Model-based D/E designs: Current status and next steps
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Background of early phase clinical trials
Main objective and challenges

Main Objective in phase I dose escalation (D/E) trials:

- Identify a safe dose for future development, usually to establish a maximum tolerated dose (MTD) or a recommended phase II dose (RP2D)

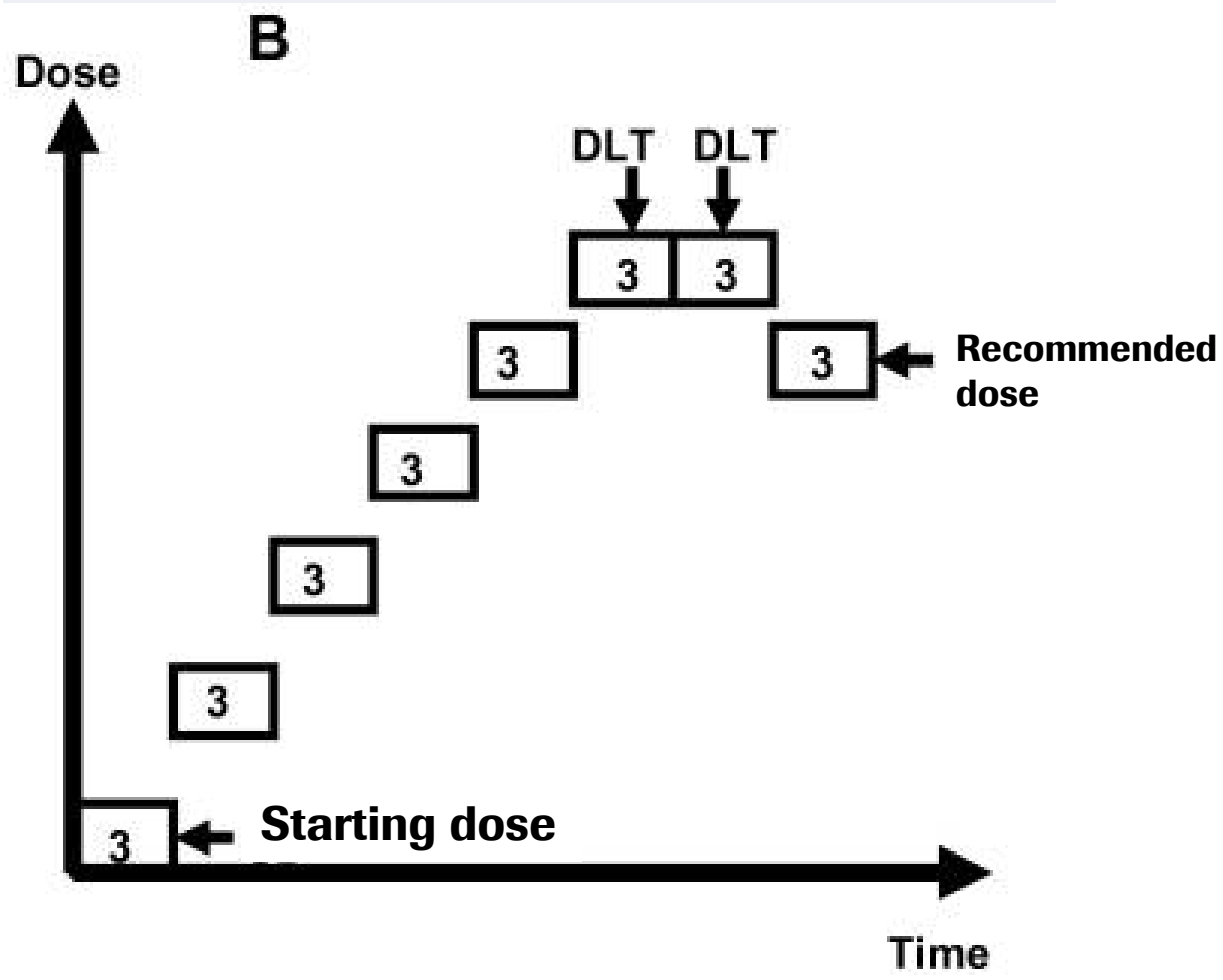
Main challenges in phase I clinical studies:

- A balance between safety and ethical issues
  - Potential risk of high toxicities, especially for first in human trials
  - To avoid sub-therapeutic doses for Ph2 (non-Oncology) or already Ph1 (Oncology) patients
- Specifically in Oncology: accurate estimation of the MTD or RP2D in phase I required
  - Limitations in conducting large phase II dose selection trials
- Requires careful assessment of potential dose limiting toxicities (DLTs)

Adapted from Zhu et al., AACR annual meeting, Washington, DC April 1-5 2017

Traditional 3+3 D/E design

Few advantages and numerous challenges



Advantages:

- A widely used D/E design, simple and straightforward

Challenges:

- It is NOT statistically justified: no clear estimand (i.e., what it estimates)
- Underestimates the MTD – it does *not* estimate the dose with 33% DLT rate*
- Tends to treat patients at low or inefficacious doses
- Only uses data from the last available cohort of subjects
  - Precision of the estimate is poor (max 6 subjects)

*Storer et al., 1989;
Figure: modified based on Le Tourneau, C. et al., 2009

Adapted from Zhu et al., AACR annual meeting, Washington, DC April 1-5 2017

Experience in Roche

Current methodology and research focus

Limitations and next steps

Summary

Evolution of D/E designs in our oncology early phase trials

Timeline from 2009 until today

Traditionally 3+3 designs were used

A **mCRM**[2] design (**m**odified **C**ontinual **R**eassessment **M**ethod) was first implemented. It aims to have a better estimate of targeted MTDs comparing to the EWOC design

Other explored CRM extensions:

- CRM with both safety and efficacy endpoints
- CRM to handle late onset DLTs
- PK driven CRM

Model based adaptive D/E design **EWOC**[1] (**E**scalate **W**ith **O**verdose **C**ontrol) was first employed in 2010 (specific type of CRM)

Customized software (R-package *crmPack*[3]) was developed to support CRM designs

1. Piantadosi S. et al., 1998; 2. Neuenschwander et al., 2008;
3. *crmPack* is available at the Comprehensive R Archive Network (CRAN).

