Transitioning from algorithmic to adaptive model-based designs

Phase I dose-escalation trials in oncology at Servier

Symposium on Early Phase Dose Finding Methodology

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SERVIER

Outline

- What we used to do
- What we proposed
- What we do now
- What's next

Oncology Phase I dose escalation
Key elements

Objective

- Find the Maximum Tolerated Dose (MTD)
- MTD → Highest dose with acceptable toxicity

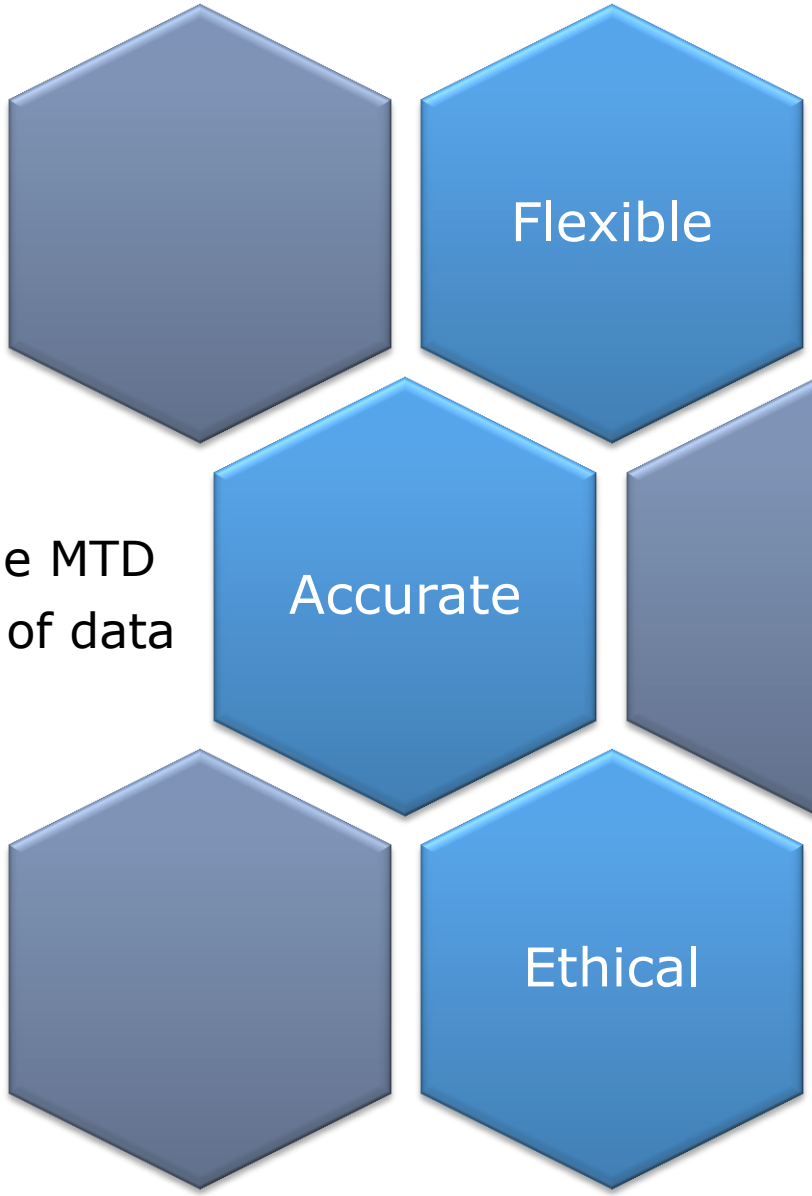
Main criterion

- Dose Limiting Toxicities
- Binary criterion (Yes / No)

