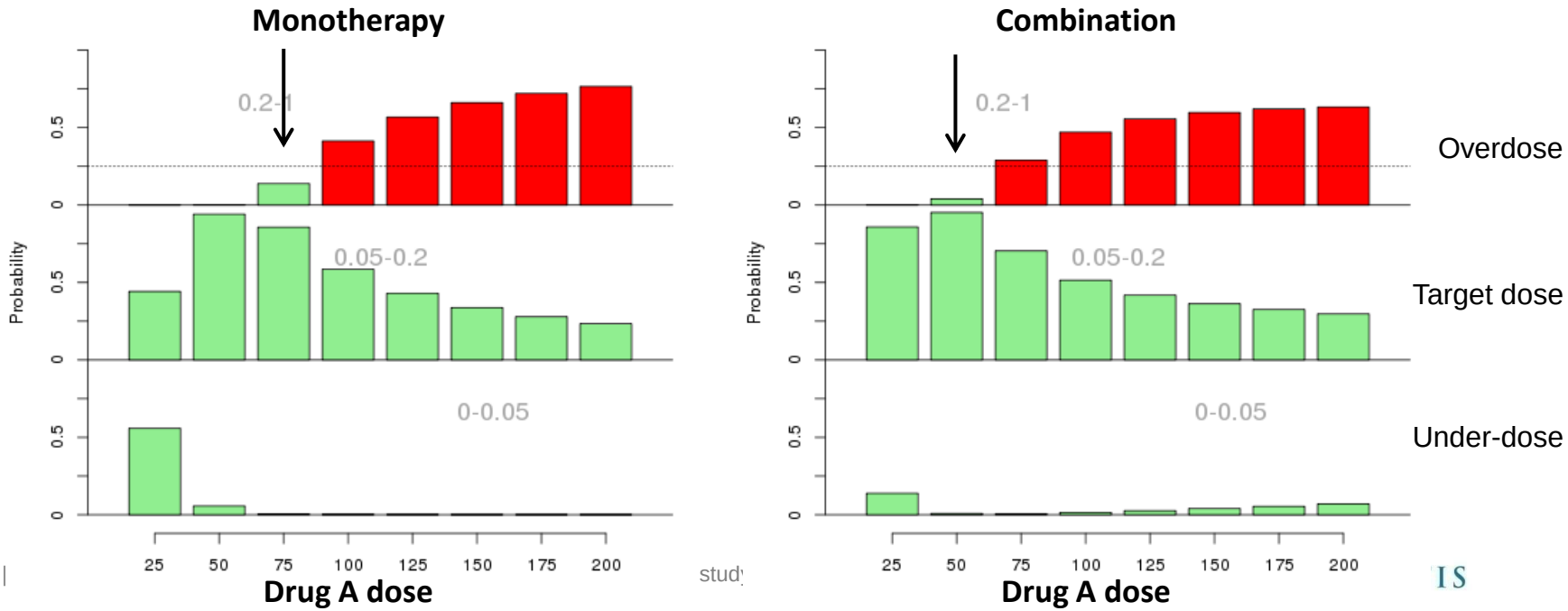


Cohort 2

Monotherapy 4/25; Combination 3/25

Mono and comb should repeat 75mg and 50mg respectively, escalation not possible due to EWOC

