Bayesian Learning in Early Phase Cancer Immunotherapy: A Case Study

Daniel Sabanés Bové

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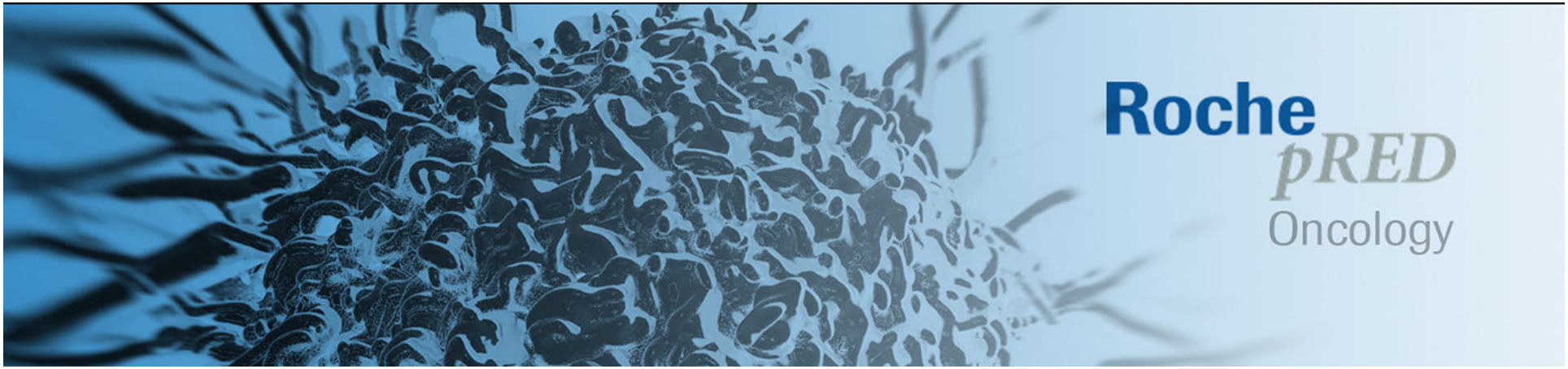


Case study on an NME (“A”) in Oncology
Introduction

- New cancer immunotherapy (CIT) “A” for the treatment of solid tumors
- Mainly expected to work in combination with other drugs
- Frontrunner for a platform of similar biologics
- Entry-into-human phase 1 study started
- Combination A + B phase 1b study to start about one year later
- Follower NME C from same platform still to enter phase 1

This talk: How to use Bayesian statistics for answering the typical clinical development questions (in blue) in this CIT project

What is the maximum tolerated dose (MTD)?