Design

- Open labeled
- Non-randomized
- Non-comparative
- Sequential cohort inclusion

Oncology Phase I dose escalation
Key requirements



Dose skipping

Escalate/De-escalate

Cohort size

Estimation of the MTD

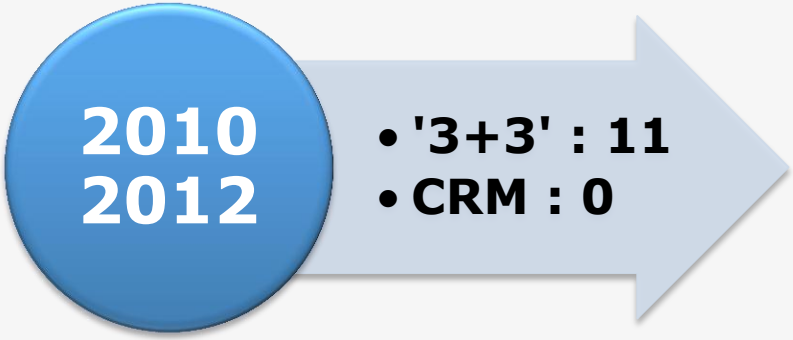
Use the totality of data

Avoid exposition to sub-therapeutic doses

Control overdosing

What we used to do

Algorithm-based design



Why ?

✓ Easy to implement
✓ Easy to understand
✓ Driven by clinician only

Some well-known limitations

× Memoryless and slow
× Too many patients to sub-therapeutic doses
× Declares wrong MTD too often

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Feedback

What we proposed

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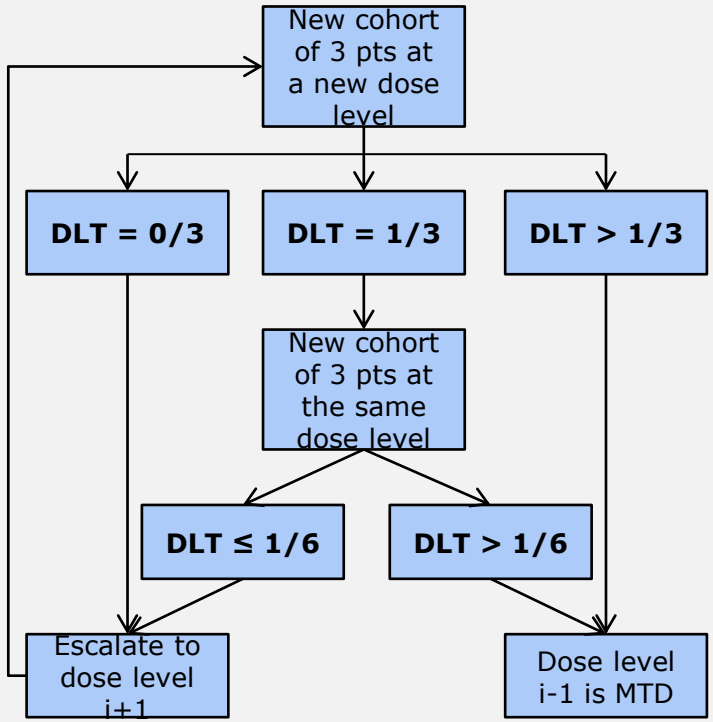
Ready for a change ?