Adapted from Zhu et al., AACR annual meeting, Washington, DC April 1-5 2017

Key features of CRMs as used in Roche trials
Different perspectives

Safety perspective:

- Overdose control when trials are ongoing (for both EWOC and mCRM designs)
- MTD estimate is more accurate in most cases. Reason: dose limiting toxicities (DLTs) from all dose levels contribute to the MTD determination

Operational perspective:

- The operation processes are similar to those in the traditional 3+3 designs, and timely D/E decision meetings are feasible for global study teams
- No pre-specified dose level: statisticians consider the possible doses when calculating a model recommendation before dosing patients in new cohorts

Ethical perspective:

- Designs allow fast escalation in sub-therapeutic dose range (single patient cohorts)
- Designs allow “mini”-expansions in dose levels which show potential benefits to patients
- Formal integration of relevant prior pre-clinical/clinical knowledge of the dose-toxicity relationship

Adapted from Zhu et al., AACR annual meeting, Washington, DC April 1-5 2017

Internal feedback was elicited in a survey

n=12 responses across functions

- Overall experience of CRM is positive: 100% rating ≥4 (scale from 0 to 5)
- The model based design concept was well accepted by HAs and IECs
- CRM design promotes discussions with clinicians, safety scientists and pharmacologists, especially in the D/E meetings
- Timely and close collaborations are required, especially for global study teams:
  - The unknown dose levels prior to study brings clinical operation challenges, but they are manageable
  - Smooth communication with sites to reassure dose levels is feasible

Adapted from Zhu et al., AACR annual meeting, Washington, DC April 1-5 2017

Roche

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In a nutshell: Current model-based dose escalation methodology

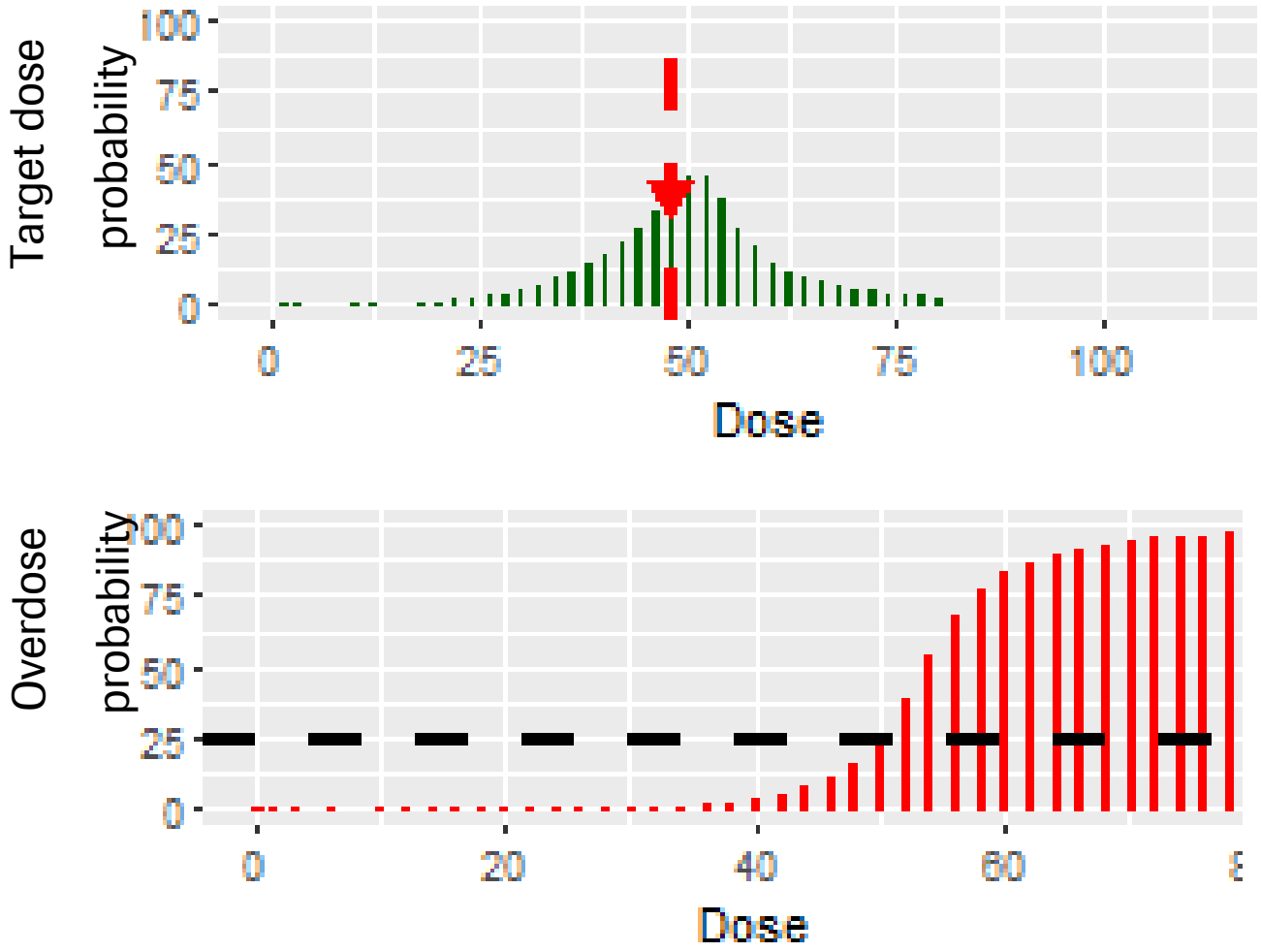
Based on Bayesian logistic regression fitted by MCMC

