Bayesian Phase I/II clinical trials in Oncology

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Outline

- Oncology phase I trials
- Limitations of traditional phase I designs
- Bayesian phase I design with toxicity endpoint
- Bayesian phase I design with toxicity and efficacy
- I-SPY 2: example of adaptive phase II trial
- Bayesian adaptive phase III trials
- Conclusion

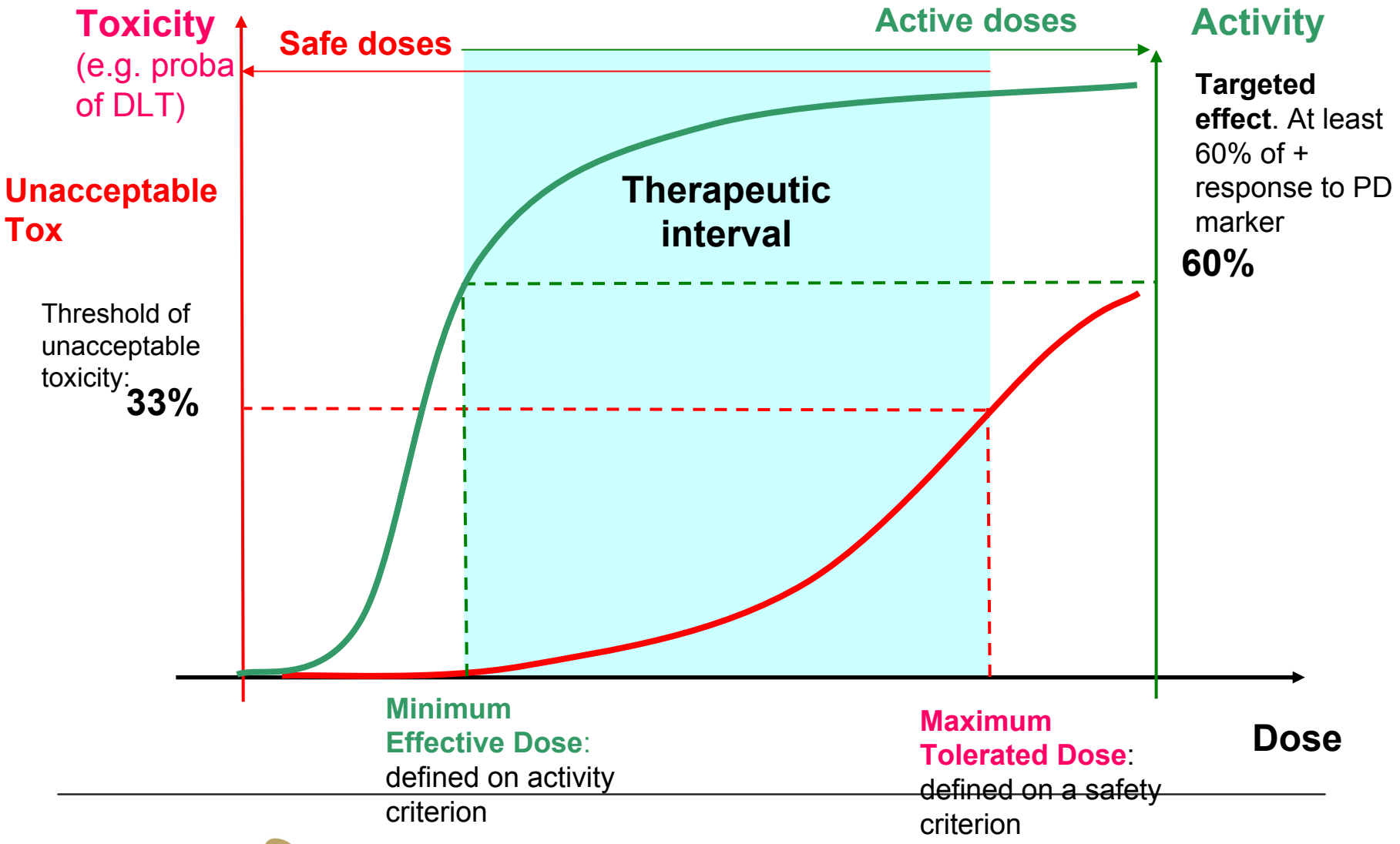
Phase I clinical trials in oncology

- Recommend a dose for Phase II clinical trial
- Design:
  - **Patients included in successive cohorts (usually n=3 in each cohort)**
  - **All patients within the same cohort receive the same dose**
    - First cohort receive the lowest dose
    - Primary **endpoint**: Dose-Limiting Toxicity
    - After completion of each cohort, decision is made on predefined algorithm to:
      - Escalate the dose
      - Stay at the same dose
      - De-escalate the dose
      - Stop the study

Original central hypothesis in cancer dose finding

- Therapeutic and toxic effect of a treatment are related to the dose given
- Monotonic dose-toxicity and dose-activity relationship
  - higher is the dose, higher is the activity
  - highly influenced oncologist in designing phase I trials
- True for cytotoxic drug but currently challenged for new generation of anti-cancer drug, e.g. targeted agents with less toxicity

Phase I purposes



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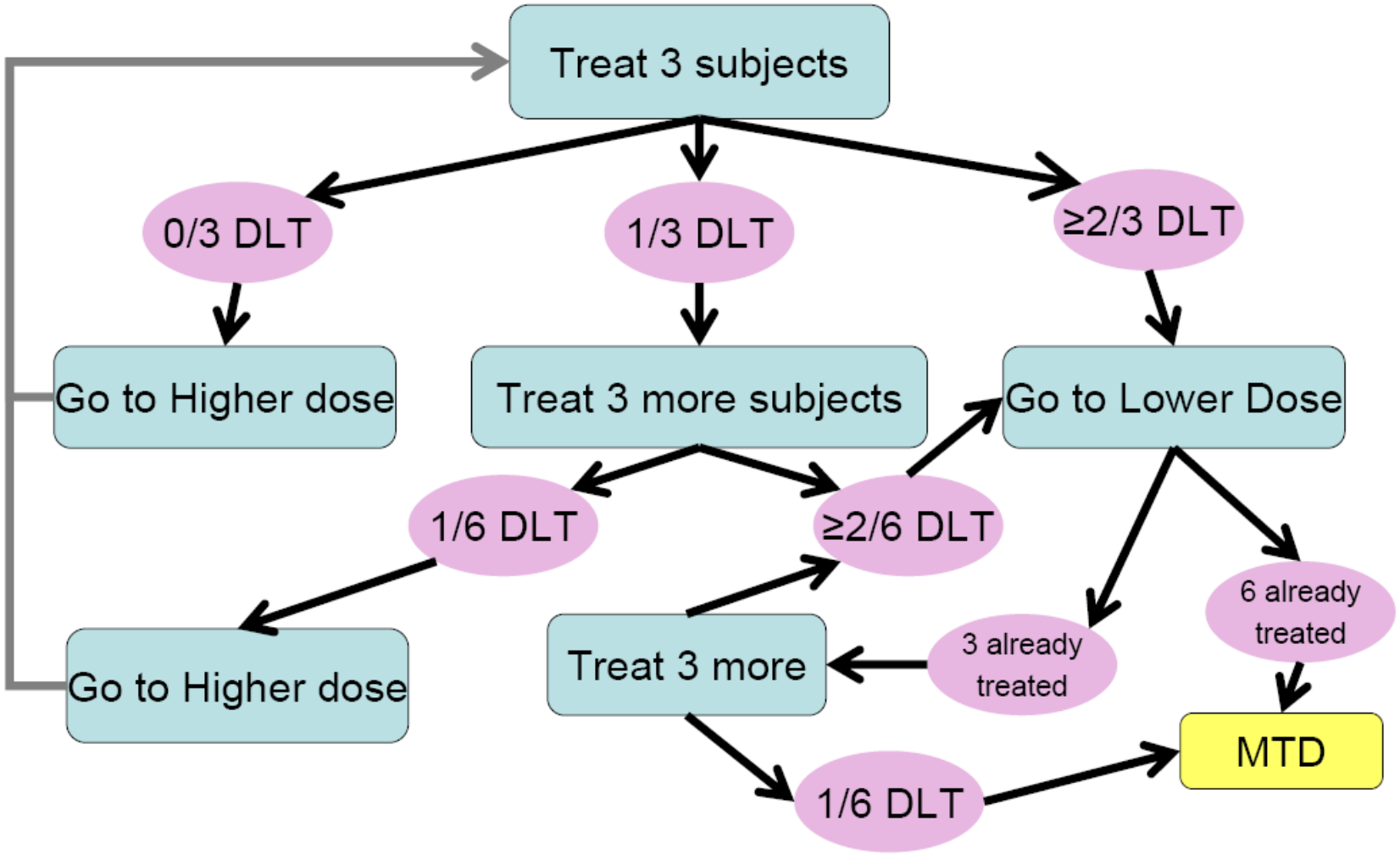
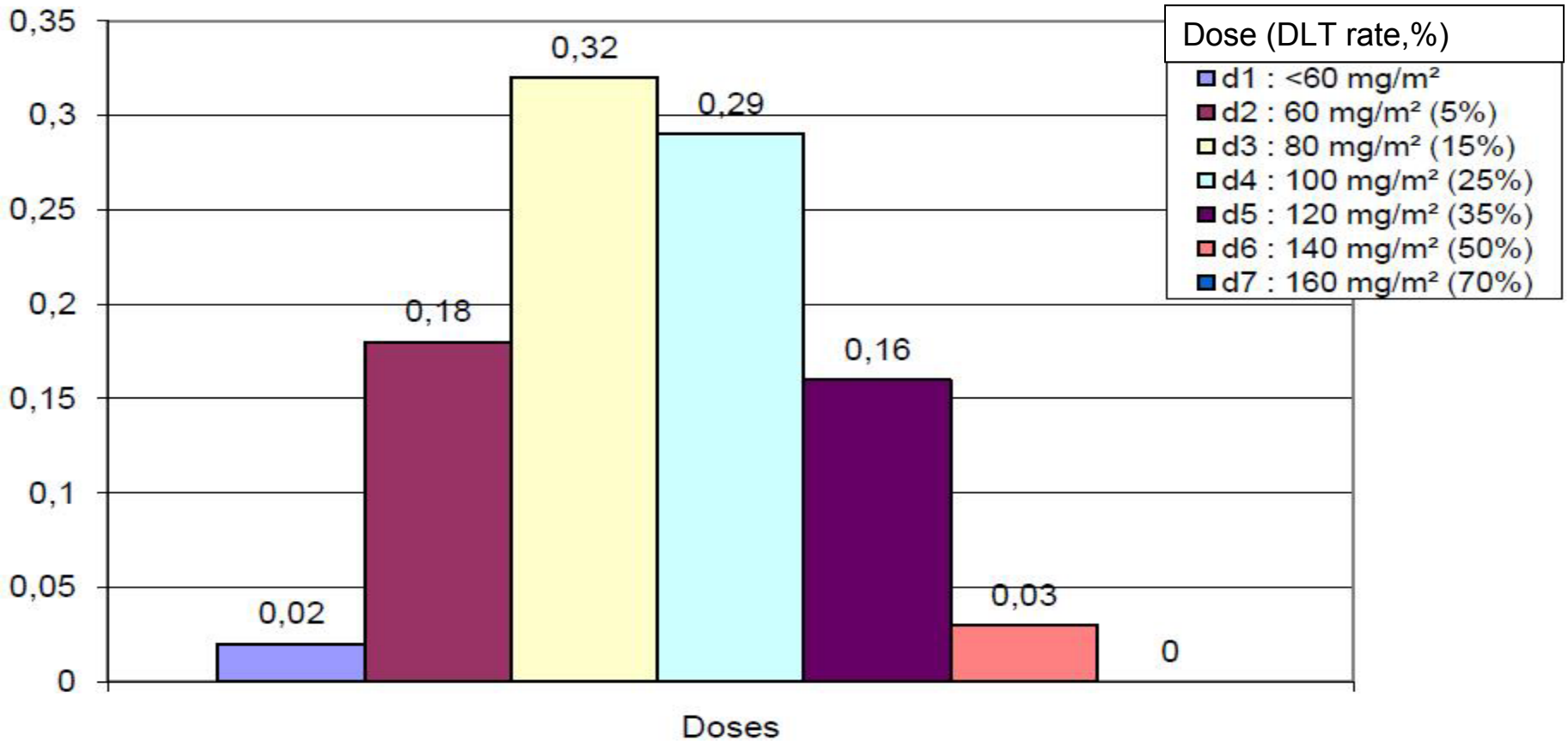
Algorithm-based (“3+3”) phase I design



