Bayesian dose-escalation models for combination phase I trials in oncology

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Combination dose-finding

- Rationale for combinations
  - Paradigm change from single agent
  - Interaction
- Model for combination dose-finding
- Interaction as a departure from independence
- Design in practice
- Design in use
- Summary and Discussion

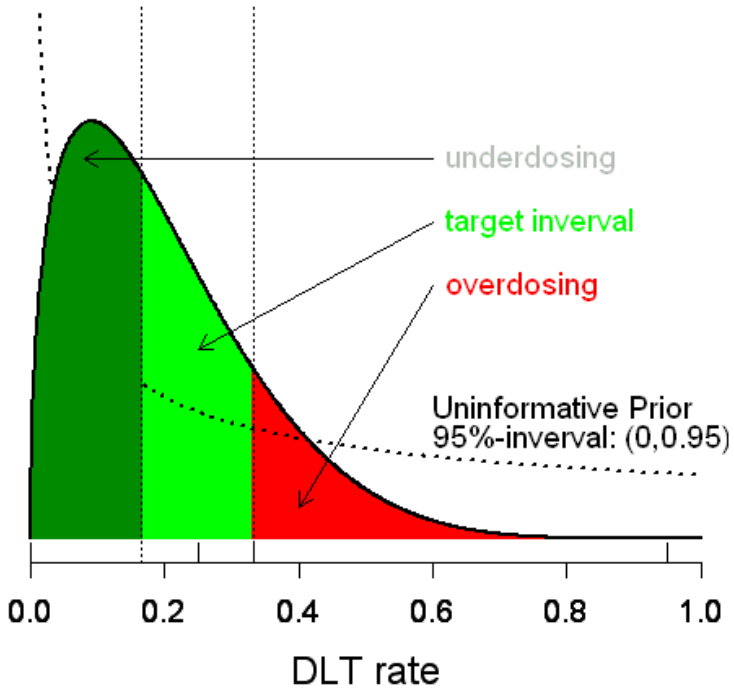
Rationale for combinations

- Recent FDA draft guidance on "Codevelopment of two or more unmarketed investigational drugs for use in combination"
  - *"Combination therapy is an important treatment modality in many disease settings, including cancer, cardio-vascular disease, and infectious diseases. Recent scientific advances have increased our understanding of the pathophysiological processes that underlie these and other complex diseases. This increased understanding has provided further impetus for new therapeutic approaches using combinations of drugs directed at multiple therapeutic targets to improve treatment response or minimize development of resistance."*
- Not just combining two new chemical entities (NCE)
  - NCE+SOC
  - NCE+SOC+SOC, NCE+NCE+SOC
- More details: [PS7c – 2:15pm – 3:30pm 14SEP2012] *Challenges in Development of Targeted Therapies in Oncology* – Kannan Natarajan, Novartis Pharmaceuticals Corporation

Paradigm change from single agent

- Standard oncology dose finding paradigm:
  - Determine the maximum tolerated dose (MTD)
    - Traditional: highest dose causing less than Γ% dose-limiting toxicity (DLT) within patients. Typically $\Gamma = 33$
    - Alternative: dose with highest chance that true DLT rate is between 16% and 33%
- Combination paradigm:
  - There is no longer one MTD but a range of dose pairs
    - e.g. given drug A = X mg, MTD of drug B is Y mg
    - Critical to determine the MTD boundary and the set of acceptable doses
  - We're in the learning phase
    - Flexibility (e.g. variable cohort sizes)
    - Inferential model summarizes knowledge, sets upper bound on dosing
    - Actual decisions use additional information (e.g. efficacy, PK, biomarkers, later cycle AE) to select dose pairs for next cohort

Summary statistics to guide dose escalation



- **Toxicity intervals (DLT-rate)**
  - [0, 0.16) – low toxicity
  - [0.16, 0.33) – target toxicity
  - [0.33, 1] – unacceptable toxicity
- **Probability of overdosing**
  - P(DLT-rate ≥ 0.33)
  - if ≥ 0.25 for a dose level, then that dose is not allowed (EWOC principle)
- **Probability of target toxicity**
  - P(0.16 ≤ DLT-rate < 0.33)
  - To declare a dose level as the MTD, this value should be high

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Interaction [Draft Guidance: Section IV and V]