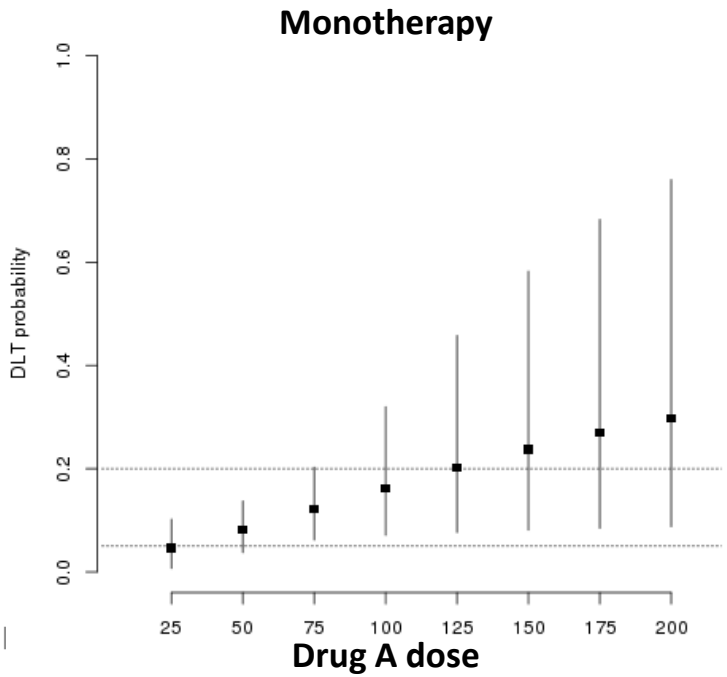
	Dose	25	50	75	100	125
Mono	# Patients	0	25	25	0	0
	# DLT		2	4		
Comb	# Patients	25	25	0	0	0
	# DLT	1	3			

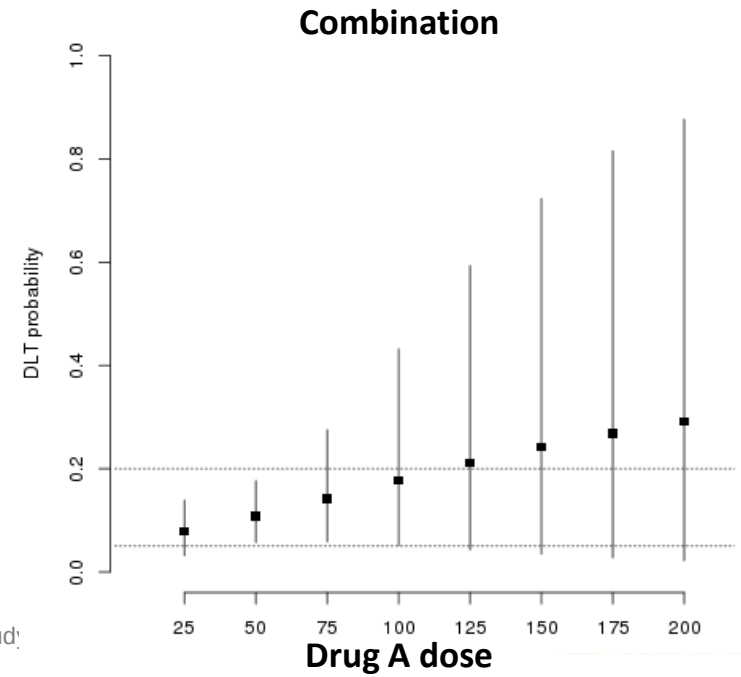


Cohort 3

Monotherapy 2/25; Combination 2/25

	Dose	25	50	75	100	125
Mono	# Patients	0	25	50	0	0
	# DLT		2	6		
Comb	# Patients	25	50	0	0	0
	# DLT	1	5			