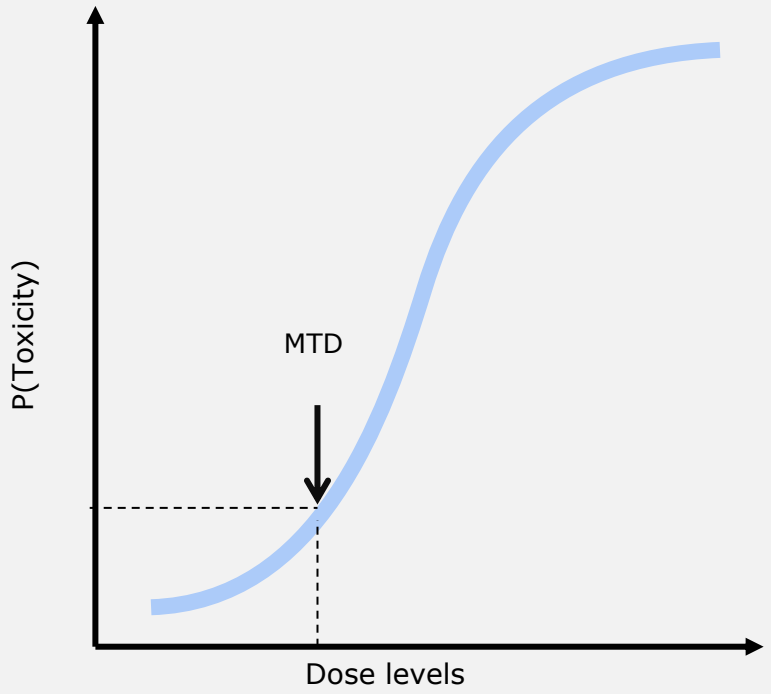
Same old way

Algorithm-based design



Something new

Model-based design



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Clinicians questions

How long will it take to develop a protocol?

What do you mean by prior?

How proceed if a DLT is ruled on during the End of Cohort meeting?

Dose recommendation will come from a black box

Will we have to strictly follow the dose recommendation from the CRM?

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Action plan

Statistical implementation plan

- ✓ Statistician experts consultations
- ✓ PhD student in collaboration with INSERM
- ✓ Internal software development

Clinical implementation plan

- ✓ Disseminate the idea among clinical teams
- ✓ Restrict model-based designs to a few projects first
- ✓ Communicate with investigators

First clinical trials with model-based design

Study	Model	Nb doses	MTD definition	Stopping rule	Patients by cohort	Skipping dose
1	Power	4	Interval	No change in MTD(1)	3 to 6	Not allowed
2	Power	11	Interval	Gain in precision(2)	2 (until 1st DLT) then 3 to 6	Not allowed
3	Power	11	Point estimate	No change in MTD(1)	3 to 6	Permitted

- ✓ Simulations provided confirmation of advantages of model-based designs over « 3+3 »
- ✓ Try out several « options »
- ✓ Protocol language

(1) O'Quigley et al. (1998)
(2) S. Zohar et al. (2001)

What we do now

Communication and education

Training on model-based design performed for:

- ✓ Statistical department
- ✓ Oncology department
- ✓ Clinical operations

Presentation of the study design during:

- ✓ Investigators meeting
- ✓ Monitors meeting

Slidepack for presentation during team meeting

Protocol development

Standardization of the study design section

Standardization of the statistical analysis section

Appendix to present the design's calibration and operating characteristics

Standardization of the timelines

Operating characteristics

Development of an **internal**  **package**

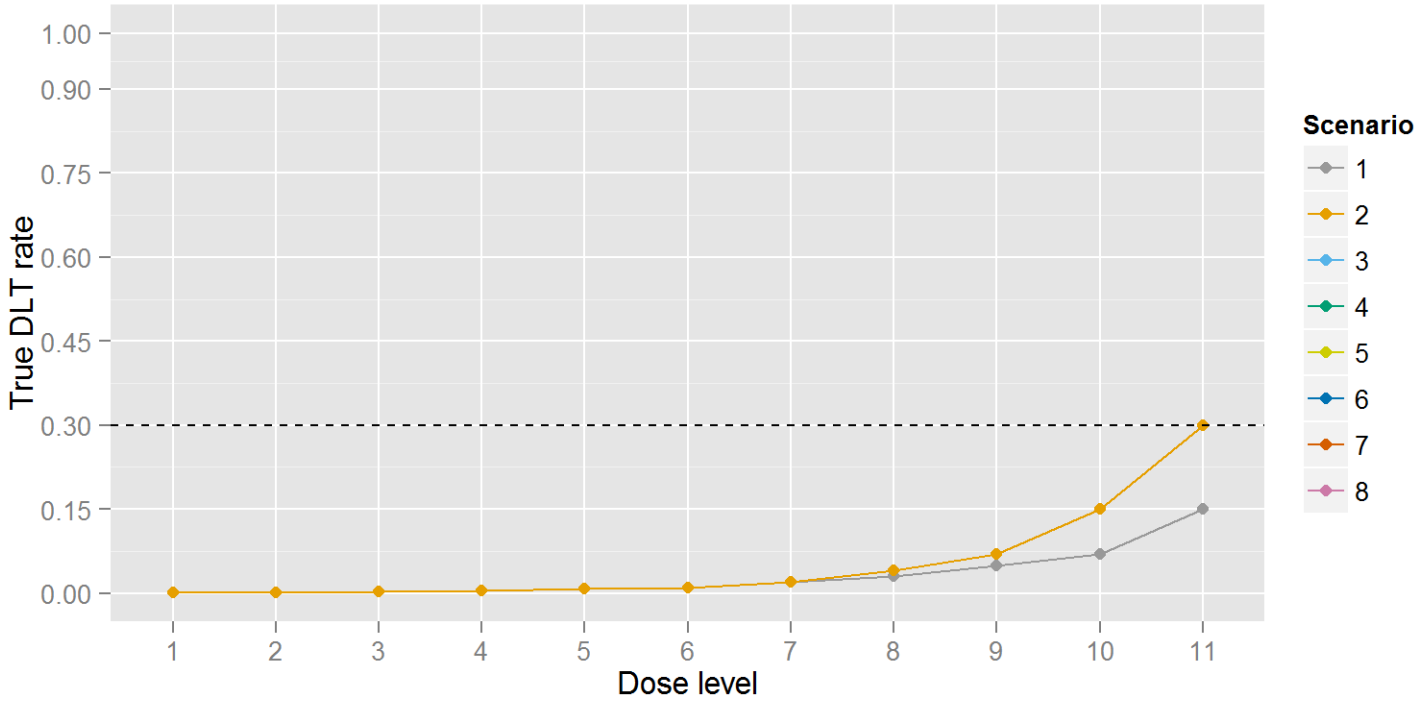
- ✓ Flexible
- ✓ Not restricted to what is implemented in a software (models, stopping rules, number of patients by cohort, …)
- ✓ See what happen in a single trial simulation

High-performance computing

- ✓ Reduce timelines for simulations
- ✓ Responsive in case of protocol amendment