Approach used in phase 1 study

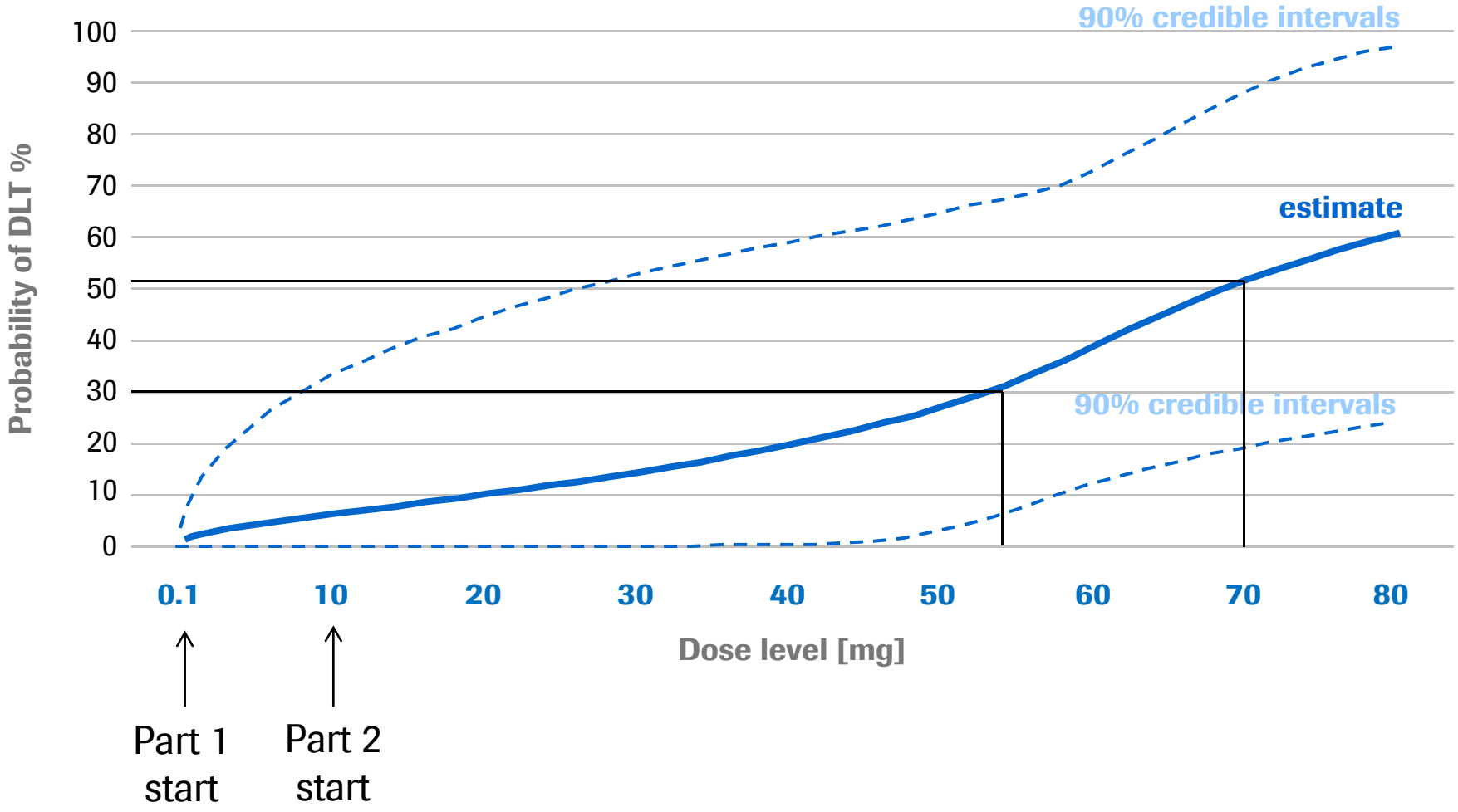
- Two-part dose escalation for our NME A
- First part: single patient cohorts in very low dose range (starting from minimum anticipated biological effect level [MABEL] x 4)
  - Reason: no good animal toxicity model exists (only one with homologous molecule)
  - Safety rules for closing this part early
  - Rule-based escalation: step up dose “staircase”
- Second part: modified Continual Reassessment Method (mCRM) design
  - Dose-limiting toxicities (DLTs) defined in protocol (3 weeks period)
  - Logistic regression for modelling DLT rate in relation to dose
  - Start with biweekly (Q2W) schedule evaluation, afterwards Q3W
- Prior information which was used for mCRM setup:
  - In-vitro assays
  - In-vivo non-human primates study with a homologous molecule

Neuenschwander, B., Branson, M., & Gsponer, T. (2008). Critical aspects of the Bayesian approach to phase I cancer trials. *Statistics in Medicine*, *27*(13), 2420–39. http://doi.org/10.1002/sim.3230

Prior dose–DLT rate model

Logistic regression with bivariate normal prior

$$\text{logit}[p(x)] = \alpha + \beta \cdot \log\left(\frac{x}{x^*}\right), (\alpha, \log(\beta)) \sim \text{N}_2(\mu, \Sigma)$$



Dose escalation with mCRM

Standard design to find MTD

1. Gather DLT data (binary) for each patient
2. Update the dose-DLT rate model with Bayesian inference (get posterior distribution of parameters with MCMC)
3. Use updated model to estimate the next best dose:
   - **Priority No. 1: overdose control**
     Dose must have < 25% risk that DLT rate is > 35%
   - **Priority No. 2: "target toxicity window"**
     Dose should maximize chance that DLT rate $\in (20\%, 35\%)$
4. Are prespecified stopping criteria met? (relating to precision reached)
   - Then define MTD = next best dose.
   - Otherwise continue to step 5.
5. Treat next cohort of 3 patients at next best or a lower dose (clinical judgement has always final call!)