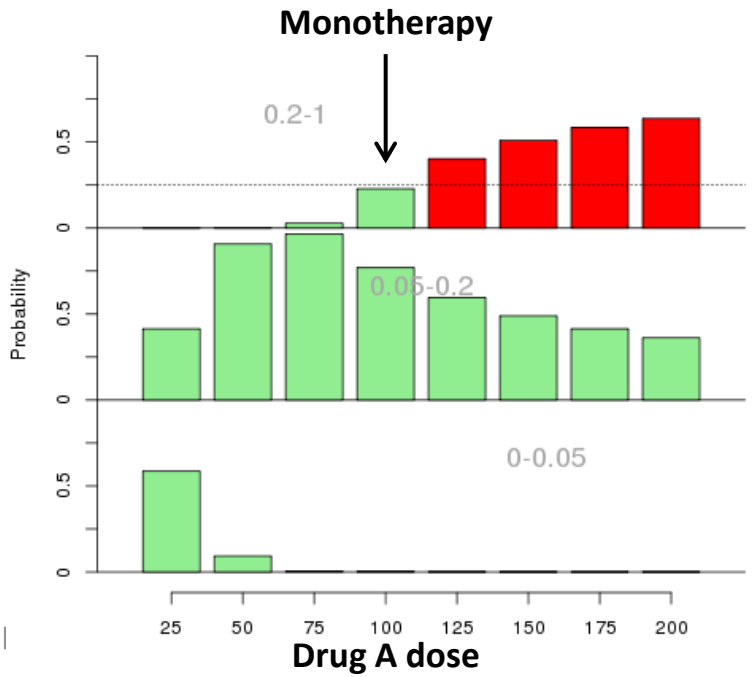


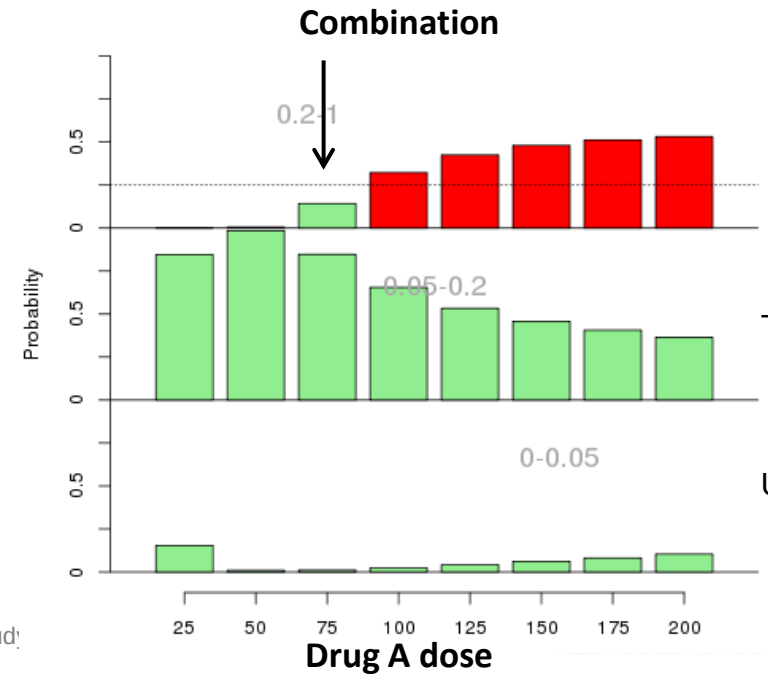
Cohort 3

Monotherapy 2/25; Combination 2/25

Both mono and comb may escalate, 100mg and 75mg respectively

	Dose	25	50	75	100	125
Mono	# Patients	0	25	50	0	0
	# DLT		2	6		
Comb	# Patients	25	50	0	0	0
	# DLT	1	5			