A statistical model is used to estimate MTD. **But, how is it done?**

The idea is to associate the binary DLT information with the dose level

Bayesian statistical method which utilizes **prior information** handles the small sample size issue during D/E

The ultimate goal, i.e. MTD, is clearly defined by a DLT rate or a range of DLT rates, subject to overdose control*

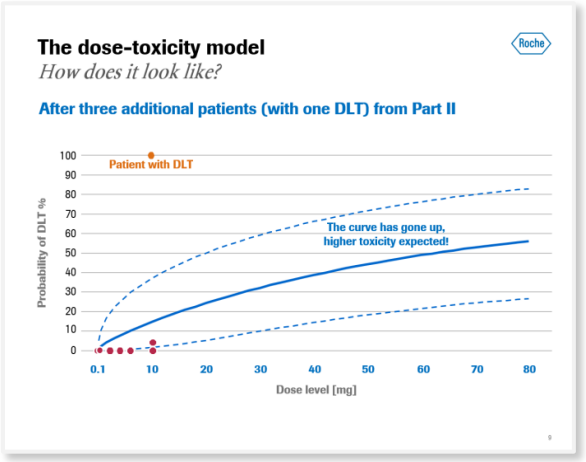


*control the risk of overdose (DLT rate above target) to below certain level (e.g. 25%) (*Neuenschwander et al.*, 2008)

Adapted from Zhu et al., AACR annual meeting, Washington, DC April 1-5 2017

Running model-based dose escalation

Generic flow chart



Estimate dose-[DLT rate] model

Apply maximum increment rules

Predict next best dose

Stopping rules fulfilled?

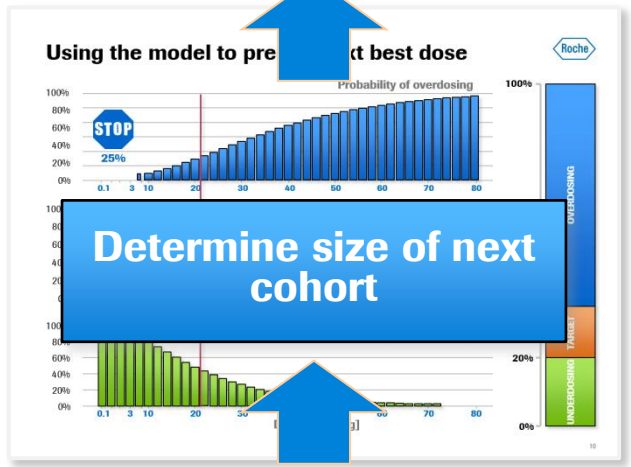
Yes

Declare MTD = next best dose

No

Decide with investigators on next dose

Treat next cohort at next dose and update data



Determine size of next cohort

Development of R-package “crmPack” for model-based D/E

Motivation for this work

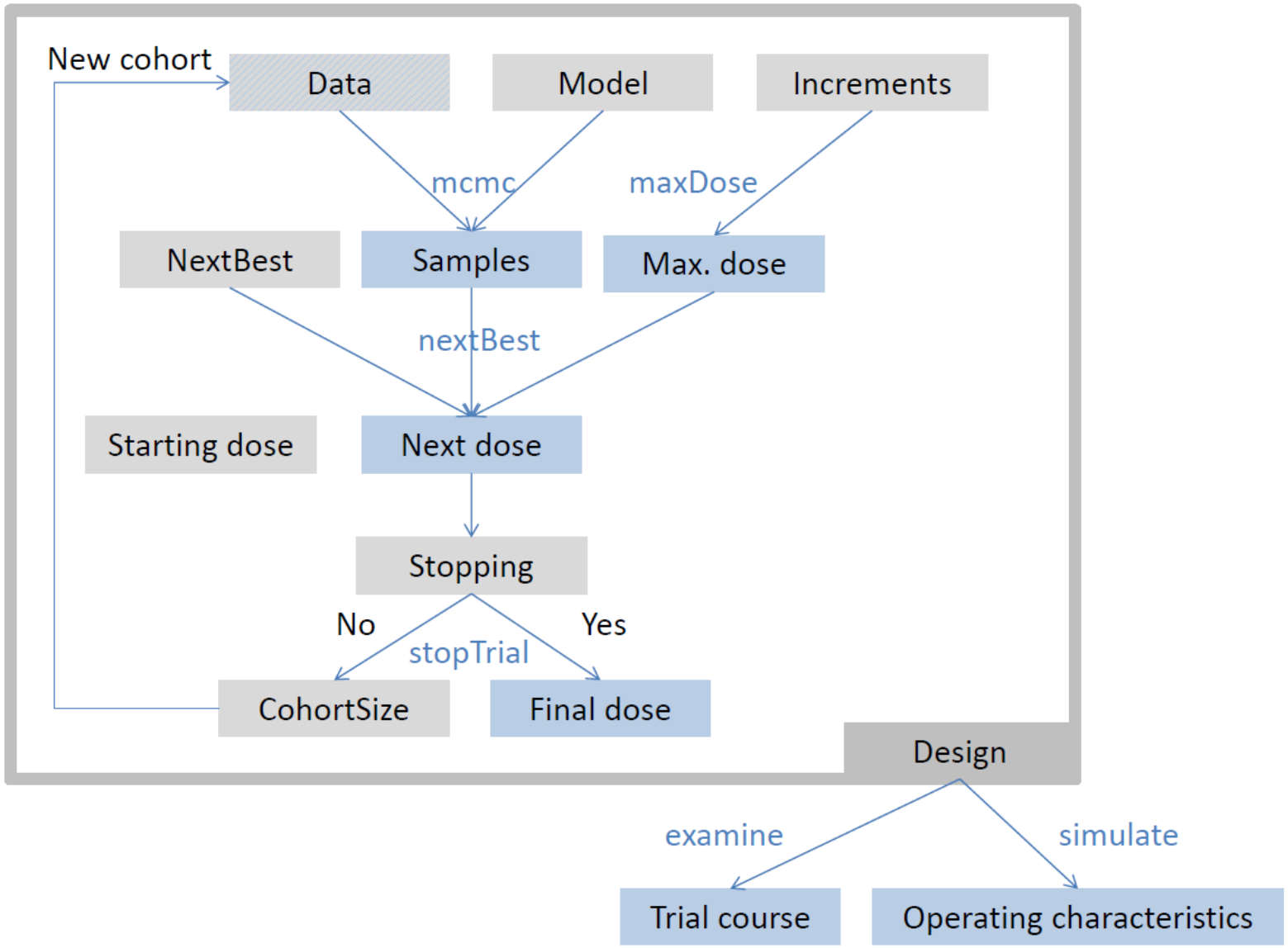
- More flexible than commercial software (FACTS, East, Addplan DF)
- Wish to adopt and implement new designs quickly – and there is a common structure to the designs!
- Reproducible reporting with R, also into Word and Powerpoint using the ReporteRs package (see my BaselR presentation from 2015)
- Other R-packages on CRAN (bcrm, dfcrm, CRM) are not (easily) extensible
  - Object-oriented structure of crmPack was critical for successful use in Roche