Simulation of 1000 phase I trials using “3+3” design

Distribution of estimated MTD



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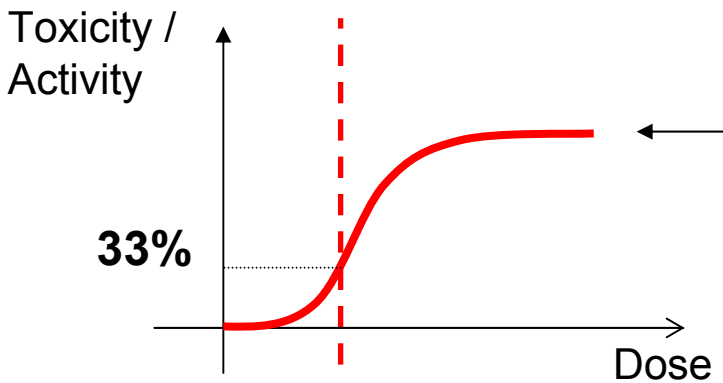
Algorithm-based designs: Pros and Cons

- Pros
  - Simplicity, Classical
  - Generally « safe »
- Cons
  - Short memory (only the current dose level used to decide about next one)
  - High variability
  - Tend to under-estimate MTD
  - Too many pts treated at non-toxic (and non-active?) dose
    - but accelerated titration design better than « 3+3 »
  - Choice of targeted toxicity level severly limited

What means « Dose-response model based » approach ?

- Try to assess a dose-response relationship using mathematical function
- Use mathematical tool (model) to define probability of DLT as a function of dose



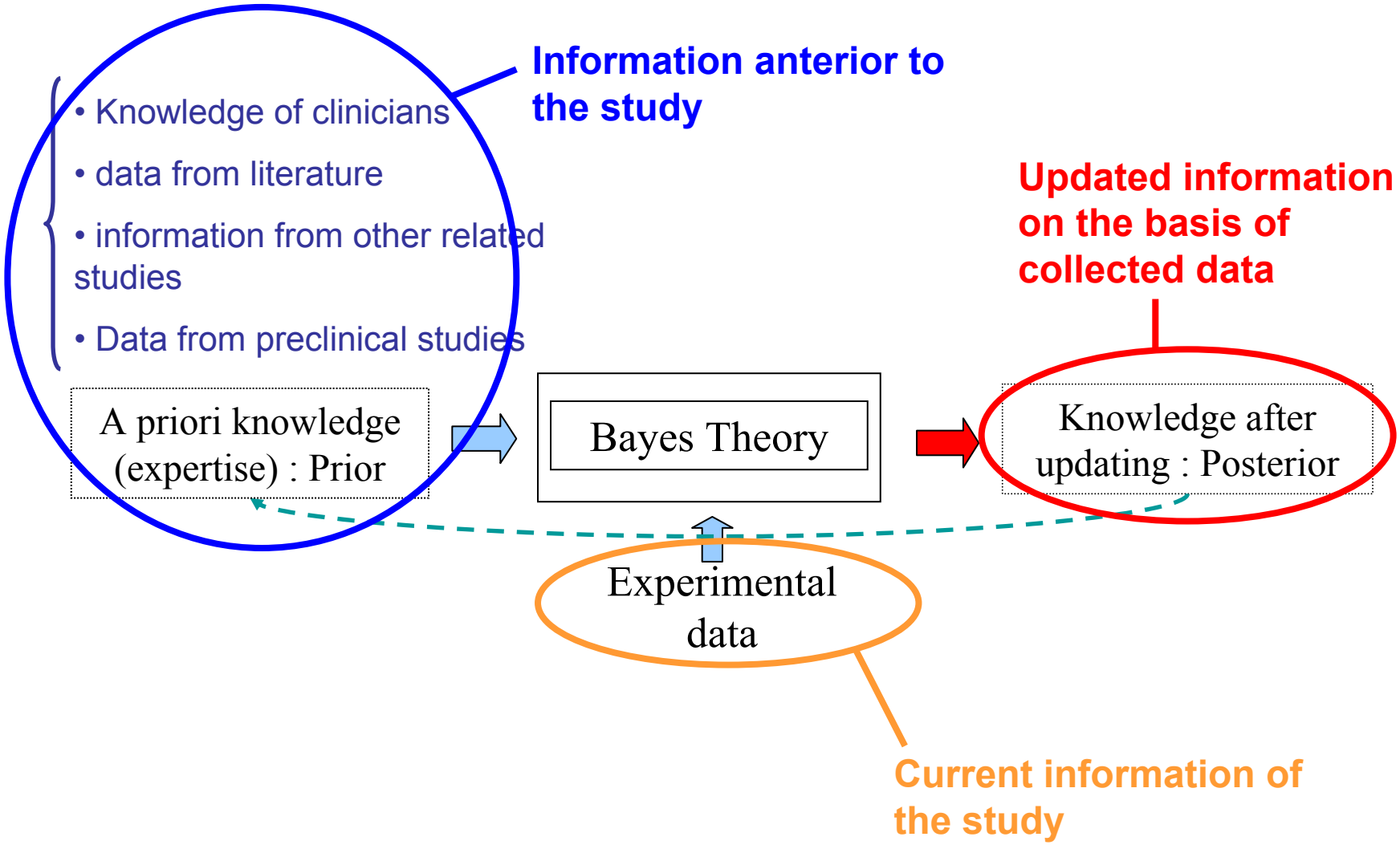
Toxicity effect. No more than 33% of DLT.