Overdose

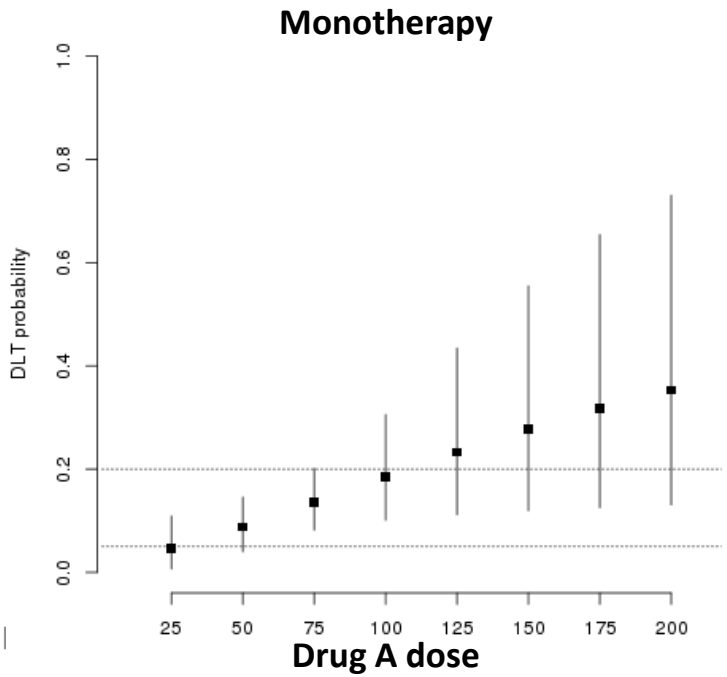
Target dose

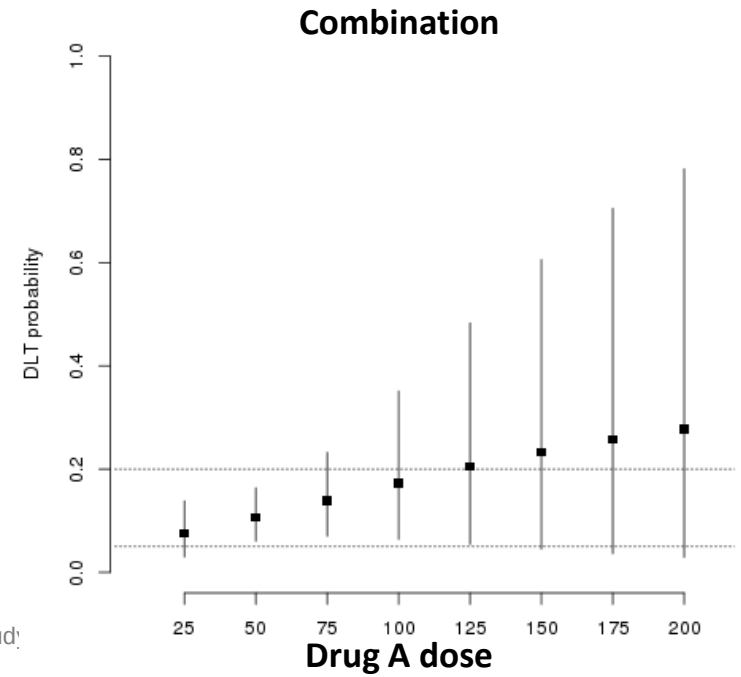
Under-dose

Cohort 4

Monotherapy 6/25; Combination 3/25

	Dose	25	50	75	100	125
Mono	# Patients	0	25	50	25	0
	# DLT		2	6	6	
Comb	# Patients	25	50	25	0	0
	# DLT	1	5	3		