Antagonism, independence or synergy

- There are a number of factors that may lead to increased or decreased risk of toxicity
  - Drug-Drug Interaction seen in the PK profiles, e.g.
    - AUC or Cmax for one or both compounds is significantly increased/decreased compared to being given alone
    - May be competitively using/inhibiting CYP enzyme causing lower clearance
  - Overlapping toxicities, e.g.
    - If drug 1 and drug 2 have similar toxicity profiles, giving them together may cause a significant increase in the observed rate
    - Equally, the combination may cause the same toxicity in the same subset of patients but at a higher grade, whilst other patients are unaffected
    - Two toxicities that, when they occur together increase the risk of DLT in a patient
  - Pathway interactions, feedback loops that either trigger additional toxicities or provide protective effects

Model for combination dose-finding: Interaction as a departure from independence

Reparameterization with an explicit interaction term

- Real no interaction model: $\pi^0_{12} = \pi_1 + \pi_2 - \pi_1\pi_2$
- Interaction model: $\text{odds}(\pi_{12}) = \text{odds}(\pi^0_{12})\exp(\eta)$

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

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

$$5 \text{ parameters}: \alpha_1, \beta_1, \alpha_2, \beta_2, \eta$$

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

- "Simplest" interaction model [η = log*(odds-ratio)*]: η*=0* means no interaction
- Typically η*>0*, but not necessarily!
- η could be more complicated, e.g. depend on doses/other covariates

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Model for combination dose-finding: Interaction as a departure from independence

Priors for Model Parameters

- Priors for single agent parameters
  - $log(\alpha_1), log(\beta_1)$
  - $log(\alpha_2), log(\beta_2)$

  } As "usual" bivariate normal (Neuenschwander et al. 2008, Bailey et al. 2010)
- Prior for interaction parameter η
  - Start from no interaction model:
    - Single agent π_1 and π_2 imply probability for DLT under no interaction
  - Use **log-normal** prior for η if a toxic synergistic mechanism is (structurally) assumed to take place when the two drugs are administered together – strong assumption!
  - Otherwise use **normal** prior for η allowing for a protective effect of the combination (shifted mean?) – more appropriate?
  - If possible, incorporate "relevant" information on potential interaction
  - If using dose dependent interaction – allow enough uncertainty at both ends of the dose range

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Model for combination dose-finding: Interaction as a departure from independence