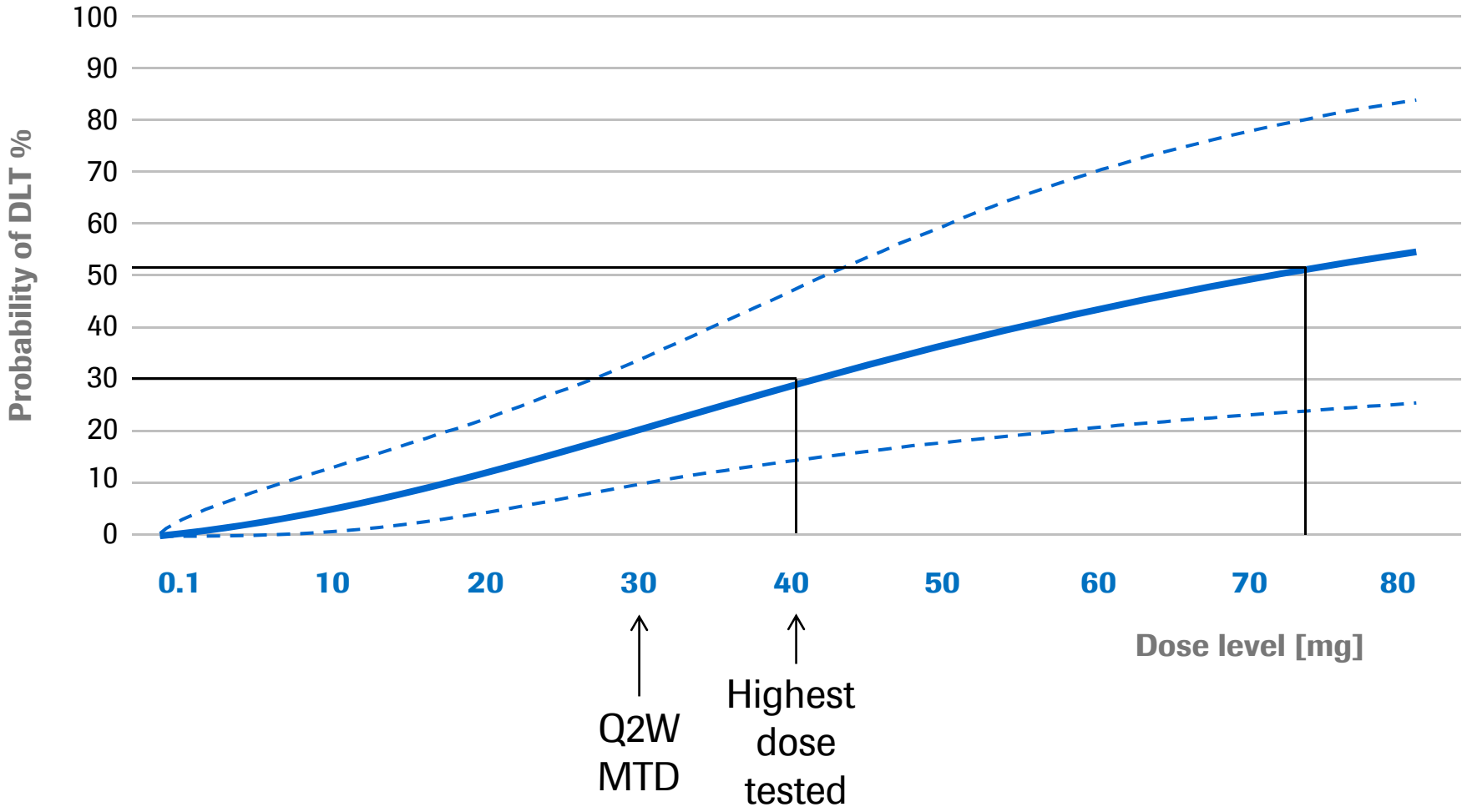
Practical experience in the case study
Benefits, challenges and opportunities

- High flexibility of the mCRM design:
  - Number of patients per cohort could be increased as needed (e.g. to get additional pharmacodynamic data – biopsies are important in CIT)
  - Parallel enrollment at different doses possible (e.g. from an imaging substudy for biodistribution data generation)
  - Later detected DLTs could be incorporated (e.g. due to immune-mediated adverse events)
- Some practical challenges encountered:
  - Clinicians were more conservative due to non-DLT adverse events (AEs)
  - Change from originally planned Q3W to QW schedule during the study
  - Newly proposed escalation in cycle 2 or cycle 3 instead of only in cycle 1
- Opportunities for extensions of mCRM:
  - Ordinal AEs / multiple schedules / stepwise escalation / …

BBS seminar
26 June!