➔ crmPack development started in 2014, first only internally (together with Giuseppe Palermo, Jiawen Zhu), then also together with Lancaster University (Winnie Yeung, Thomas Jaki)

➔ Package is available on CRAN since 2016 (latest version: 0.2.1)

➔ Package is described in upcoming article in Journal of Statistical Software (conditionally accepted)

Framework for crmPack: Use of package classes and methods



Motivation for dual-endpoint designs

New challenges in Oncology: contrasting yesterday and today

Yesterday

- Cytotoxic drugs
- Primary objective: find highest dose with tolerable toxicity (MTD)
- Implicit assumption: efficacy increases with dose
- Mainly look at safety
- Model dose-toxicity relationship

➔ Safety endpoint dose escalation design

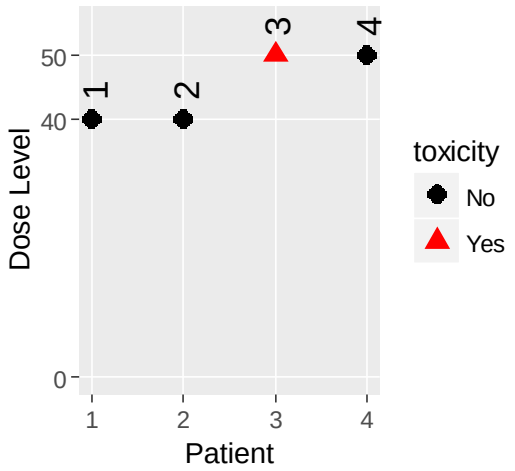
Today

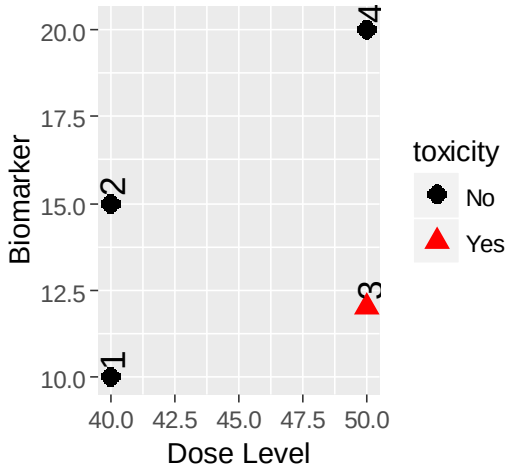
- Immunotherapeutic drugs
- Primary objective: find optimal biological dose with tolerable toxicity (OBD)
- Dose-efficacy relationship may plateau or be non-monotonic
- Use biomarkers to obtain early signs of drug activity
- Model dose-toxicity/biomarker relationship

➔ Dual-endpoint dose escalation design

How does a dual-endpoint design work?
Outline of the idea by describing one iteration

- Gather data for each patient:
  - Presence or absence of dose-limiting toxicity (DLT)
  - Continuous PD biomarker measurement
    - Biomarker reflective of clinical activity
    - Biomarker measurements should be comparable between patients





- Estimate the dose-toxicity/biomarker model
- Predict the next best dose, target:
  acceptable overdosing risk and (almost) optimal biomarker level (maximum or range targeted)
- Treat next cohort of patients at next best dose
- Repeat until maximum sample size or stopping criteria are met
  ⇨ estimate of an optimal biological dose

Modeling the joint dose-toxicity/biomarker relationship
Probit model for toxicity and normal model for biomarker

- Biomarker W at dose x follows Normal model:
  - With variance σ_W^2 and Emax mean trend: $m = E_0 + \frac{E_{max}\, x}{ED_{50}+x}$ (note: here ED50 for biomarker!)
  - Uniform prior distributions on E_0, E_{max} and ED_{50} parameters can be used, along with inverse-gamma prior on variance σ_W^2
- Similar to before, we assume a probit model for the binary safety / DLT outcome:
  - $\text{probit}[\varphi(x)] = \alpha_0 + \alpha_1 \cdot \log(x)$
  - And again $(\alpha_0, \log(\alpha_1))^T \sim \mathcal{N}_2(\mu, \Sigma)$ ensures monotonicity
- Then, we can assume a joint bivariate normal likelihood for the biomarker W and the probit of DLT Z (details not shown here)
  - ρ is the correlation parameter with beta prior scaled to the range (-1, 1)
  - $\rho > 0$ ($\rho < 0$): a higher (lower) biomarker correlates with higher toxicity risk

Related paper: Yeung, W. Y., Whitehead, J., Reigner, B., Beyer, U., Diack, C., & Jaki, T. (2015). Bayesian adaptive dose-escalation procedures for binary and continuous responses utilizing a gain function. *Pharmaceutical Statistics*, *14*(6), 479–487. http://doi.org/10.1002/pst.1706

Motivation and ideas for incorporating information on PK

Exposure driven - CRM

Thanks to Sandrine Micallef!