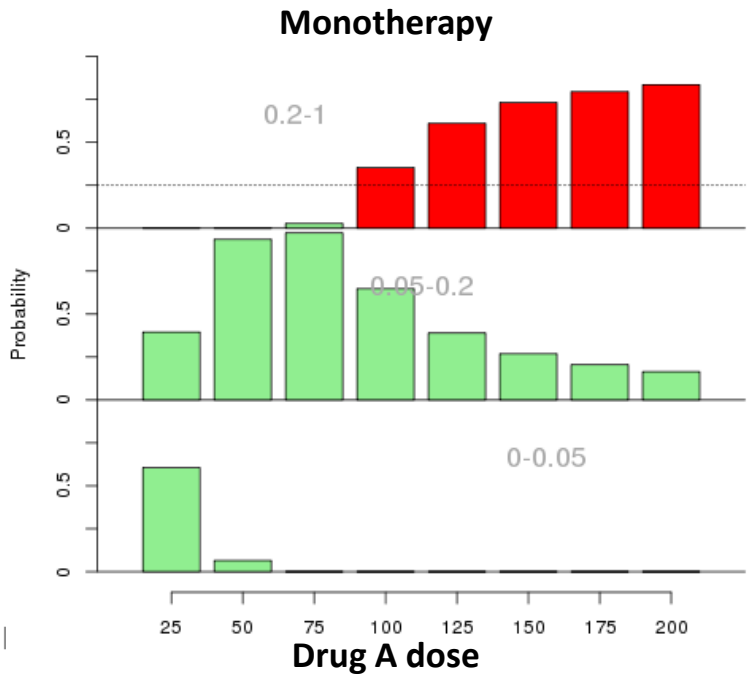


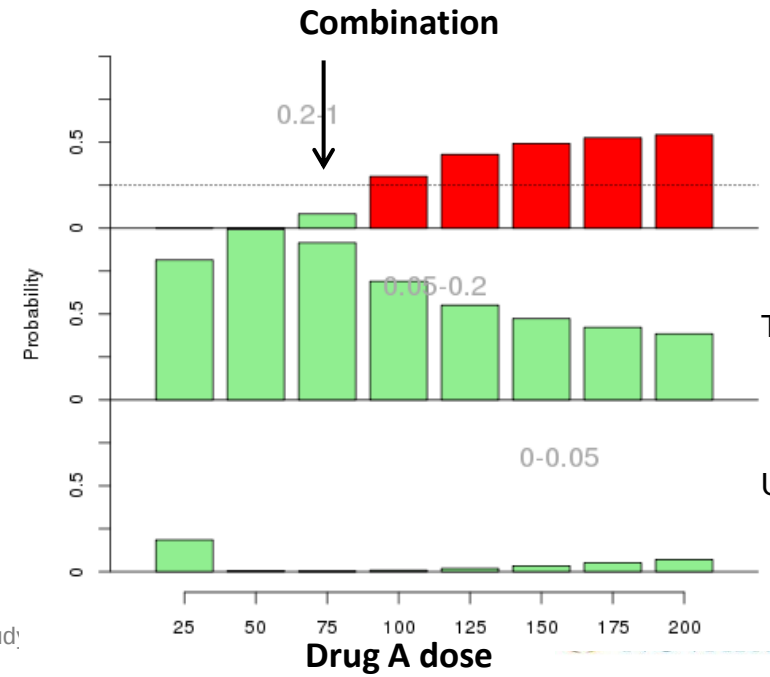
Cohort 4

Monotherapy 6/25; Combination 3/25

Monotherapy MTD established = 75mg; Continue with combination therapy

	Dose	25	50	75	100	125
Mono	# Patients	0	25	50	25	0
	# DLT		2	6	6	
Comb	# Patients	25	50	25	0	0
	# DLT	1	5	3		