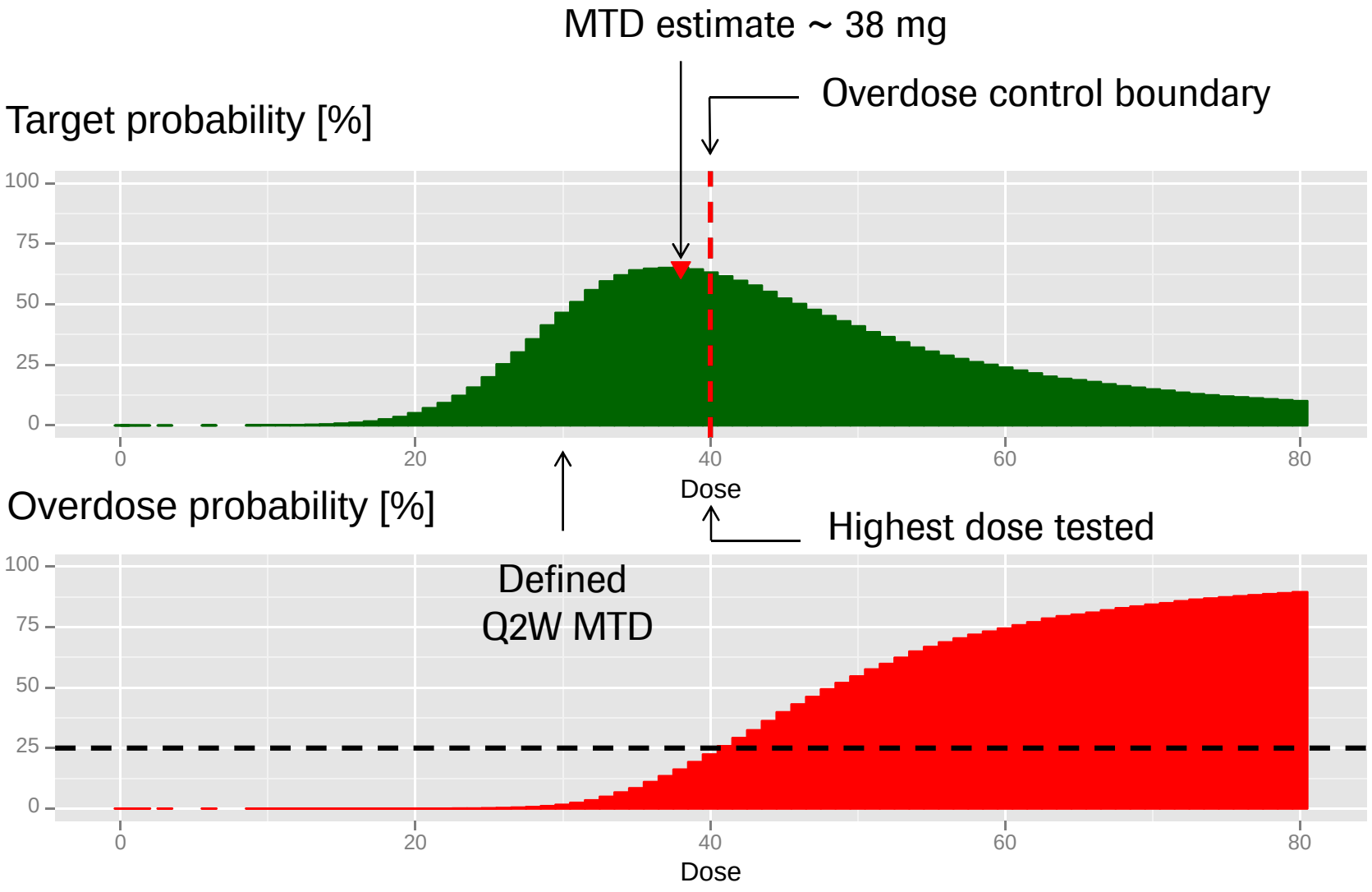
Posterior dose–DLT rate model

Example status after including 58 patients



Example target and overdosing probabilities

mCRM design would give higher MTD than defined



Combination study with NME B
Introduction

- No tumor shrinkage was observed so far in the phase 1 of our NME A
- As per clinical development plan, proceed to 2NME combination A + B with another CIT molecule “B”
- Synergistic toxicity cannot be excluded, especially due to concomitant administration of A and B