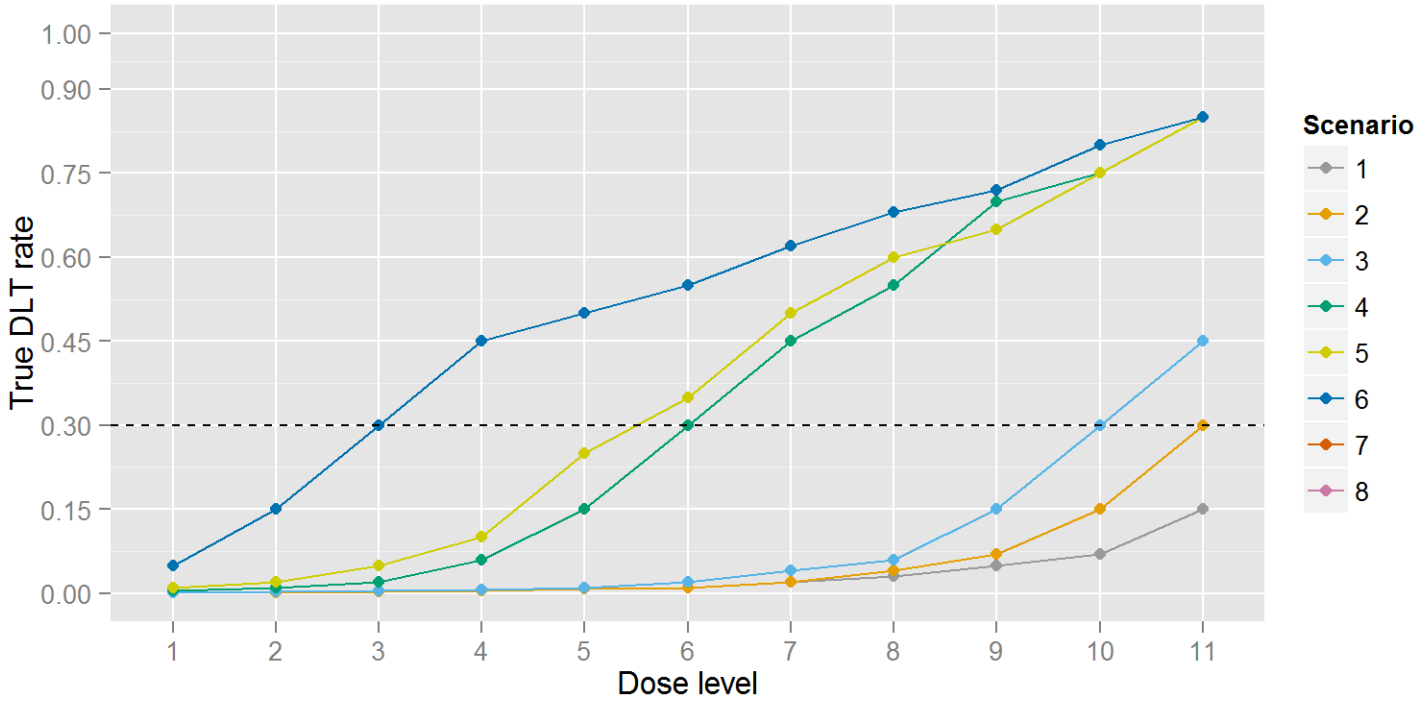
Standardization of the metrics and the outputs to evaluate the performance of the design