Overdose

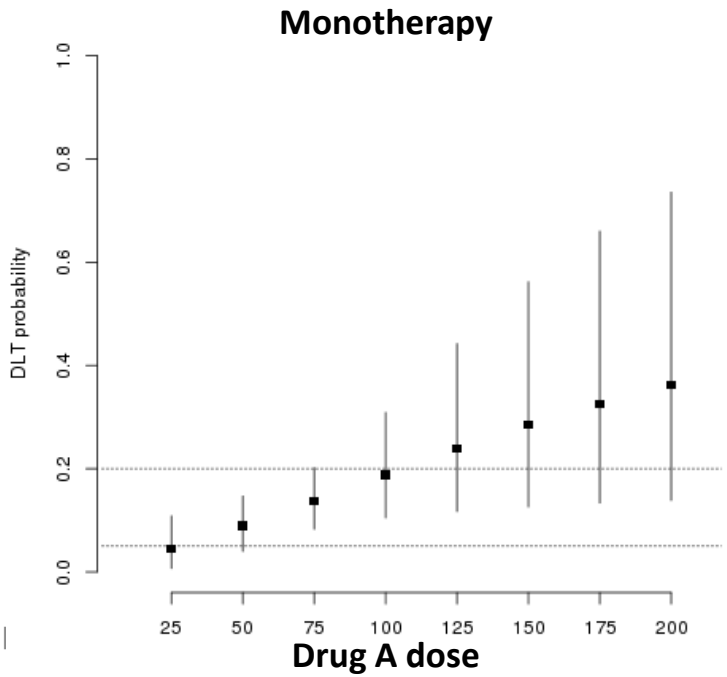
Target dose

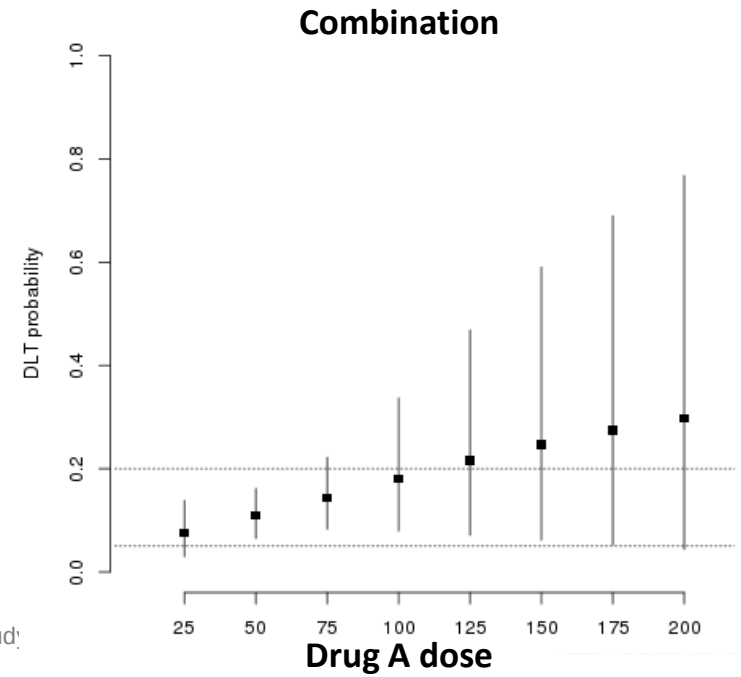
Under-dose

Cohort 5

Combination 4/25

	Dose	25	50	75	100	125
Mono	# Patients	0	25	50	25	0
	# DLT		2	6	6	
Comb	# Patients	25	50	50	0	0
	# DLT	1	5	7		