Mathematical model:

Tox = f (dose, parameter)

- provides quantification for the dose response relationship
- Allows interpolation: « what happened between two dose levels ? »

Principle of the Bayesian approach



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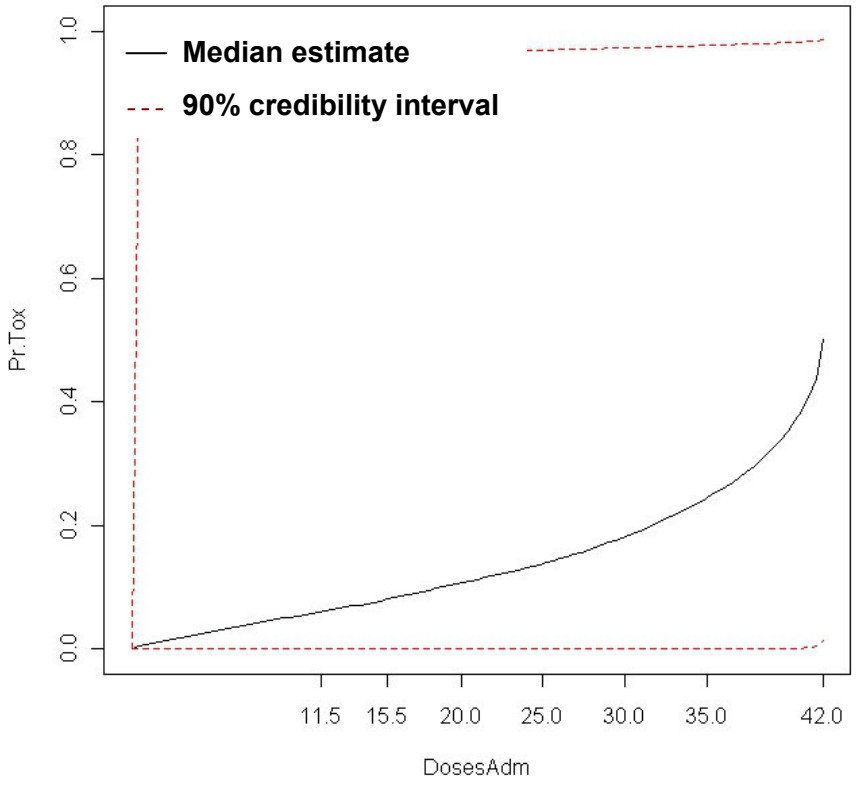
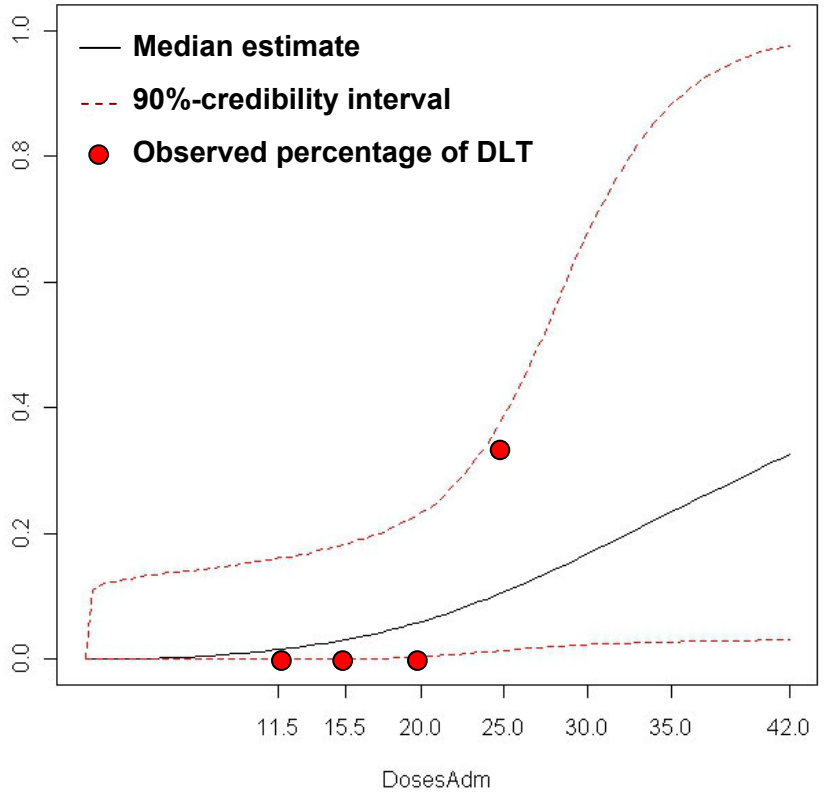
Estimated dose-response relationship: *a priori* and *a posteriori*

A priori



A posteriori



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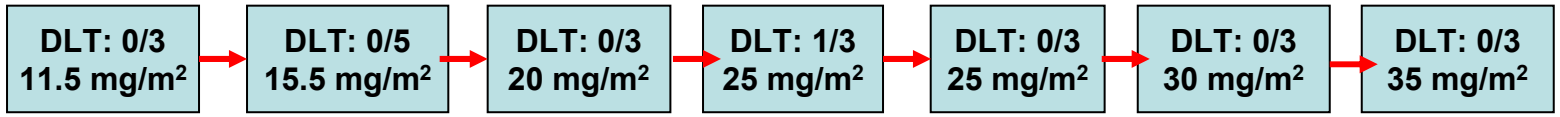
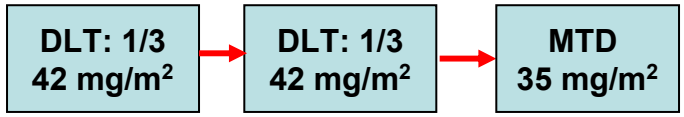
Phase I trial of Agent A + Agent B

- Chronology of escalating using the ‘‘3+3’’ design

Data



Data



What is the final estimated MTD?

“3+3” → 35 mg/m²

Bayesian Design → ????

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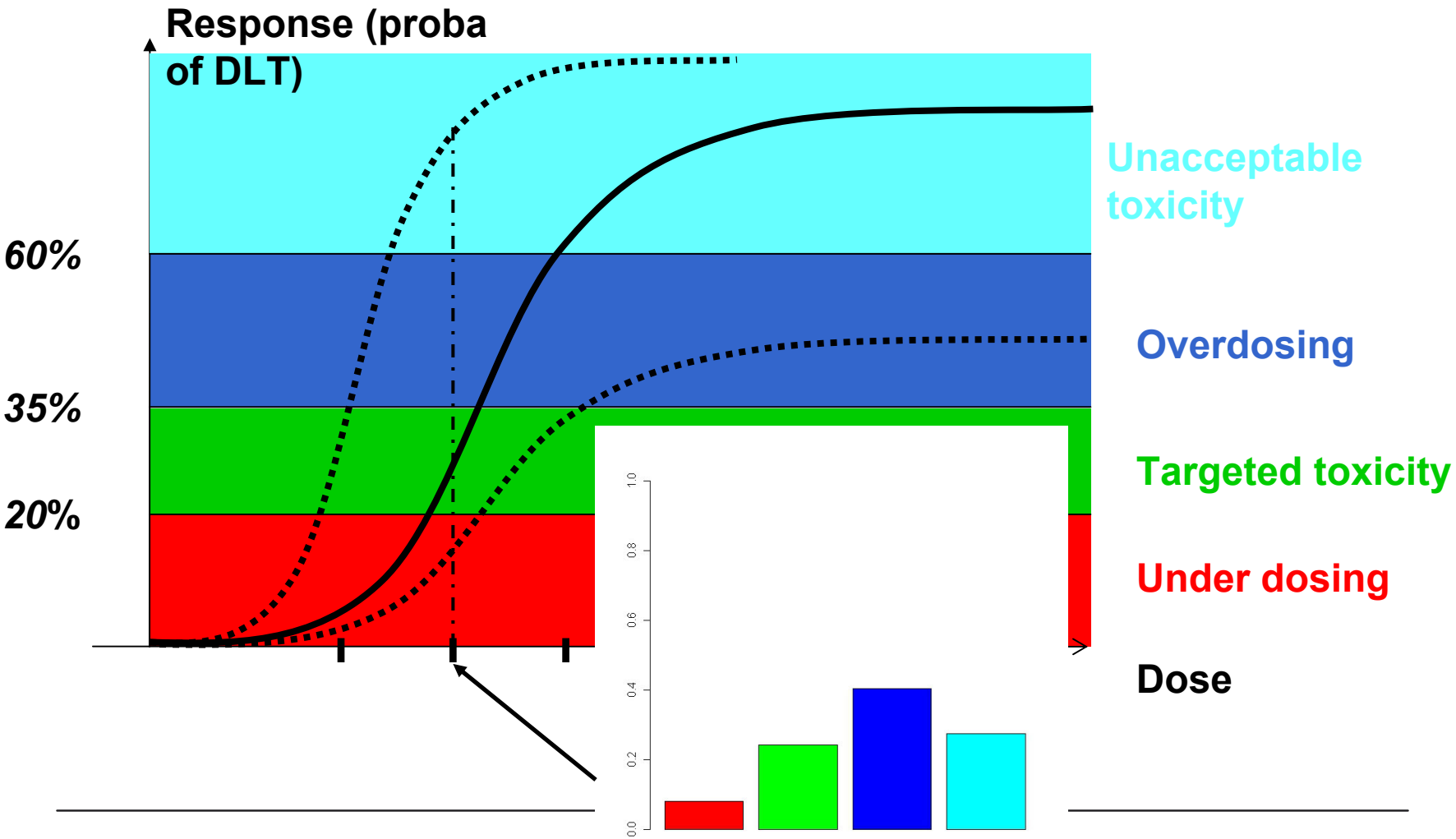
Dose escalation based on probability of toxicity for the next DL