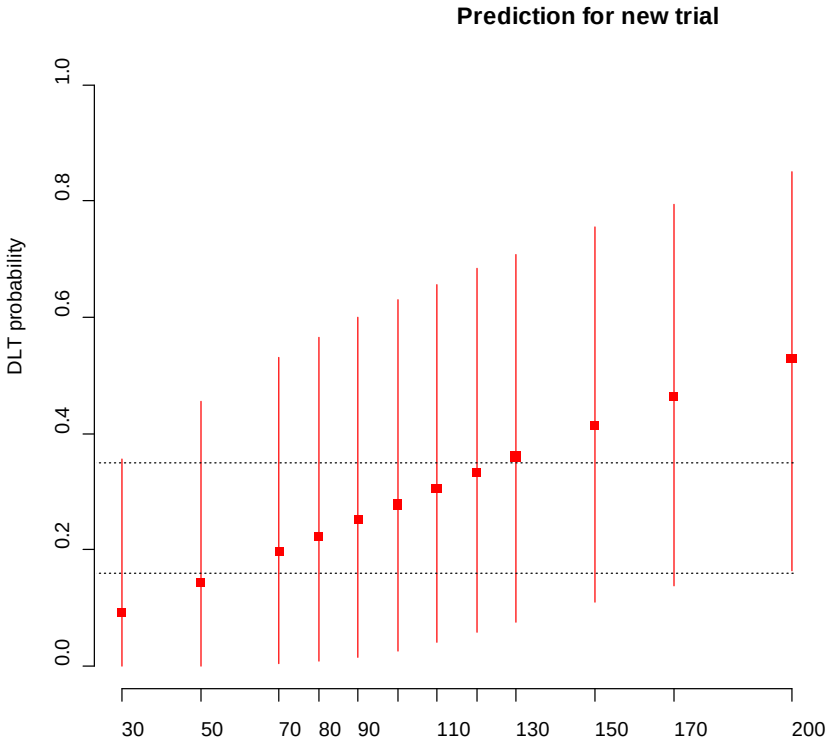
Benefits

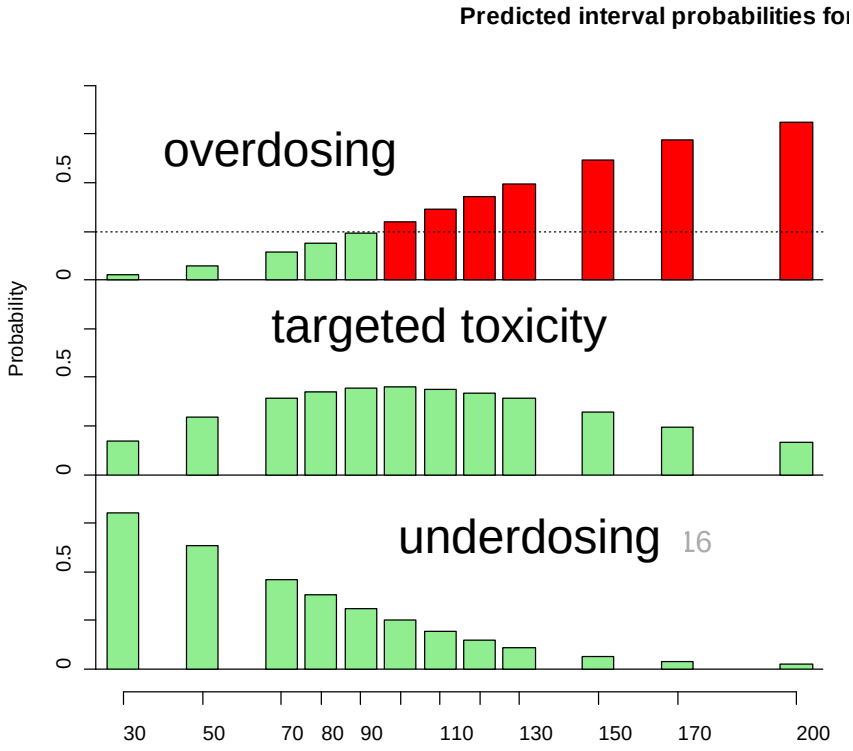
- Holds to principles introduced by Thall *et al.* (2003)
  - Marginals represent single agent information
  - Dose-response surface can model all three cases of interaction
  - All dose combinations may be “available” for study
    - Not the same as “are ok to study”!
    - Controls must be in place to control risk to patients
- Additionally
  - Easily interpretable interaction $\Rightarrow$ easier elicitation of prior
  - Easily extended to include covariates in the marginals (change in schedule, formulation)
  - Can be generalized to the case of more than two drugs in combination
- Both designs allow consideration of more complex studies
  - Ask yourself (and partners) the question - benefit or not?

Design in practice

Single agent data for drug A (limited phase I data)

- Drug A – MTD = 100 mg as a single agent
  - After discounting for potential heterogeneity we have the following
  - Overdose risk controlled to be < 25% (EWOC – Babb *et al.* 1998)