Scenarios



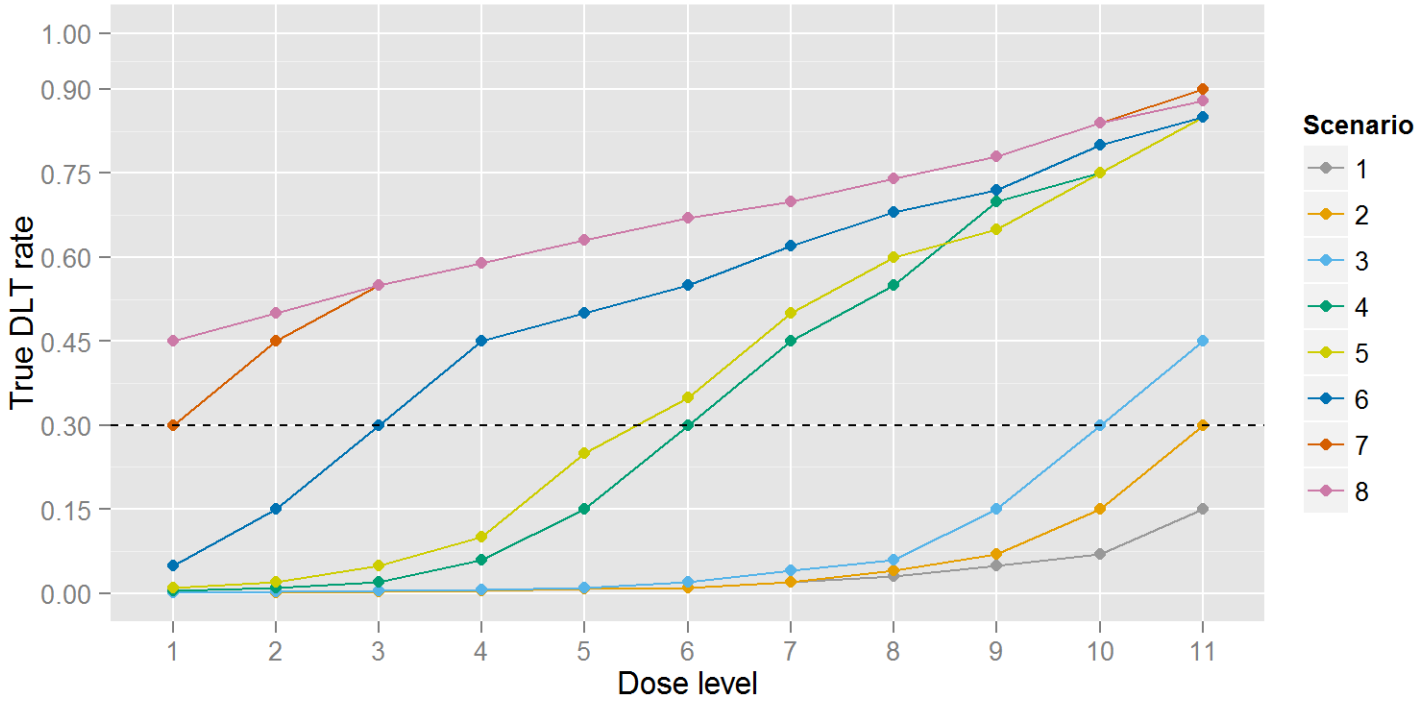
Undertoxicity

Scenarios



MTD within the doses

Scenarios



Overtoxicity

Summary of results – by scenario

Varying parameters			Probability of selection			Average number of patients			Total Number of patients			Total Number of DLTs	Stopping Rules		
Param. 1	Param. 2	…	Dose 1	Dose 2	…	Dose 1	Dose 2	…	Min	Med	Max	Over all doses	Rule 1	Rule 2	…

Varying parameters
- ✓ Cohort size
- ✓ Skipping dose
- ✓ Stopping rule