- Dose and schedule of NME B are given and should not be changed
- Therefore do single agent dose escalation only on our NME A
- How can we include the prior information from the phase 1 of A and the existing safety data from B?
- How can we decide whether the safety and efficacy of the 2NME combination A + B warrants further development? (“gating”)

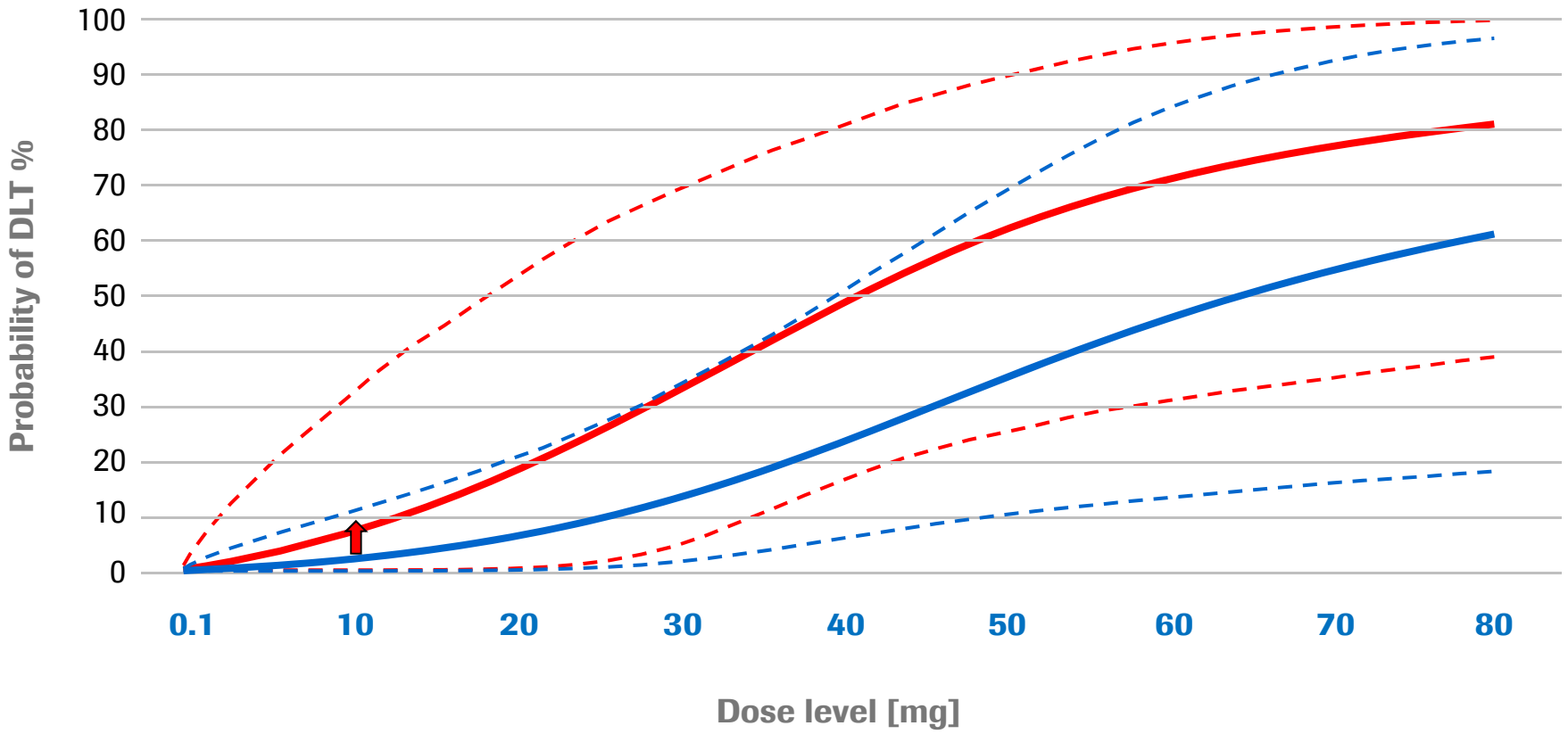
How to include prior information from A and B?