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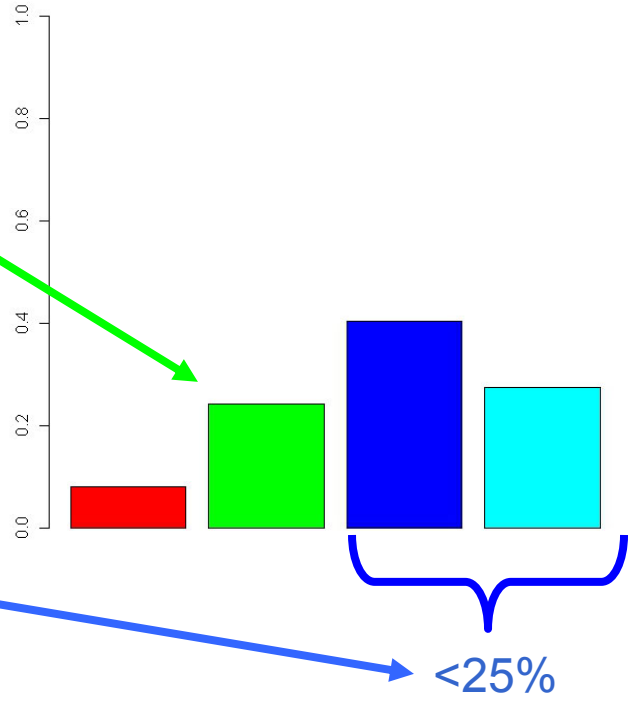
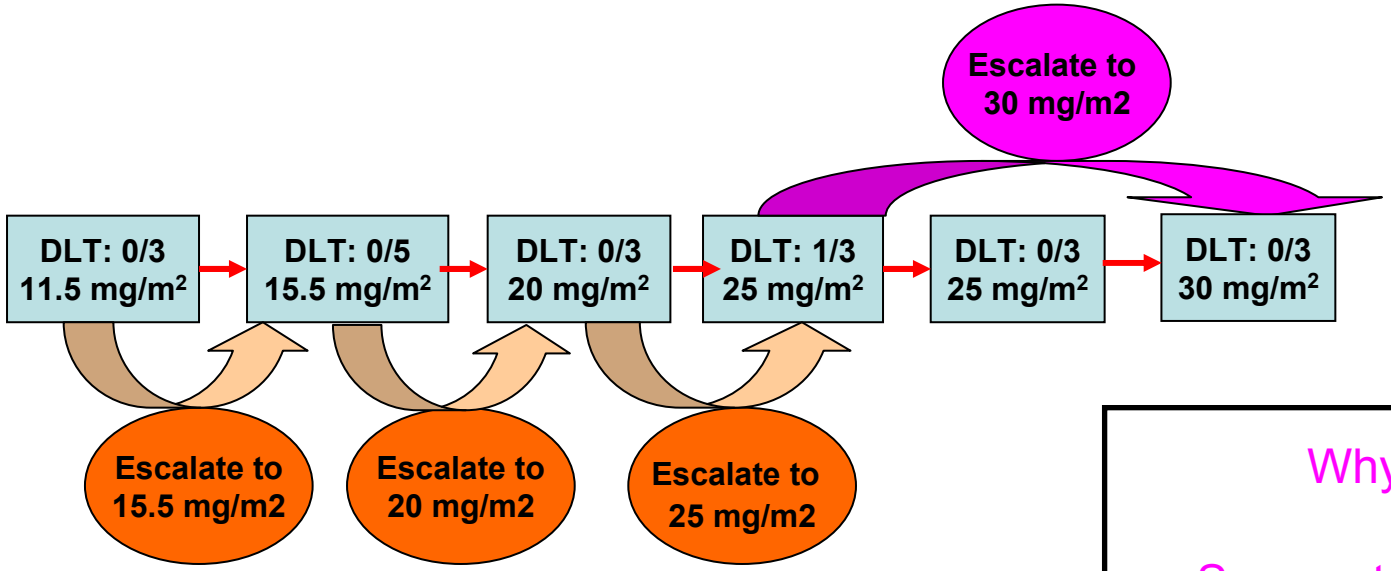
Select the dose level with :

- Highest probability to be in the targeted toxicity interval
- Safety rules:
  - **A Probability to be "overdosing or unacceptable tox" < 25%**
  - **Adjacent to the tested one (No skip allowed)**



Phase I trial example

Data



Why ?

See next slide =>

→ Reality

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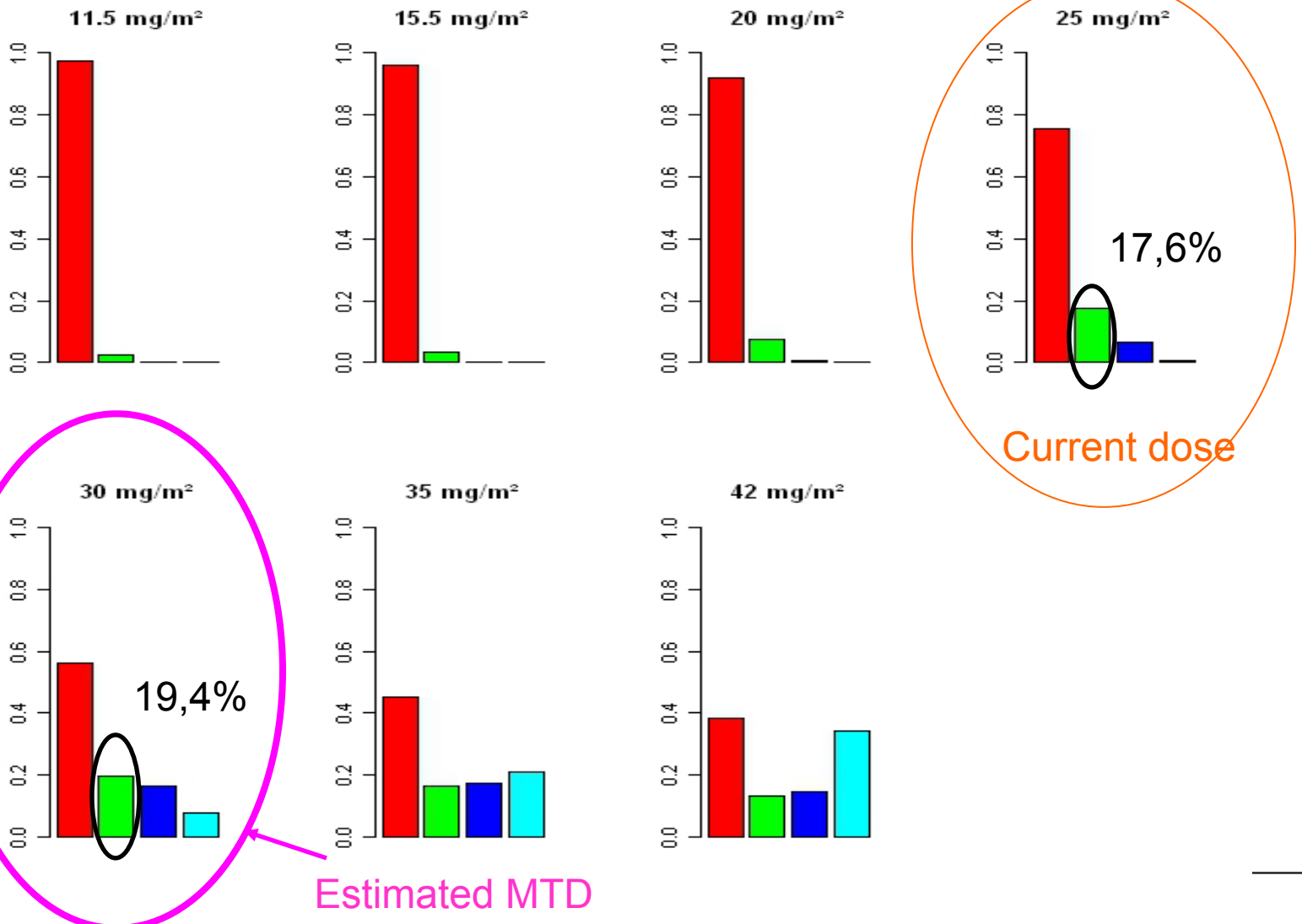
Bayesian decision principle