- ✓ …

All possible combinations

Optimal selection of the parameters

Decision rules for the first cohorts

Cohort	Dose level	Nb of DLT(s)/Nb of patients	Next dose level proposed
1	Starting Dose	0/3	Dose A
		1/3	Dose B
		2/3	Dose C
		3/3	Dose D
2 (0 DLT in cohort 1)	Dose A		
…	…		

End of cohort statistical report

Standardization of the **End of cohort statistical report**

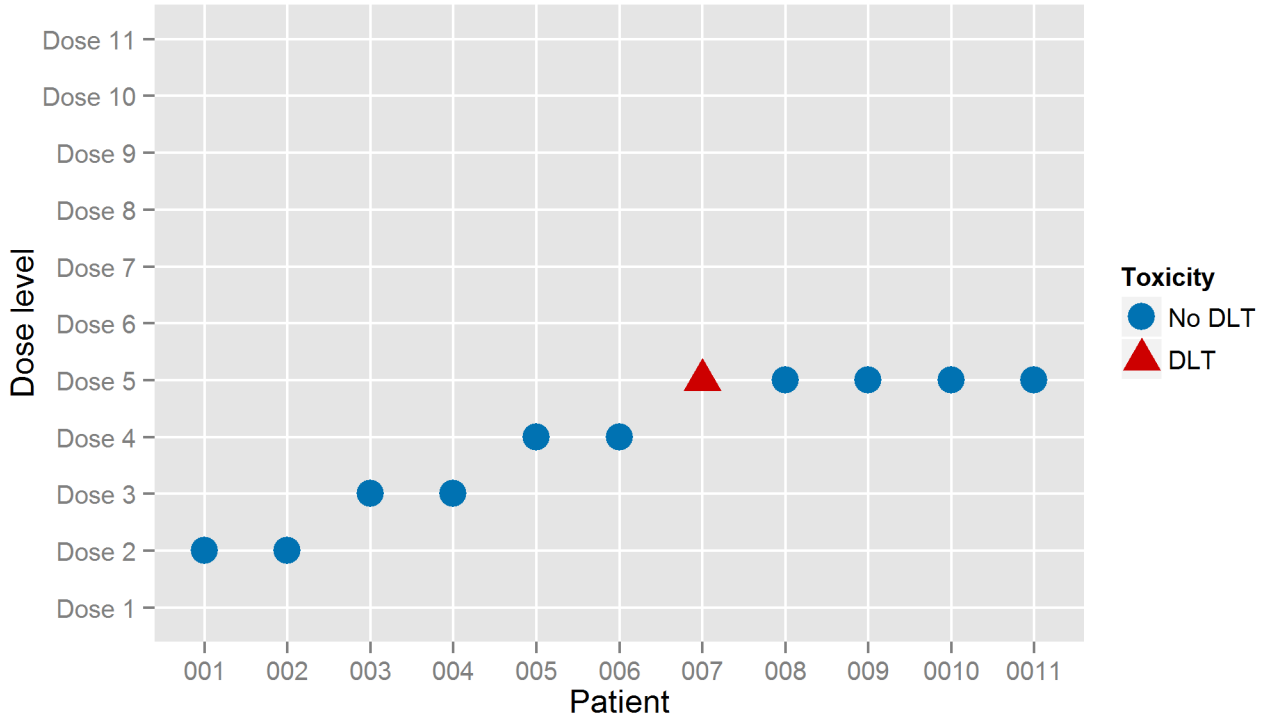
Word-based document automatically generated using 