Pragmatic approach *(not the only or best one)*

- Take the posterior model from phase 1 for NME A at the cutoff date, approximate parameter posterior with bivariate normal
- Add additional toxicity to be expected from the combination with NME B, by shifting the prior mean of the intercept
- Here: expect 5% additional DLT probability at dose of 10 mg (based on prevalence of potentially overlapping G2 toxicities in B)
- Some uncertainty about it taken into account, by increasing the prior variance of the intercept
- This leads to the prior dose-DLT rate model for the combo A + B
- With target toxicity window of 20-30%, the prior MTD estimate is 28 mg (22 mg with overdose control)

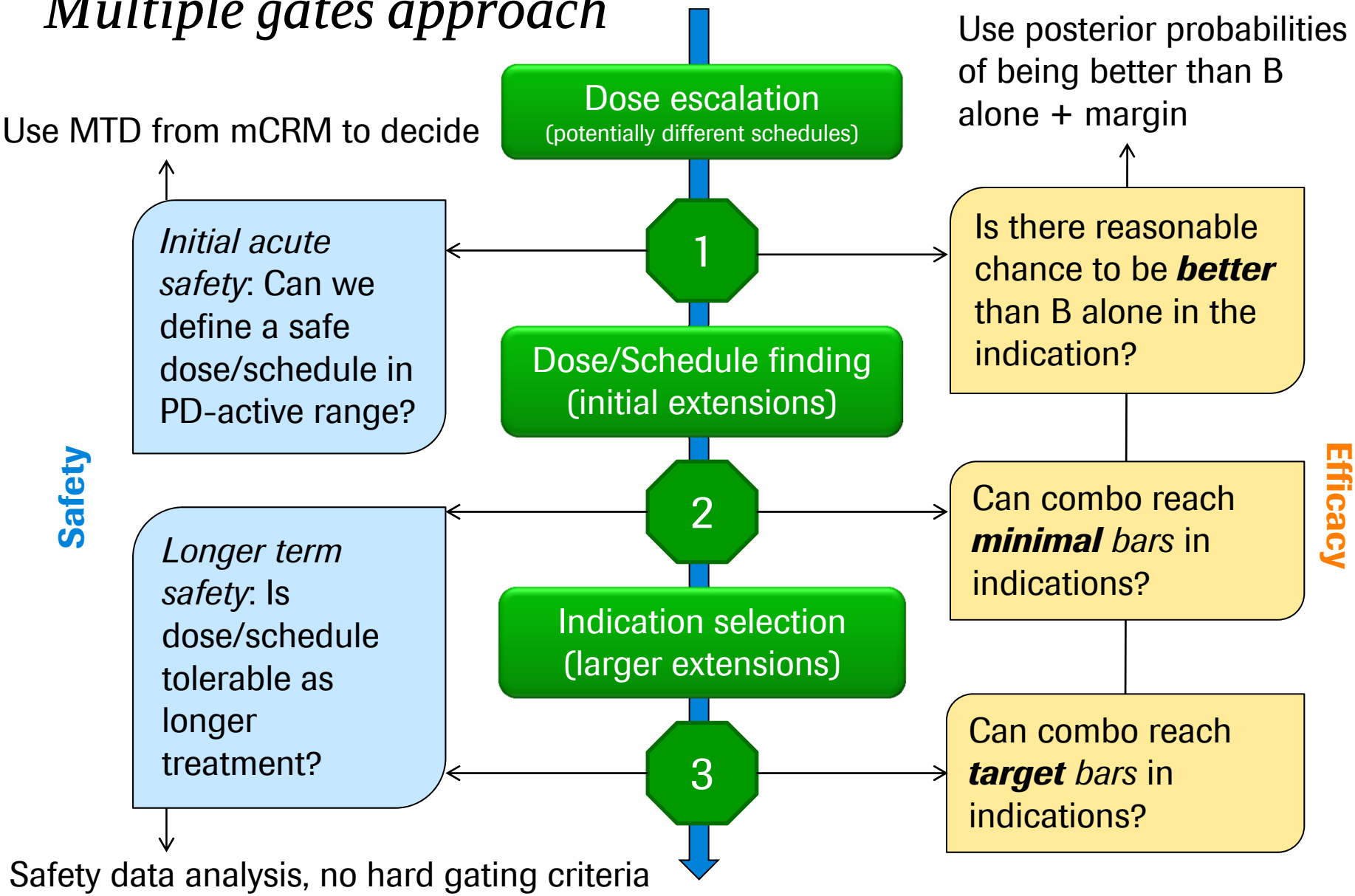
Comparison: posterior for A vs. prior for A (+B)