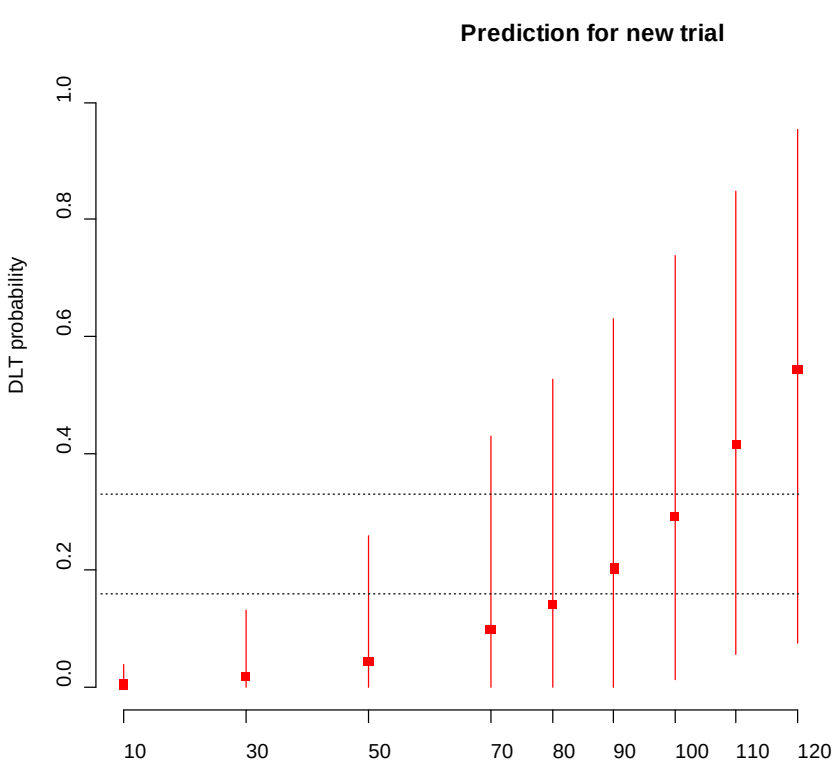


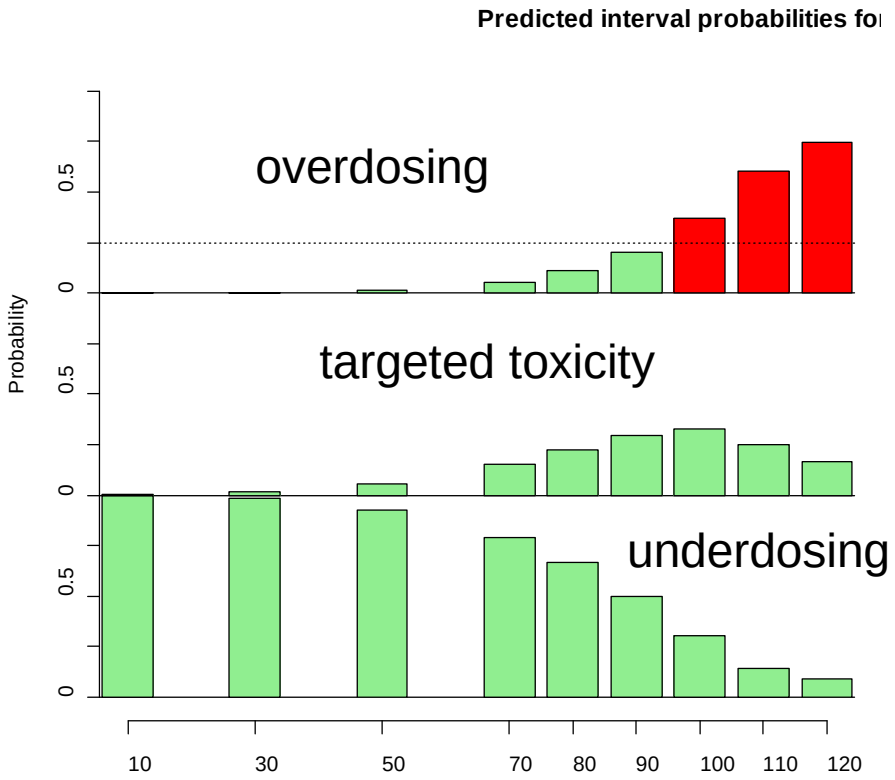
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Design in practice

Single agent data for drug B (well known compound, lots of data)

- Drug B – MTD = 90 mg as a single agent
  - After discounting for potential heterogeneity we have the following