- **Background**:
  - More than 4/5[1] of published phase I studies define PK analysis as primary objective
  - Dose finding and PK analysis performed in parallel (separately)
- **Idea**: Use the information related to exposure to inform
  - Dose escalation process (dose allocation for the following cohort)
  - Dose selection for further development
  - ➢ Optimize dose finding in better handling variability in exposure.
- **Different approaches already proposed … but, to our knowledge none of them implemented in a "real" study**
  - PK measurement as covariate[2,3,6]
  - PK as a dependent variable in regression[4,5,6] – for example, model PK as "biomarker" with previous method

(1) Comets, E., & Zohar, S. (2009). A survey of the way pharmacokinetics are reported in published phase I clinical trials, with an emphasis on oncology. *Clinical pharmacokinetics*, *48*(6), 387-395.
(2) Piantadosi, S., & Liu, (1996). Improved designs for dose escalation studies using pharmacokinetic measurements. *Statistics in Medicine*, *15*(15), 1605-1618.
(3) Whitehead, J., Zhou, Y., Stallard, N., Todd, S., & Whitehead, A. (2001). Learning from previous responses in phase I dose-escalation studies. *British journal of clinical pharmacology*, *52*(1), 1-7.
(4) Patterson, S., Francis, S., Ireson, M., Webber, D., & Whitehead, J. (1999). A novel Bayesian decision procedure for early-phase dose-finding studies. *Journal of biopharmaceutical statistics*, *9*(4), 583-597.
(5) Whitehead, J., Zhou, Y., Hampson, L., Ledent, E., & Pereira, A. (2007). A Bayesian approach for dose-escalation in a phase I clinical trial incorporating pharmacodynamic endpoints. *Journal of* biopharmaceutical statistics, 17(6), 1117-1129.
(6) Toumazi A., Zohar S., Lentz F., Alberti C. , Stallard N., Comets E. , Moreno, U., dfpk: an R package for a practical implementation of PK measurements in dose-finding studies, poster PAGE 2017, Budapest

Motivation for Rolling-CRM design
Late onset DLTs and drawbacks of traditional designs

- **Challenges in the current Phase I D/E trials**
  - With the emergence of novel monoclonal antibody (mAb) biologics such as immunotherapies that target the human immune system, **late-onset or cumulative toxicities** could occur due to a longer pharmacokinetic half-life and a potential delayed effect on the disease
  - This issue becomes more prominent for phase I trials of combination therapies (Muler et al., 2004) as combining two or more agents of different mechanisms of action often results in unexpected cumulative toxicities.

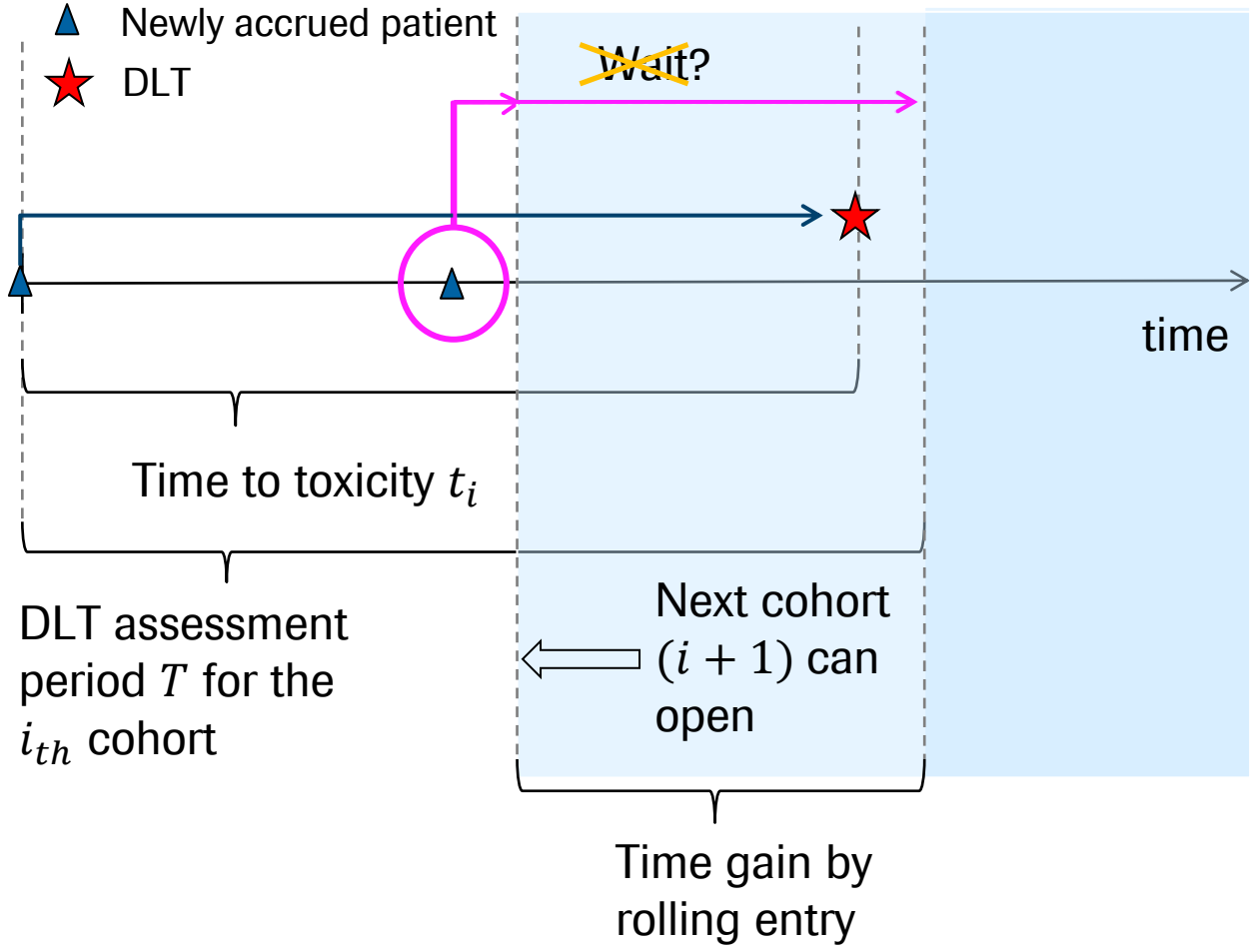
- **Drawbacks of the traditional phase I approaches**
  - The traditional approach is to wait for the first cycle of treatment for each patient, which is called the "DLT observation period".
  - In a cancer phase I dose finding study, the traditional first-cycle DLT observation window may not be able to detect treatment-related toxicities that occur in later treatment cycles, which leads to
    - the trial may fail to identify the MTD
    - the trial may select a dose that appears to be safe in cycle 1 but cannot be tolerated by patients beyond it