- ✓ Faster
- ✓ Easier to quality-controlled

Document provides

- ✓ Dose allocation methodology summary
- ✓ Graphical summary of previous cohorts
- ✓ Dose recommendation for next cohort

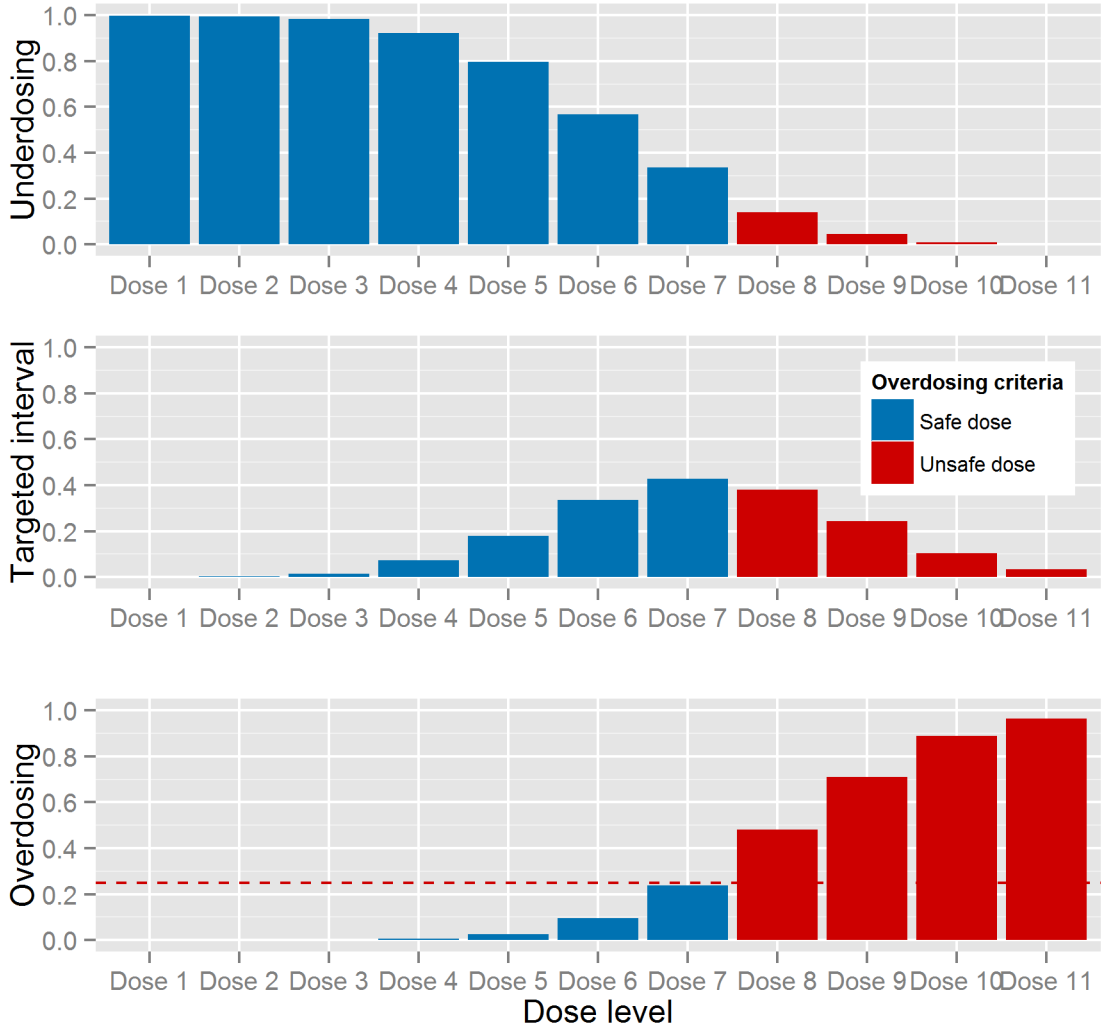
Dose-DLT trajectory



Dose recommendation summary

Current cohort's dose	Number of DLTs in the current cohort	Include a new cohort?	If NO: stopping rule reason	Next recomended dose	MTD
Dose 6	0	YES		Dose 7	NO
Dose 6	1	YES		Dose 5	NO
Dose 6	2	YES		Dose 5	NO
Dose 6	3	YES		Dose 4	NO

Predicted interval probabilities



Dose-escalation meeting

Review all available data (from current and previous cohorts)

- ✓ DLT
- ✓ Safety and PK data

Agree on the total number of DLTs observed in the current cohort

Statistician informs participants of the recommended dose for the next cohort

Discussion between participants to select the dose for the next cohort

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Dose escalation meeting

Clinical trials with model-based design

Study	Model	Nb doses	MTD def.	Stopping rule	N patients by cohort	Skipping dose	State
1	Power	4	Interval	No change in MTD(1)	3 to 6	Not allowed	On-going
2	Power	11	Interval	Gain in precision(2)	2 (until 1st DLT) 3 to 6	Not allowed	On-going
3	Power	11	Point estimate	No change in MTD(1)	3 to 6	Permitted	On-going
4	Power	3	Interval	No change in MTD(1) or Min N(3)	3 to 6	Not allowed	Protocol
5	Power	6	Point estimate	No change in MTD(1)	3 to 6	Permitted	Protocol

2013
2015

- **'3+3' : 5**
- **CRM : 5**

(1) O'Quigley et al. (1998)
(2) S. Zohar et al. (2001)
(3) At least *X* patients included in the study with at least *Y* patient at the MTD

What’s next

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New clinicians questions

We would like to implement a CRM for our study

How to account for late toxicities?

How to incorporate prior information?

How to use efficacy and safety data in a model-based design?

Could you come to our investigators meeting to present the CRM design?

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Action plan

Statistical implementation plan

- ✓ Open door for other model-based designs
  - ✓ Bivariate
  - ✓ Drug combination
  - ✓ PK
- ✓ Better use of the prior information

Clinical implementation plan

- ✓ Feedback from first studies
- ✓ Continual trainings for clinicians
- ✓ Regular updates

Conclusion

Transitioning from 3+3 to model based design was **fraught with pitfalls**

Implementation plan has **worked well**

- Disseminate the idea
- Communication and Education
- Standardization (protocol, end of cohort meeting, …)
- Internal software development

Clinicians are now **asking for** model-based design

Conclusion

Transitioning from 3+3 to model based design was **f… with pitfalls**

2016

…

'3+3' : 0

CRM : ?

Clinici… now **asking for** model-based design

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Key message

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