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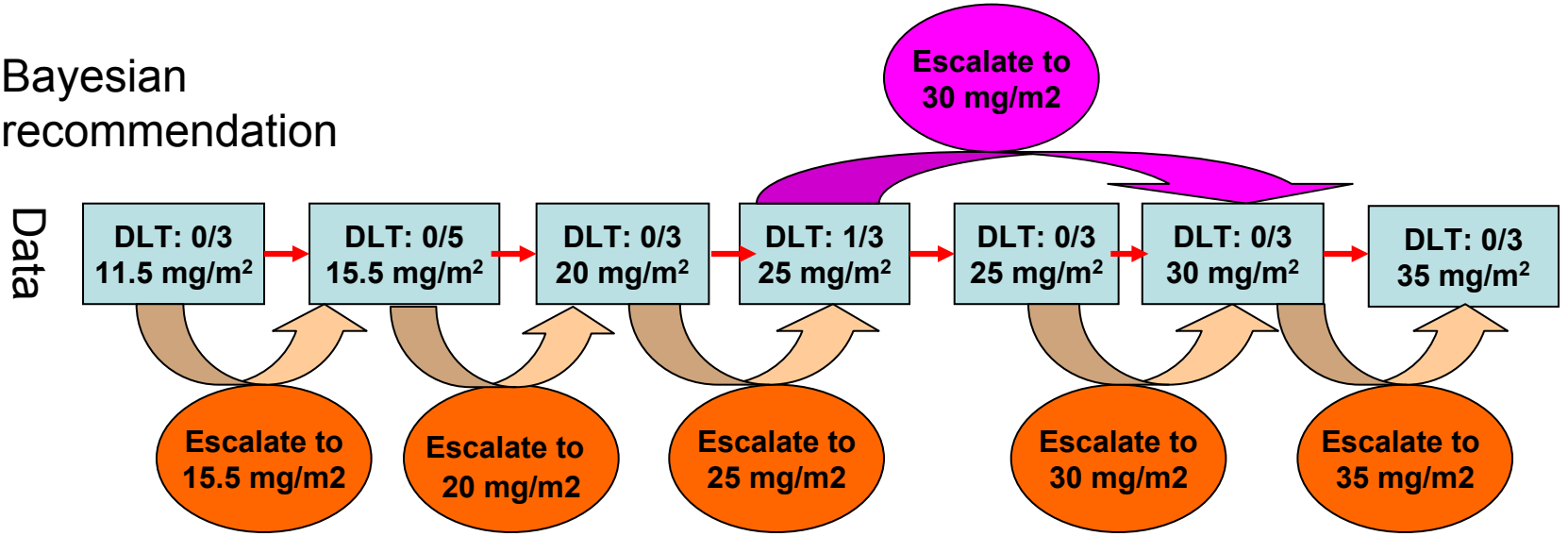
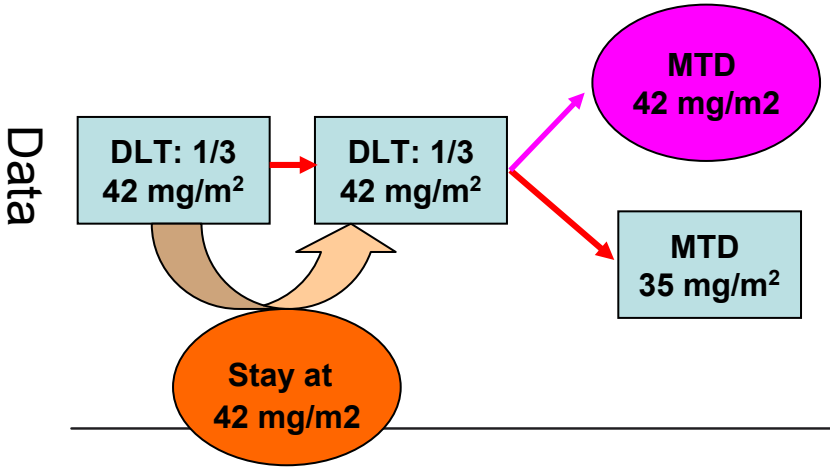
Phase I trial example

Bayesian recommendation





What is the final estimated MTD ?

"3+3" → 35 mg/m²

Bayesian design → 42 mg/m²

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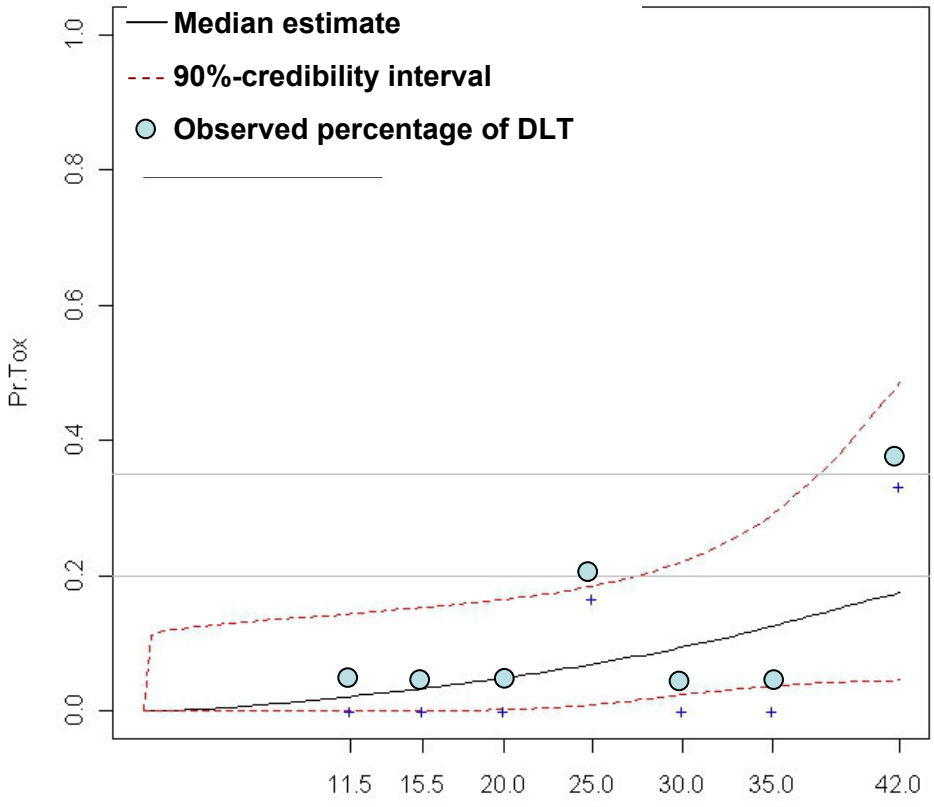
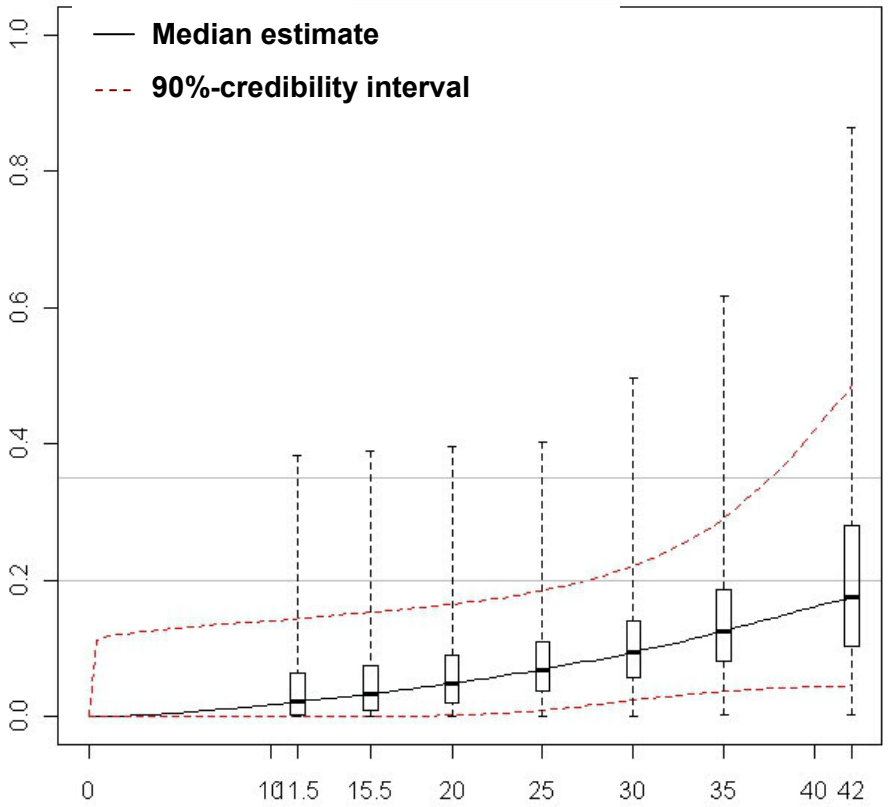
At the end of the escalation part …





Finally, among the 13 patients (escalation + expansion cohort) treated at 35 mg/m², 2 patients (15.4%) experienced a DLT

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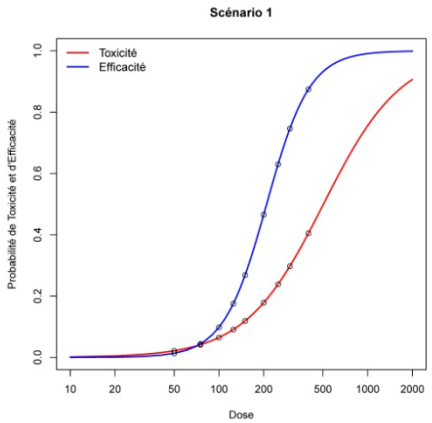
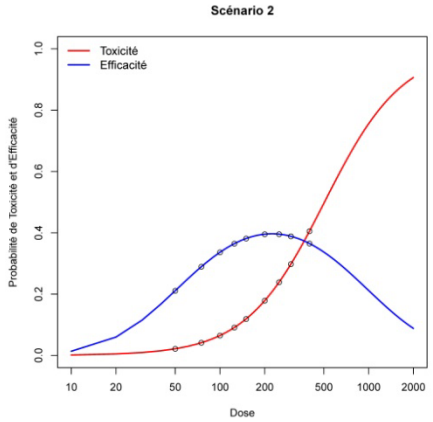
Adaptation of phase I designs to targeted therapies

- For targeted anti-cancer therapies (TT), MTD may become irrelevant if therapeutic effects are already achieved at lower doses
- Worst case, the therapeutic effect may even be lower at higher doses

Cytotoxic profile



TT profile



→ Model-based phase I designs can face such a challenge

- → By finding the optimal biological dose (i.e. joint assessment of toxicity and efficacy)
- → Indentify a range of doses and do a randomized phase II dose-finding trial