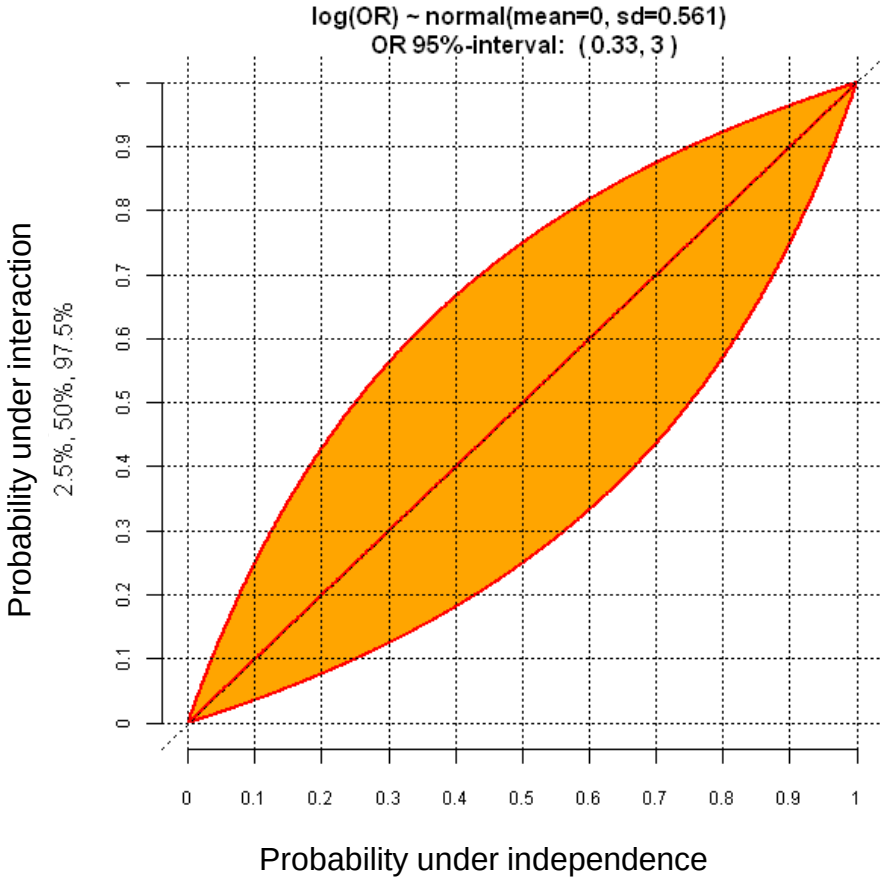


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Design in practice

Interaction

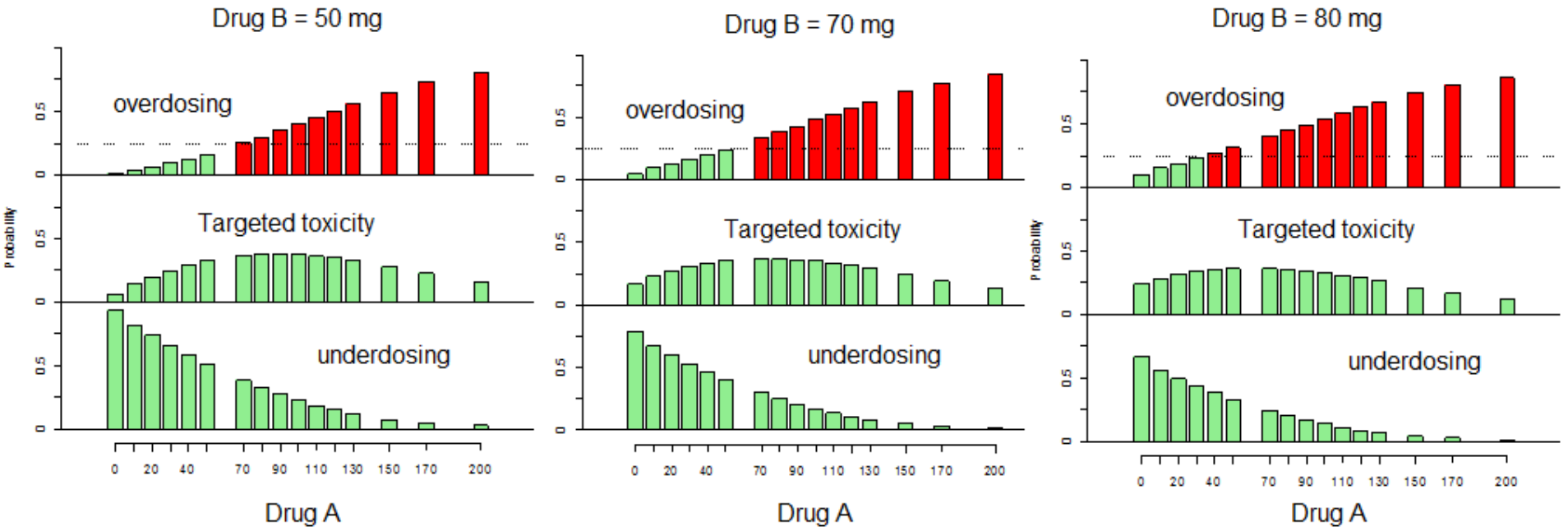
- What is our starting combination?
  - Generally determined ad-hoc... 50% of each MTD?
  - What about interaction? Uncertainty?
- No evidence of synergistic or antagonistic interaction between the two compounds
  - But don't want to rule it out
  - Normal distribution for η
    - Antagonism
    - Independence
    - Synergy