Joint work with Jiawen Zhu and Uli Beyer

Idea of Rolling-CRM design

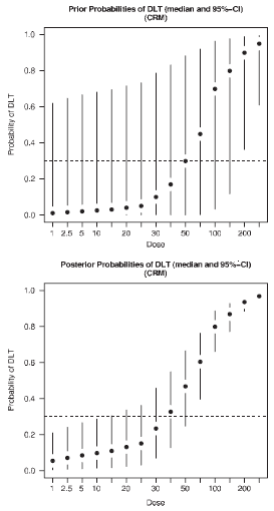
Illustration and Advantages

- **For the Patients**
  - No need to delay treatment until having observed the outcome of the previous patients
  - Not necessarily increase the safety risk
  - Escalation with overdose control (EWOC) implemented
- **For the Projects**
  - Shorten trial duration while not necessarily increase safety risk
  - Use richer clinical trial information (time to toxicity information, late onset toxicity)
  - Continually accrue patients
  - Handles patient drop-out
  - Captures the distribution of time to DLTs



Joint work with Jiawen Zhu and Uli Beyer

Rolling-CRM: Comparison with existing CRMs



CRM

EWOC

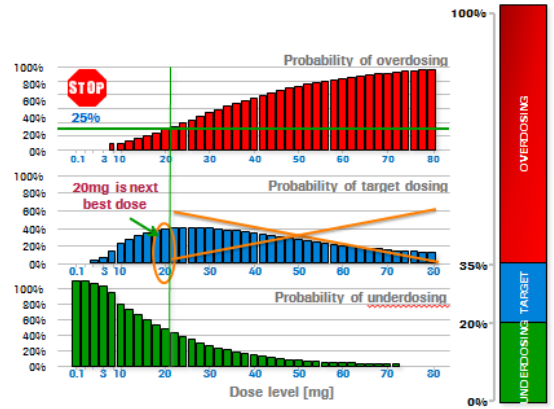
- Escalate with overdose control

TiTE-CRM

- Rolling entry
- Weighted likelihood

DA-CRM

- Rolling entry
- PEM conditioned on DLTs



Rolling-CRM

- Rolling entry
- PEM conditioned on DLTs
- Escalate with overdose control
- Safety observation window constraints

Rolling-CRM's latest reference: Jiawen Zhu, Daniel Sabanés Bové and Ulrich Beyer, Rolling dose escalation with overdose control: an efficient and safe phase 1 design, Poster presentation at ICTMC 2017, Liverpool

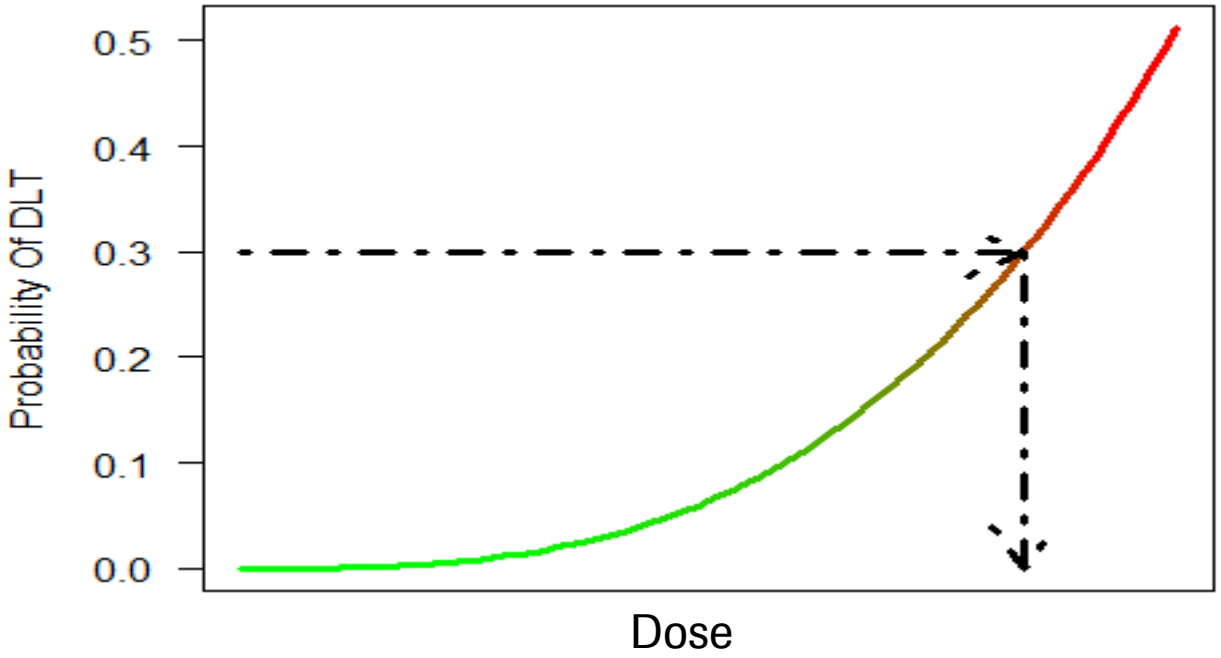
TiTE-CRM: Cheung YK and Chappell R "Sequential designs for phase I clinical trials with late-onset toxicities". Biometrics. 56 (2000) : 1177-1182

DA-CRM: Suyu Liu, Guosheng Yin, and Ying Yuan. "Bayesian data augmentation dose finding with continual reassessment method and delayed toxicity." The Annals of Applied statistics 7.4 (2013): 1837.