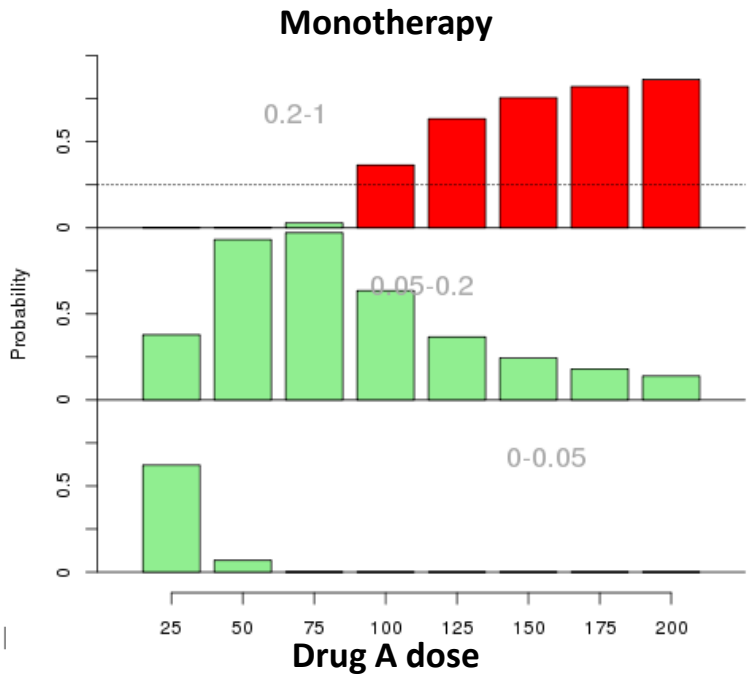


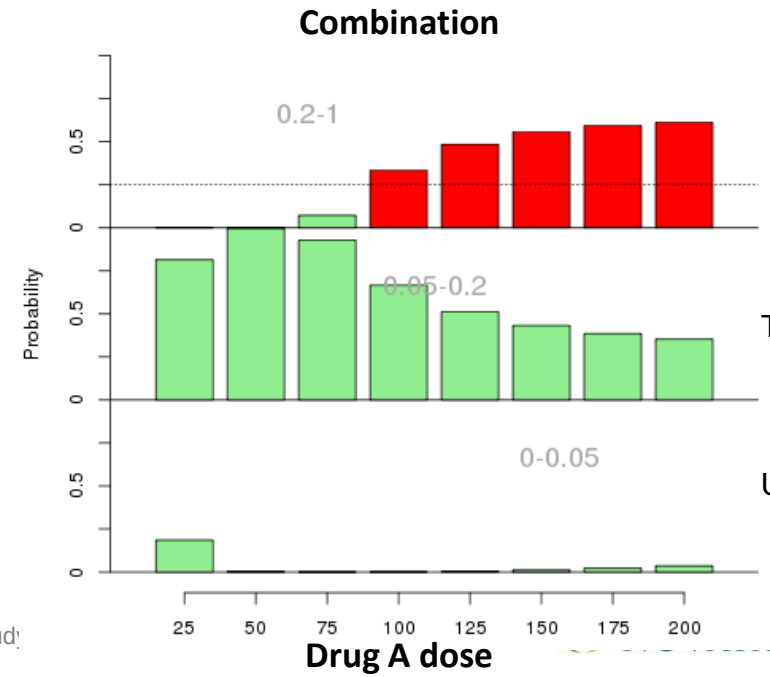
Cohort 5

Combination 4/25

Combination MTD established = 50mg (75mg could also be chosen)

	Dose	25	50	75	100	125
Mono	# Patients	0	25	50	25	0
	# DLT		2	6	6	
Comb	# Patients	25	50	50	0	0
	# DLT	1	5	7		





Overdose

Target dose

Under-dose

Design evaluation

Simulating study operating characteristics

- A simulation plan was written in collaboration with the clinical team
- Key simulation parameters
  - Cohort size: 10, 20, 25, 30
  - Minimum number of patients enrolled: three cohorts
  - Maximum number of patients enrolled: eight cohorts
  - Minimum enrolled at the MTD combination: two cohorts
- Dose-toxicity scenarios:
  - Mild: 75 borderline under / 100 target / 125 over
  - Moderate 1: 75 target / 50 borderline under / 100 over
  - Moderate 2: 75 borderline over / 50 target
  - Toxic: 50 borderline over / 25 target

Design evaluation

Simulating study operating characteristics

- Metrics for evaluation:
  - Proportion of patients receiving target dose, overdose, and under dose
  - Probability of recommending a target dose, overdose, or an under dose as the MTD
  - Expected total sample size
- Simulations done with an internally developed library (R & JAGS)
- High-performance computing cluster for fast execution
- For simplicity, each arm (mono/comb) was simulated separately
  - Simulated OCs are thus likely “conservative” as the real trial will use information from both arms at each IA
- For each simulation configuration:
  - Summary of metrics – high-level check of OC and suitable for protocol
  - Detailed diagnostic plots – essential for fine-tuning of design parameters

Simulation output

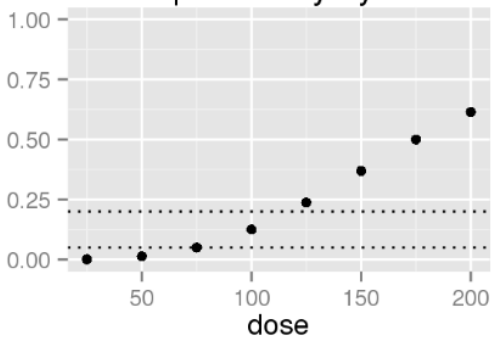
High-level summary table

```
## [1] mild
## Levels: mild
## Metric   I :   57.83 - Average proportion of patients in target dose region (>= 5 % - 20 %)
## Metric  II :   25.14 - Average proportion of patients in over   dose region (>= 20 %)
## Metric III :   17.03 - Average proportion of patients in under  dose region (<  5 %)
## Metric  IV :   81.40 - Proportion of trials with MTD  in target dose region (>= 5 % - 20 %)
## Metric   V :   13.70 - Proportion of trials with MTD  in over   dose region (>= 20 %)
## Metric  VI :    0.40 - Proportion of trials with MTD  in under  dose region (<  5 %)
## Stopped    :    4.50
##
## Average  N :  148.45
## Average DLT:   18.20
```