Design in practice

Prior summaries

- Incorporation of historical data and uncertainty on potential interaction allows formal support of starting doses
  - 60 mg drug A + 50 mg drug B
  - 50 mg drug A + 70 mg drug B
  - 30 mg drug A + 80 mg drug B



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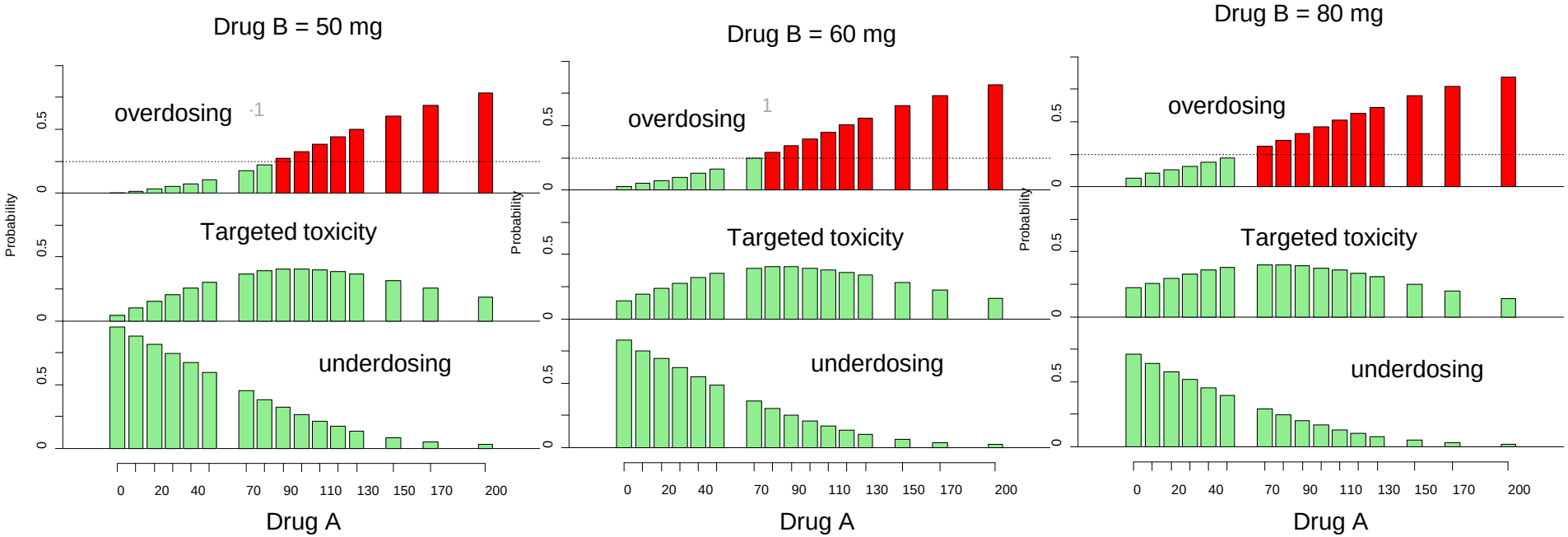
Design in practice

- All of these dose pairs are prior predicted MTD
  - Is it acceptable to begin at one of these?
- Was chosen to begin on study with:
  - Drug A = 40 mg (40% of single agent MTD)
  - Drug B = 60 mg (66% of single agent MTD)
- Operating characteristics
  - Simulations
    - "Group Ethics"
    - always asked for, but not perfectly representative of "learning" studies
  - Inference of scenarios that could occur on study
    - "Individual Ethics"
    - generally overlooked but **essential** for patient protection