Motivation for Combination Dose Escalation

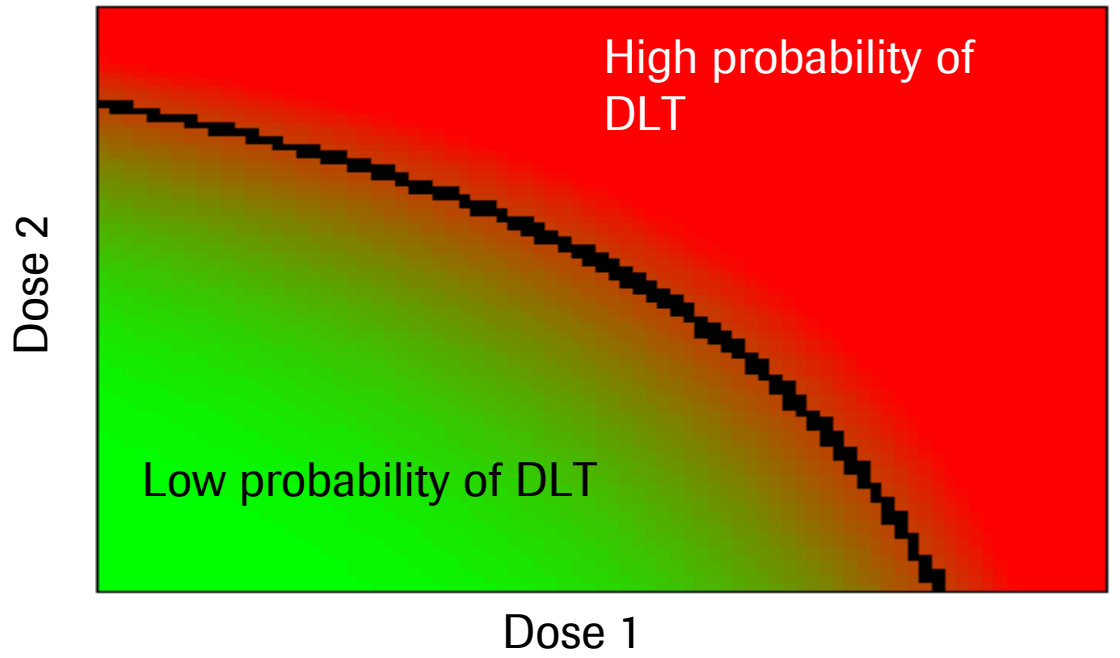
What's Different About Combination Studies?

Single Agent



➔ **Single MTD**

Two Agents



➔ **Contour Of MTDs**

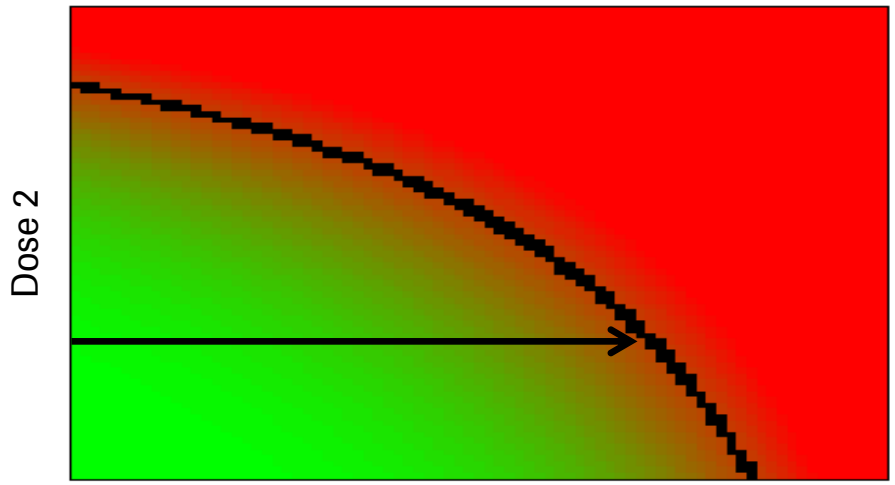
Selected dose may be modified by considering efficacy/biomarkers/pK

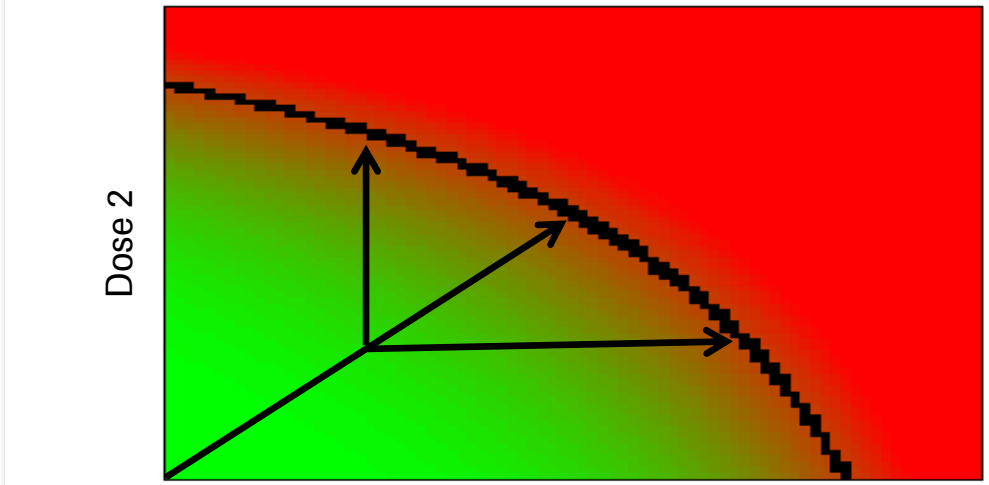
Choose between family of MTDs by considering efficacy/biomarkers/pK