At cutoff date included in the protocol



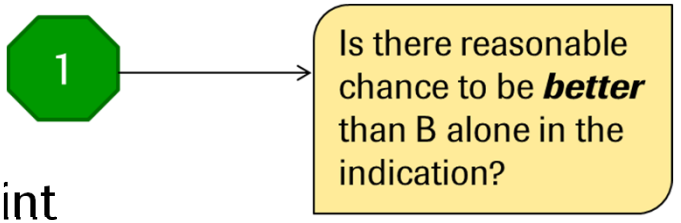
Should we continue developing combo A + B ?

Multiple gates approach



Use posterior probabilities for gating decisions

Example at the first efficacy gate



- Use objective response rate (ORR) as endpoint
  (note: all of this can be extended to coprimary / composite endpoints)
- Define “reasonable chance” = “at least 30% posterior probability”.
  Use uniform prior, and conjugate beta-binomial model for computations.
- Assume we have n=9 patients in an indication during dose escalation,
  (across all doses and schedule to avoid «cherry picking»)
- Assume with NME B alone there were 7/43 responses (obs. ORR: 16%)
  in this indication
- → Possible ORR / probability / decision outcomes for this indication:

Responses:	0	1	2	3	4	5	6	7	8	9
Obs. ORR [%]:	0	11	22	33	44	55	67	78	89	100
Probability to be better than B alone [%]:	17	47	73	89	97	99	100	100	100	100

STOP ↑ 30% threshold **GO**

Immunogenicity of A and pretreatment with X

Introduction

- Many of the phase 1 patients developed anti-drug antibodies (ADAs), not untypical for CIT molecules given interaction with immune system
- However, no safety impact and most of them also no PD impact
- Idea: Does pretreatment with drug "X" reduce the proportion of ADAs ?
- Proof-of-concept study with n=20 patients and binary ADA endpoint
- Patients will be randomized 3:1 to pretreatment, and control arm will be enlarged / have informative prior from the relevant phase 1 patients.
- Compute posterior probability $\mathbb{P}(\pi_1 < (1-\delta)\pi_0 \mid \mathcal{D})$

  ADA prop. with pretreatment; Target reduction of ADA prop.; ADA prop. in control
- If > 70% → success; if < 30% → failure; otherwise → inconclusive.
- Look here for large effect $\delta = 50\%$; reasonable power for detecting this.

How to decide if pretreatment is effective?

Illustration of the Bayesian answer with example

Numbers just for illustration

Data from n=20 patients

+

ADA results in suitable control patients from EIH study: 12/21 patients ADA+

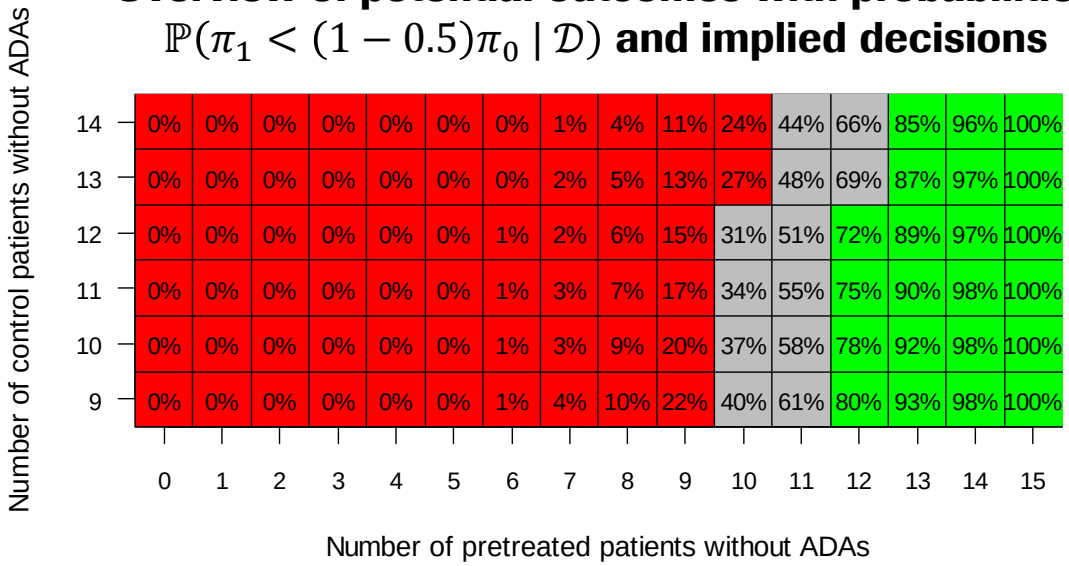
>70% probability that ADA proportion is at least 50% lower → **GO**: Conclude sufficient pretreatment effect