Design in practice

Posterior summaries – 0 DLT in 3 patients at starting combination

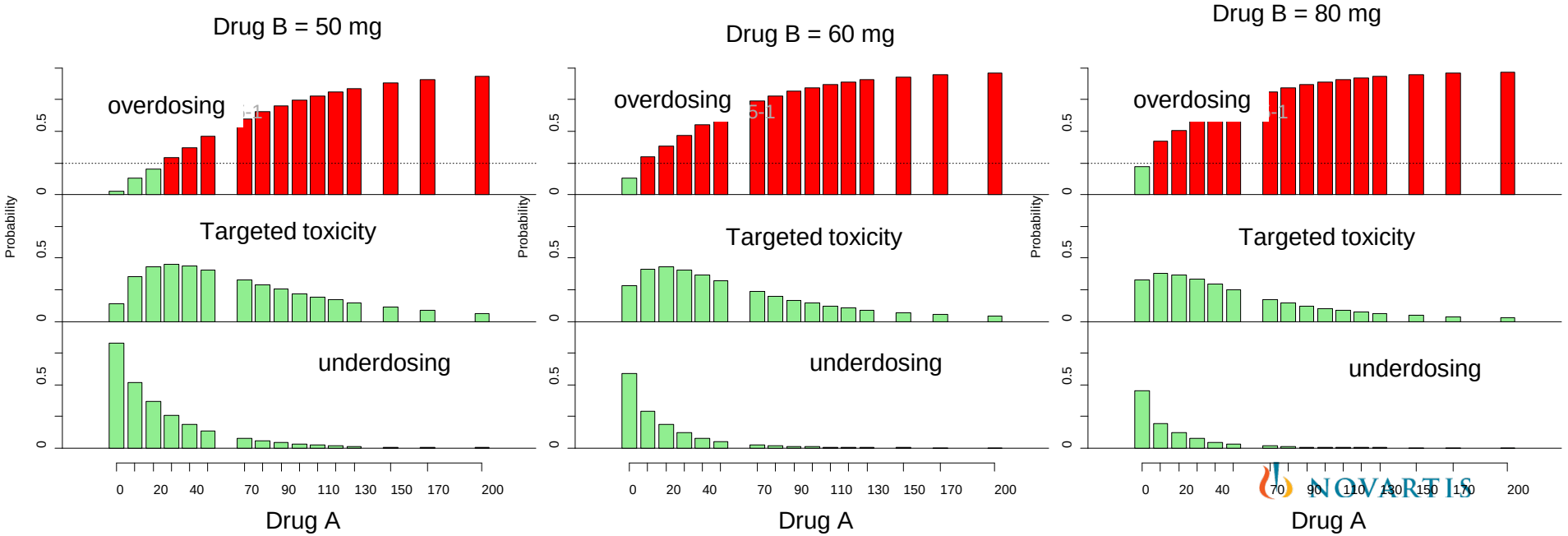
- Inferential risk assessment would allow escalation to
  - 80 mg Drug A + 50 mg Drug B
  - 70 mg Drug A + 60 mg Drug B
  - 50 mg Drug A + 80 mg Drug B
- Note: operational rules for escalation defined in protocol