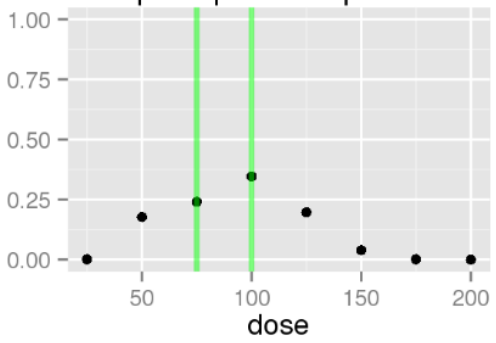
Simulation output

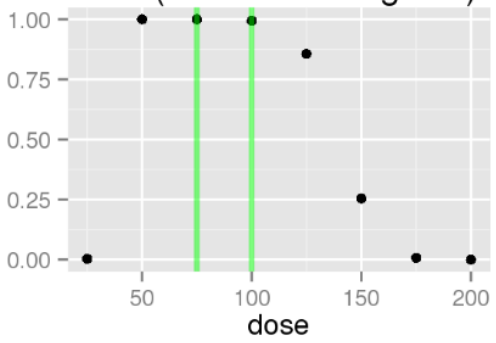
Detailed diagnostic plots

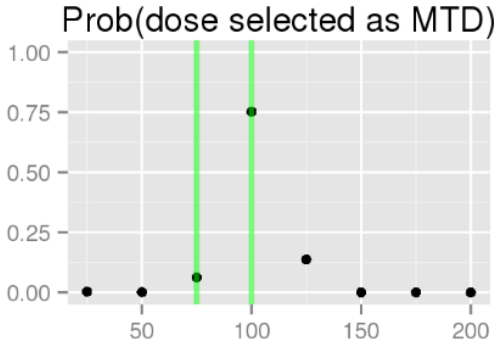
Reasonable doses?



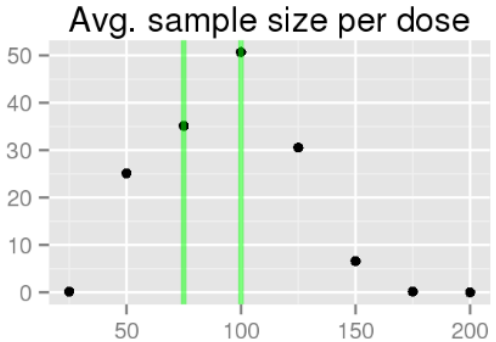
How often is each dose investigated?

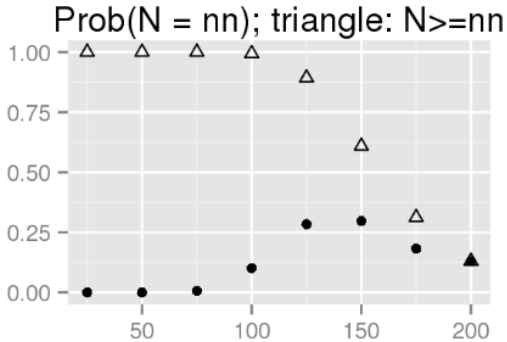






Reasonable selections?





How many patients (per dose/overall)?

Discussion

- Historically, dose finding in malaria has been limited
  - Desirable to administer doses as high as possible (efficacy, resistance)
  - Ethically questionable to treat with doses expected to be subtherapeutic
- Dose finding program tailored to estimate the upper limit for dosing
- Methodology for Bayesian phase 1 oncology trials translates naturally to our setting
- Necessary (though perhaps not sufficient) ingredients
  - Open-minded clinical team
  - Frequent discussions with study team – favor visualizations over statistical jargon
  - Hypothetical examples of dose-escalation recommendations
  - Of course...
    - Familiarity with Bayesian statistics
    - Effort/willingness to conduct fairly large-scale simulations to evaluate the design

References & acknowledgements

- Selected references:
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- Acknowledgments:
  - Novartis malaria clinical team
  - Simon Wandel and Sebastian Weber (Novartis oncology)

Thank you!

Questions?