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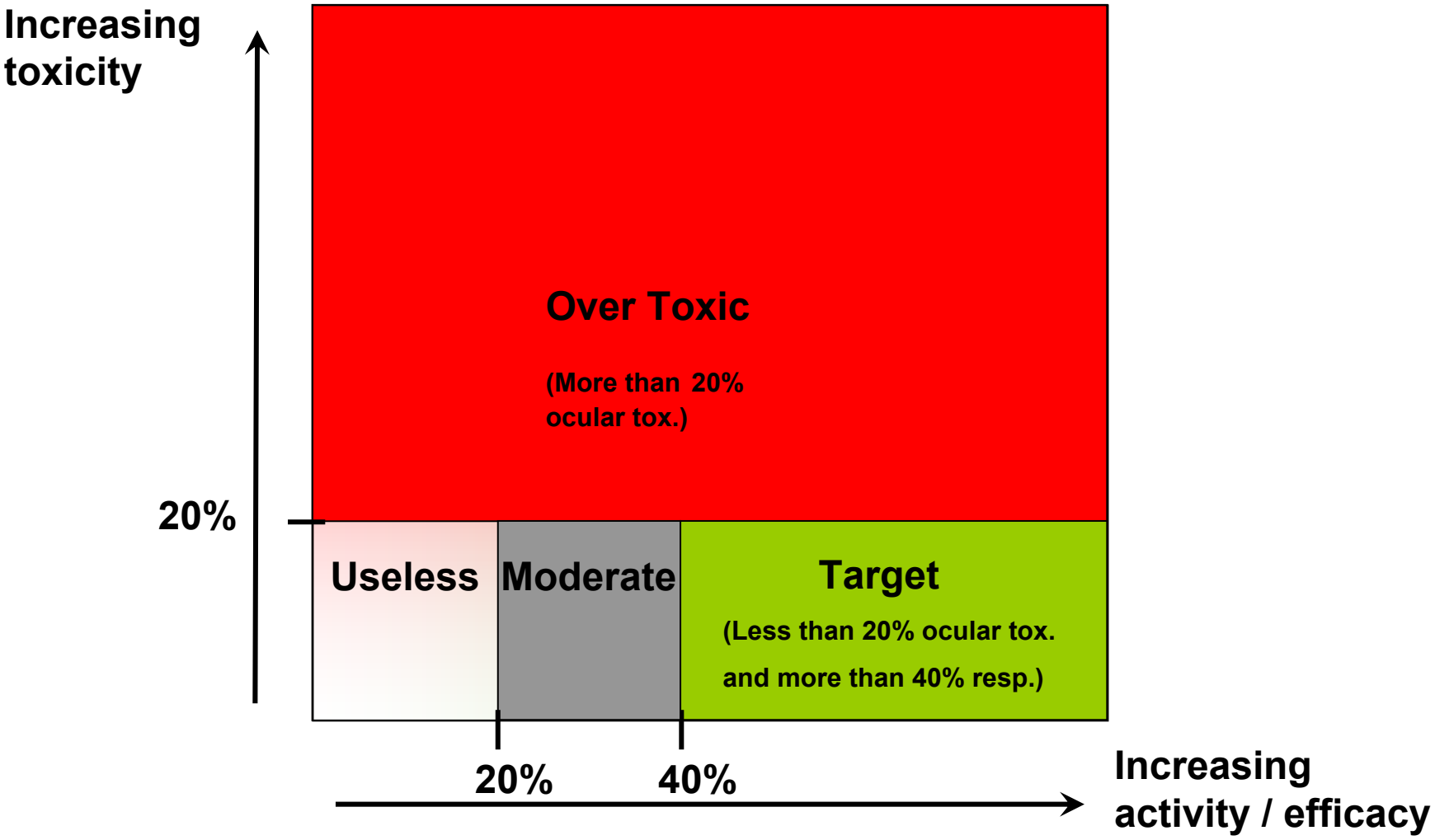
Toxicity vs Activity (2/2)



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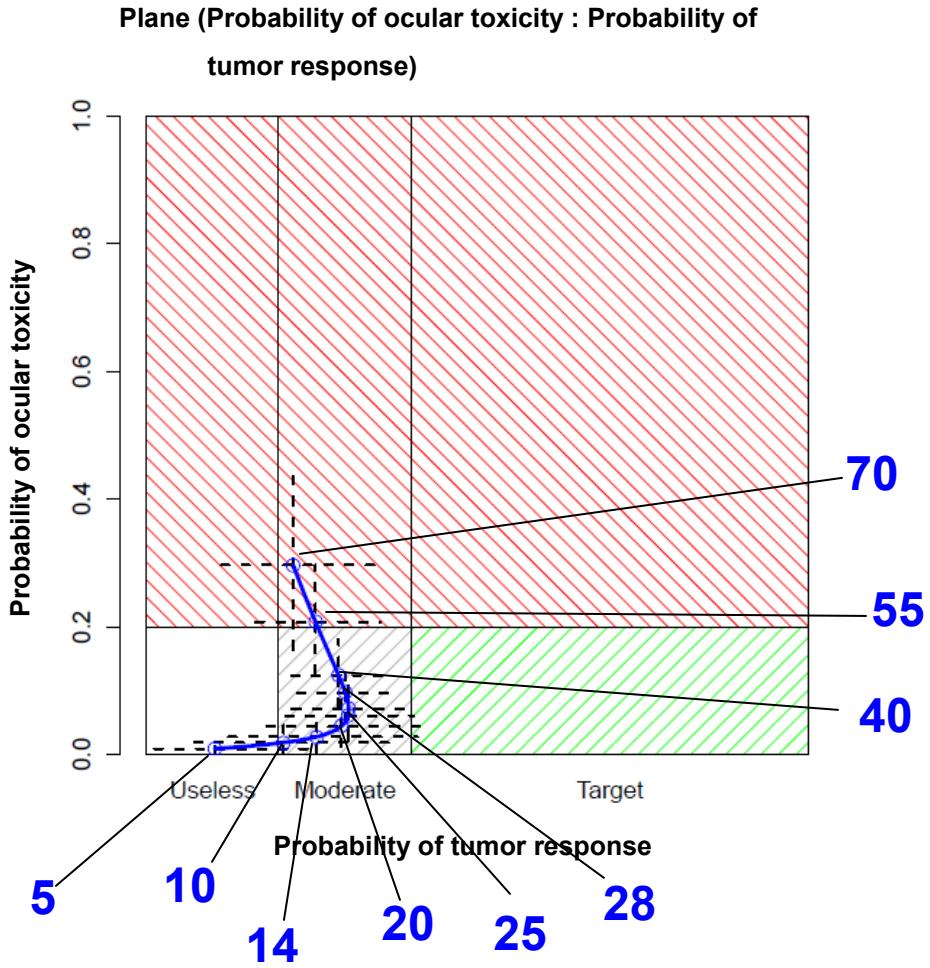
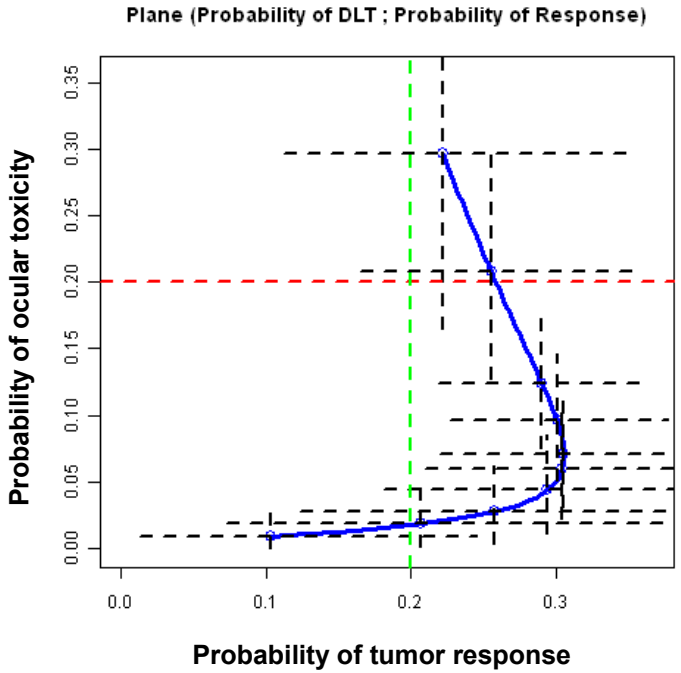
Balancing probability of ocular toxicities and probability of tumor response