Design in practice

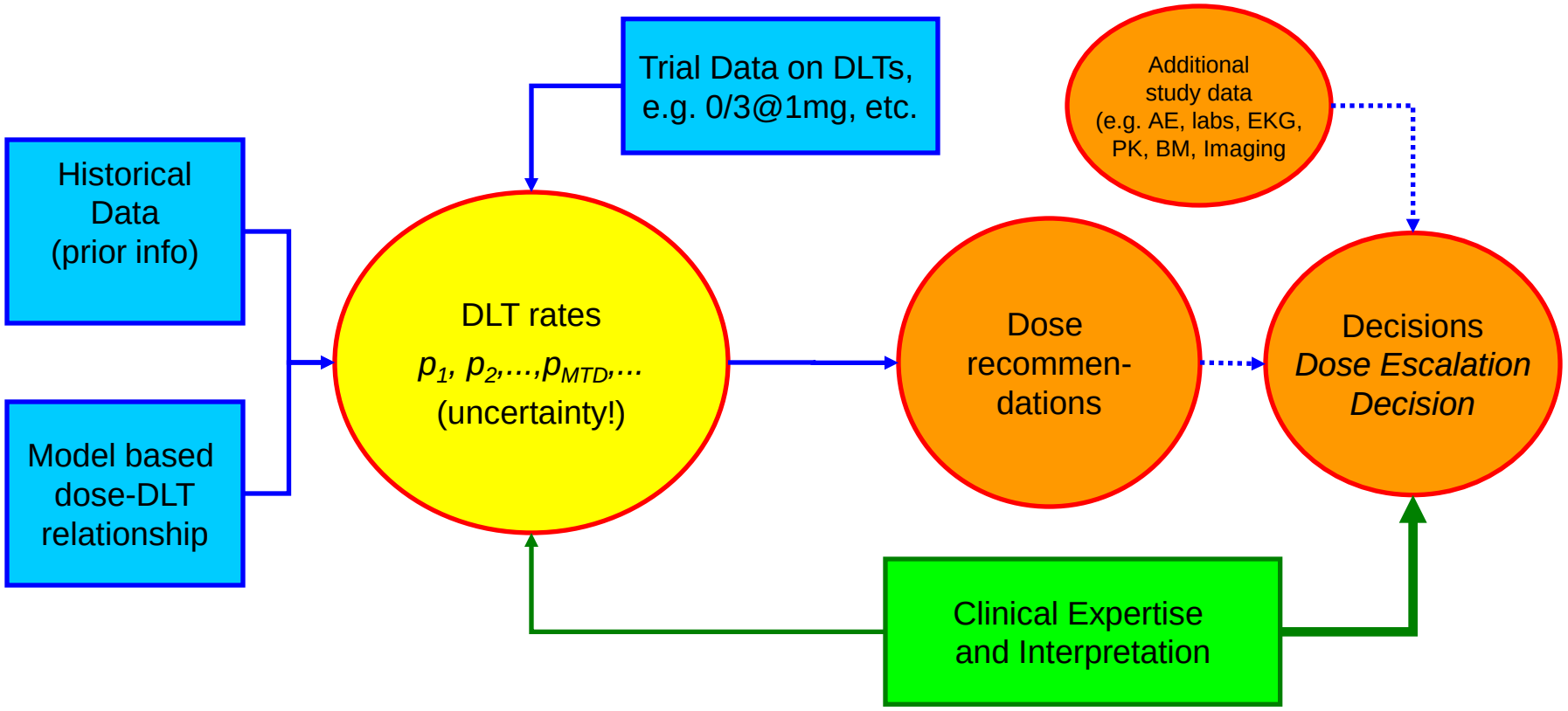
Posterior summaries – 2 DLT in 3 patients at starting combination

- Inferential risk assessment would lead to major reduction
  - 20 mg Drug A + 50 mg Drug B
  - No doses of drug A can be administered in combination with 60 mg or higher of drug B



Design in practice

Combination of clinical and statistical expertise



Protocol development → Study conduct → Preparation → Discussion/decision

Design in use

Comparing to recent history

- Rogatko *et al.* (2007)
  - 20/1215 - 1.6% trials use Bayesian methods
- Le Tourneau *et al.* (2009)
  - 6/181 - 3.3% trials use Bayesian methods
- Novartis implemented Bayesian methods in phase I Oncology trials in 1998, as standard from 2004
- Since 2006
  - Global phase I and Ib: **100%**
    - >20 FTIH, >30 compounds, >60 studies
  - Japan (since 2008): only 1 CTN did not implement a Bayesian phase I approach

Design in use

- Major investment in training and communication
  - Statisticians
  - Internal clinicians
  - Clinical operations
  - Investigators
  - Medical advisors
- Discussions with HA
  - Addressing regulatory concerns
  - Achieving consistency in the review process
  - Helping understanding of methodology

Summary

- Effective designs require an understanding of the science
  - What “could” happen?
- Collaboration with non-statisticians increases acceptance
  - No more black boxes, Conceptualize the approach instead
  - Speak their language
    - “Posterior probability that the probability of the true DLT rate exceeding...” $\Rightarrow$ “Risk of overdose for future patients”
- These designs are being implemented
  - Provide major benefit to our identification of doses with future potential and can reduce numbers of amendments, even studies
  - Efficient use of limited data in small populations
  - Flexibility comes with a price, but is worth it
    - Steps must be put in place in protocols to provide appropriate risk control
  - Meet the needs of an evolving Early Development environment

Discussion

- Need guidance on development of combination therapy when one of the partners is a standard of care.
- Similar to the FDA's Critical Path Initiative and CHMP's guideline for Clinical Trials in Small Populations, guidance on methodologies for combination development is needed.
- [PS7c – 2:15pm – 3:30pm 14SEP2012] Current and Future Challenges in Moving Forward with Precision Medicine in Oncology
  - *Challenges in Development of Targeted Therapies in Oncology* – Kannan Natarajan, Novartis Pharmaceuticals Corporation

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