> 30% & < 70% probability → **Evaluate**: Consider ADA specificity and biomarkers

<30% probability that ADA proportion is at least 50% lower → **STOP**: Conclude insufficient pretreatment effect

May consider further evaluation of pretreatment concept

Overview of potential outcomes with probabilities $\mathbb{P}(\pi_1 < (1-0.5)\pi_0 \mid \mathcal{D})$ and implied decisions



How to use the data for the follower NME C ?

General and statistical aspects

- Follower NME C from the same platform was still to enter-into-human.
- Safety and PK profile expected to be very similar to that of our NME A.
- Therefore, we should learn as much as possible from A to design the dose escalation trial for C as efficient as possible, for example general aspects:
  - Starting dose?
  - Schedule?
  - DLT period: could it be shortened? / account for later DLTs? Etc…
- Specifically, for the mCRM design, we would like to use the DLT data from A to specify an informative prior for C.
- Still, the design should be robust against surprises.

Robust mixture prior approach
Overview of the concept

- Take the posterior distribution of the model parameters and approximate it with a bivariate normal → informative component
- Construct a minimally informative prior → «neutral» component
- Mix the two components in a ratio such that the prior sample size is adequate (note: pragmatic approximations here)
- For example: If the informative prior is constructed from 60 patients, and prior sample size should be 10 patients, then choose 1:5 ratio (1/6 weight for informative component)
- The neutral component makes the design robust against surprising deviations from the informative component.
- Still, the dose escalation can be more efficient using the previous data.

Schmidli, H., Gsteiger, S., Roychoudhury, S., O'Hagan, A., Spiegelhalter, D., & Neuenschwander, B. (2014). Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics*, *70*(4), 1023–32. http://doi.org/10.1111/biom.12242

Conclusions

Early phase cancer immunotherapy case study

- Dose escalation with new CIT agents needs to accommodate:
  - Very low starting doses, due to lack of adequate tox models
  - Flexible schedule is needed, due to a priori unclear optimal schedule
  - Late toxicities can occur (e.g. Immune-mediated AEs), to consider
- Many combinations are tested in the clinic:
  - Synergistic efficacy is hoped for, but also here preclinical models not conclusive
  - Efficient decision making is required and statisticians need to lead
  - Bayesian tools can help with well interpretable decisions
- Reverse translation to follow-on molecules / other combinations:
  - Bayesian inference ensures consistent borrowing of information
  - Optimally also the starting dose is informed by previous compound

Basel Biometrics Society Seminar 26 June 2017

Innovative model-based dose escalation designs

Clinicians welcome too!

Please come! ☺

CRM and more

- **Date:** June 26, 2017, Time: 13.30-17.00
- **Venue: Here!**
  (Roche IT Training Center / Aeschentor, Aeschenvorstadt 56, 4051 Basel)
- **Registration:** Free, please send an email to Barbora Martinec (barbora.martinec@roche.com)
- Overview of the current status of the application of such designs in the pharmaceutical industry (Roche, Novartis, Actelion)
- Current research areas for improving the methodology
- Moderated panel discussion around the question “What next?” about the upcoming challenges and opportunities in model-based dose escalation designs and the corresponding clinical trials

Thank you! Questions?

Doing now what patients need next