Joint work with Chris Harbron, Francesca Michielin & Giuseppe Palermo

Possible choices: Single Agent vs. Combination Dose Escalation

Single Compound	Two compounds
Fix dose of one compound and vary the dose of the other	Vary dose of both compounds





DLT rate < TTL*

DLT rate = TTL

DLT rate > TTL

*TTL = Target Toxicity Level, often chosen as ca. 30%

- Simpler
- Potentially quicker in presence of DLTs
- Precedent of use with internal experience

- Greater opportunity to find combination dose of maximum benefit-risk ratio
- Mitigation against unexpected MTD contour shape
- Choice between different safety profiles
- Choice of most attractive PK/PD profiles

Joint work with Chris Harbron, Francesca Michielin & Giuseppe Palermo

Which methods to use?

Two most attractive are Curve-Free and Parametric Models

- **Curve-Free** recommended when the dosing region (lowest to highest dose) is well defined with a limited range
  - Benefits
    - Few assumptions
    - Highly visual
  - Drawbacks
    - Incorporation of prior knowledge challenging
    - Method does not foresee inclusion of additional doses
- **-> PIPE design**

  Mander, Sweeting (2015) A product of independent beta probabilities dose escalation design for dual-agent phase I trials *Statistics in Medicine*, 34, 1261–1276

- **Parametric models** recommended when dosing region is wider or pre-study knowledge is limited
  - Benefits
    - Flexibility
    - Can cope with many dose levels
    - Additional doses can be easily added or continuous dosing levels used
    - Can incorporate prior knowledge
    - Highly visual
  - Drawbacks
    - Choice of model formula may not represent reality
  - Gasparini, M. (2013). General classes of multiple binary regression models in dose finding problems for combination therapies. *Journal of the Royal Statistical Society: Series C*, *62*(1), 115–133.

Joint work with Chris Harbron, Francesca Michielin & Giuseppe Palermo

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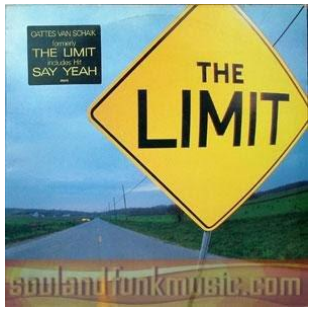
Limitations and next steps

Summary

Logistic regression model deficiencies
Only global use of binary information



- Binary only:
  - We don't differentiate between a related G3 AE (e.g. Diarrhea) and death (G5), but it is a big difference for the clinical decision making!
  - We only care about higher-grade AEs, but often also specific AEs of lower grade can be worrying if they show unexpected off-target toxicity e.g.
- Global model:
  - Phase 1 studies are becoming larger, and different dose levels are expanded, thanks to the flexibility of CRMs
  - However, can lead to problem: if many patients at lower dose levels enrolled, and suddenly toxicity occurs at higher dose, the logistic regression model will «smooth over» this increase
  - Clinical decision making probably more «local», i.e. taking into account more the closer doses

Logistic regression model deficiencies (cont.)

Dose range given by prior, Longitudinal aspects are not captured

- Dose range:
  - Is a critical parameter when setting up any D/E design
  - Even with «minimally informative prior distribution» on the logistic regression model parameters, the maximum dose is strongly expected to be too toxic
  - Therefore, typically even if all doses including the highest dose are safe without DLTs, the CRM would not “allow” the further escalation above highest doses, or only with very small increments
  - Amendments might be necessary to increase the dose range by changing the prior distribution
  - Can be «rescued» by allowing to dose above the CRM recommendation due to clinical judgment… But certainly not optimal
- Longitudinal aspects are not captured:
  - Transient vs. Persistent AEs over time: at the moment only in DLT definition mentioned, not modelled

What could be bold steps going forward?
Provocative proposals for discussion

- Bed to bench reverse translation:
  - Preclinical tox models inform the dose escalation model setup, via the dose range and prior information, assuming certain translation from bench to bedside
  - Learning about the bedside, this could be fed back to the bench, i.e. Inform later tox experiments, and also could be used in extrapolation of the dose/toxicity curve in the current trial
- Applying joint safety/efficacy modelling in D/E trials:
  - A lot of literature on this, but it is not (or only rarely?) applied in the trials
- Building more complex models – essentially we are predicting what happens at higher doses
  - With today's computational tools and statistical/machine-learning tools, could we not use much more fine-grained information than just binary DLT? E.g. Use the full AE information across time?
  - Pooling data across the company (or even beyond) could improve the prediction quality
  - Probably it would not be a big difference for clinicians – for them the CRM is already a black box

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Current status and important next steps

Experience in Roche: Broad experience with different extensions of CRM in different disease areas (not only Oncology, but also CNS, Inflammation, etc.) Software tools help to make setup more efficient. Accepted by clinicians and external investigators and other stakeholders.

Current status and focus areas: Current methods research/implementation is focusing on Rolling-CRM to allow for faster and still safe D/E while including later DLTs, combination dose escalation and formally modelling dose-exposure-DLT.

Next steps: The logistic regression model approach and all extensions have limitations, based on simplicity of the endpoint, the global model and the dose range restrictions. Next bold steps should involve bed-to-bench reverse translation of information, application of safety/efficacy D/E designs, and using the data we collect in a more holistic and fine-grained manner.

Doing now what patients need next