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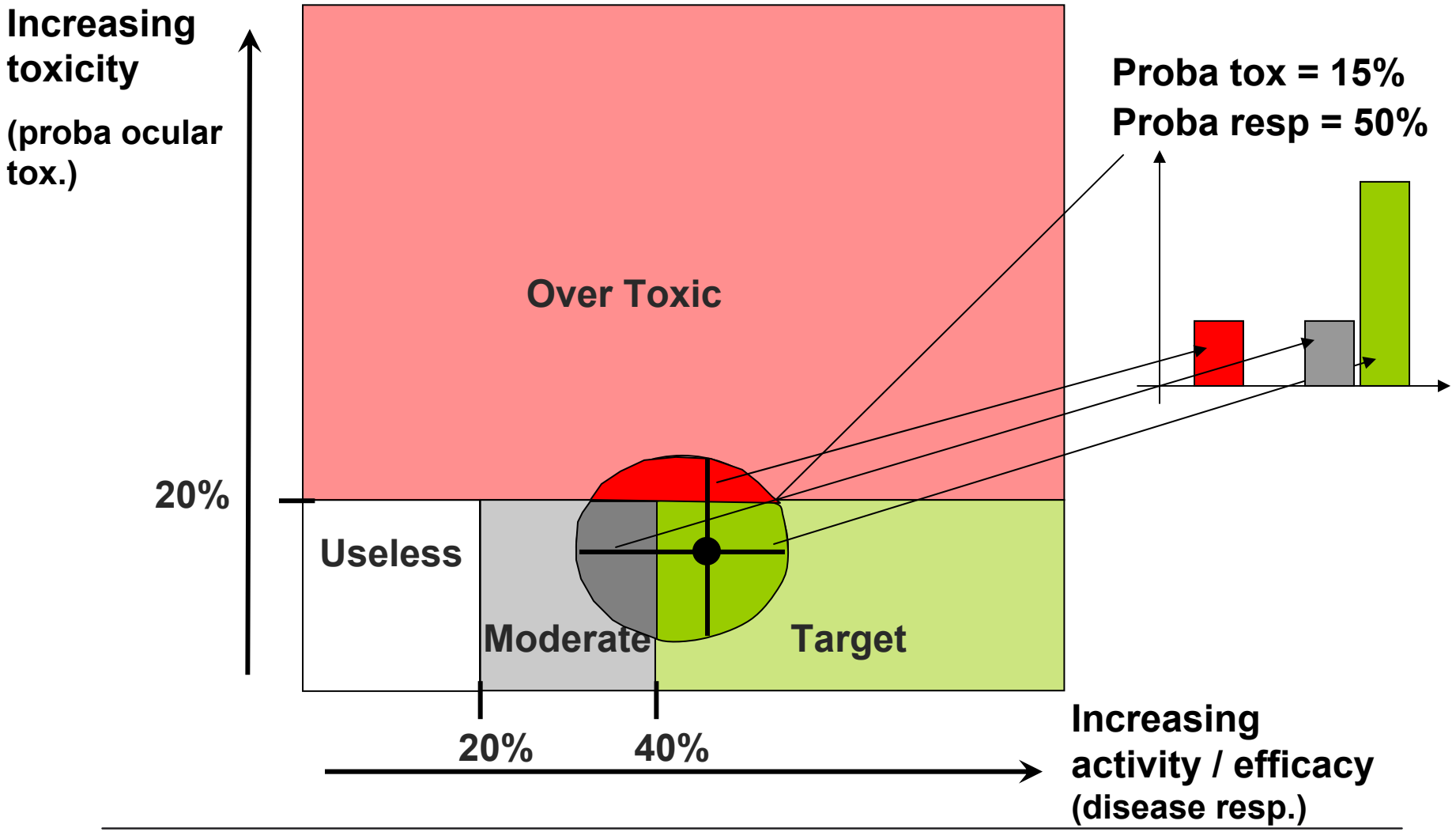
Increasing toxicity
(proba ocular tox.)
Over Toxic
20%
Useless
Moderate
Target
20%
40%
Increasing activity / efficacy
(disease resp.)
Proba tox = 15%
Proba resp = 50%

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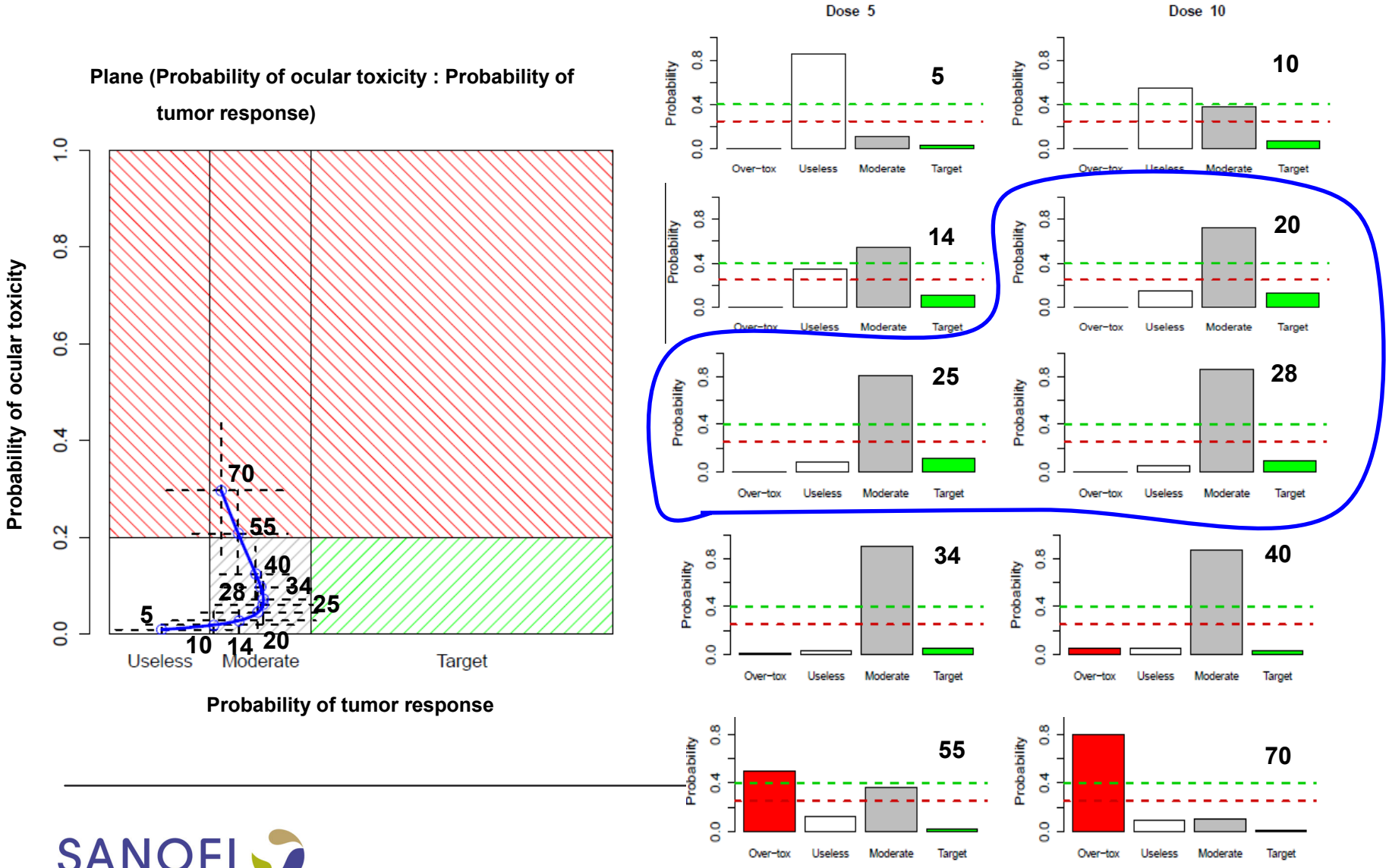
Balancing probability of ocular toxicities and probability of tumor response



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Why using the Bayesian approach ?

- Bayesian design show better performances than the algorithmic « 3+3 »
- Decision tool
- Takes uncertainty into account
- Able to handle prior information when wishable
- Modeling approach : Assessment of the dose-toxicity relationship
  - Probability of toxicity is assessed whatever the dose :
  - Range of targeted toxicity can be chosen (not only 33%)
  - Ability to recommend a **« better » intermediate dose** (MTD between two tested dose level)
  - Allows for **mechanistic based** approach (takes other "endpoints" into account, e.g. PK, biomarkers …)
  - Can handle **"multidrug"** approaches (Combo)

I-SPY 2 clinical trial

- Adaptive screening phase II clinical trial
- Locally advanced breast cancer, neoadjuvant setting
- Primary endpoint pCR (pathologic complete response) after 5 months
- Trial Objective:
  - To learn as quickly as possible about efficacy of novel drugs in combo with standard chemo
  - Identify treatments for patients subsets on the basis of biomarker signature
  - Use earlier efficacy endpoints (MRI-based, longidutinal data)
- 5 experimental drug simultenaously
- Trial adaptation
  - Sample size for each experimental can very from 20 to 120
  - Experimental drugs can be dropped or graduated
  - New experimental arms can come in the trial
  - Bayesian adaptive randomization

Possible adaptive confirmatory clinical trials

- Adaptive design
  - Use accumulating data to decide on how to modify aspects of the trial without undermining the validity and integrity of the trial
- Adaptations can include
  - Early stopping (futility, early rejection)
  - Sample size re-assessment
  - Treatment arms (dropping, adding arms)
  - Hypotheses (Non-inferiority vs. superiority)
  - Population (inclusion/exclusion criteria; subgroups)
  - Combine trial / treatment phases
- Bayesian tools for interim monitoring
  - Posterior distribution of parameter of interest: repeat the hypothesis test during the course of the trial
  - Predictive probability: assess the probability that the final hypothesis test will be sucessfull

Guidance
for Industry and FDA Staff

Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials

Document issued on: February 5, 2010

The draft of this document was issued on 5/23/2006

Conclusion

- More use of adaptive bayesian methods in oncology early phase clinical trials
  - Many attractive facets for data monitoring and analysis
  - Take into account uncertainty
  - Prior data can help for small trials
  - Complex data analysis models
  - Computation easier than before
- Regulatory hurdle is high for phase III trials but … door is opening
  - Bayesian interim analysis stopping rules
  - Medical device FDA guidance
  - Simulation of operating characteristics is mandatory and critical
- Perspectives
  - Broader use of adaptive designs in oncology phase I and II clinical trials
  - Use of more complex Bayesian modeling techniques for dose-finding trials (e.g. use of PK data, hierarchical models, mechanistic modeling)

References

- [1] Booth C. M., Calvert A. H., Giaccone G.,Lobbe-Zoo M. W., Seymour L. K., Eisenhauer E. A. Endpoints and other considerations in phase I studies of targeted anticancer therapy: Recommendations from the task force on methodology for the development of innovative cancer therapies. European Journal of Cancer 2008, 44, 19-24.
- [2] O'Quigley J., Pepe M., Fisher L .Continual reassessment method: a practical design for phase 1 clinical trials in cancer. Biometrics 1990, 46, 33-48.
- [3] Neuenschwander B., Branson M., Gsponer T. Critical aspects of the bayesian approach to phase I cancer trials. Statistics in Medicine 2008, 27, 2420-2439.
- [4] Berry D., Adaptive clinical trials in oncology, Nature Reviews 2011 (advance online publication)
- [5] Bretz F. *et al*, Adaptive designs for confirmatory clinical trials, Statistics in Medicine 2009
- [6] FDA. Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials [online], http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071072.htm

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Backup

Modèle Dose–réponse (DR)

- **Données** : N-uplets $(Y_1,\ldots,Y_N)$

  où $Y_i \sim B(n_i, \pi(d_j|(\alpha_1,\beta)))$

- **Modèle DR logistique à 2 paramètres** :

$$logit(\pi(d|(\alpha_1,\beta))) = \ln(\alpha_1) + \beta \ln\left(\frac{d}{d^*}\right), \qquad \alpha_1,\beta > 0$$

- d est la dose courante de l'agent
- d^* est la dose de référence
- α_1 et β sont les paramétres du modèle
- $\alpha_1 = \frac{\pi(d^*)}{1-\pi(d^*)}$ est l'odds (la cote) de toxicité de l'agent au niveau de dose d^*
- Pour deux doses d_i et d_j, β est essentiellement égal au log-odds ratio d'une DLT :

$$\beta = \frac{\text{logit}\left(\pi(d_j)\right) - \text{logit}(\pi(d_i))}{\log\left(\frac{d_j}{d_i}\right)}$$

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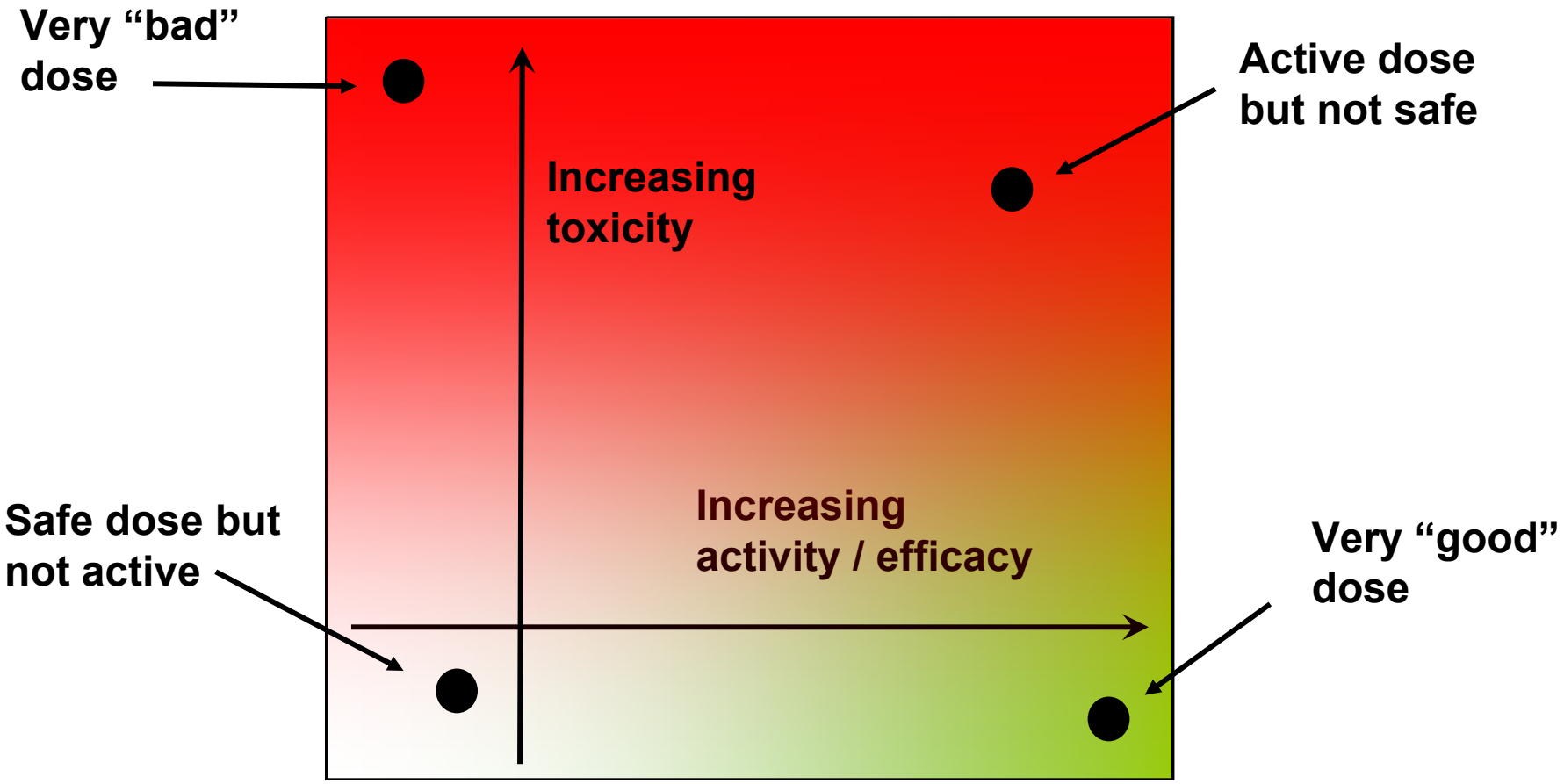
Toxicity vs Activity (1/2)



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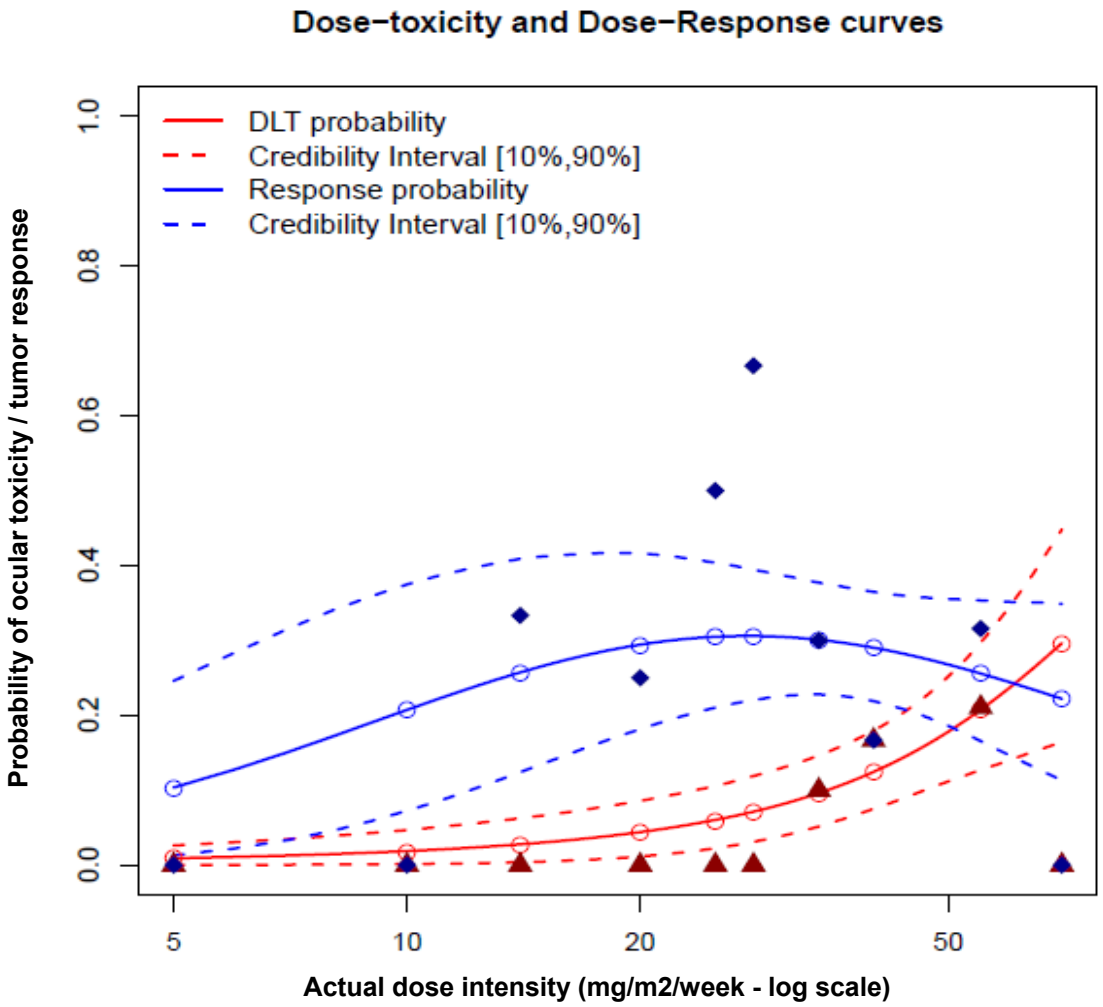
Dose toxicity and dose efficacy curves



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	Algorithmic ("3+3")	Bayesian DR- model based
Implementation	Easy	More complex due to statistical component
Flexibility	Not very flexible • fixed cohort size • fixed doses	Flexible: allows for • different cohort sizes • intermediate doses • Pursue several doses (schedule) in parallel
Build-up information / "learning process"	Empirical	Prior information Data gathered during the trial: DLT Can be extended to adjust for covariates Jointly model DLT and PD endpoints
Inference for true DLT rates	Observed DLT rates only	Full inference, uncertainty assessed for true DLT rates (as dose response relationship)
Statistical requirements	None	"reasonable" model Simulation required to assess behavior