PKPD modelling to optimize dose-escalation trials in Oncology

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M&S
Modeling & Simulation

Outline

- Motivation
- Phase I trial design in Novartis Oncology
- PKPD modeling, strenghtes and caveats
- PKPD modeling for decision making in Phase I trials
- Examples
- Conclusions

Motivation

- Want to take informed decisions about:
  - Dose/dose regimen for a future trial
  - Dose level for a next dose cohort
- Binary safety/efficacy endpoints are simplifications and often based on relatively arbitrary thresholds of underlying biological longitudinal process
- Patients' individual characteristics may have as big impact on e.g. safety response as solely a dose
- Processes underlying dose-limiting toxicities in Oncology are often reversible ➔ how do we best manage toxicity?

Phase I trial design at Novartis Oncology

- Designed to determine an MTD (maximum tolerated dose)
- Method by Neuenschwander et al. (2008) has been successfully used in the majority of Phase I trials in Oncology
- Bayesian model-based dose-finding:

$$\text{logit}(\pi_\theta(d)) = \log\alpha + \beta \log\left(\frac{d}{d^*}\right), \qquad \alpha, \beta > 0$$

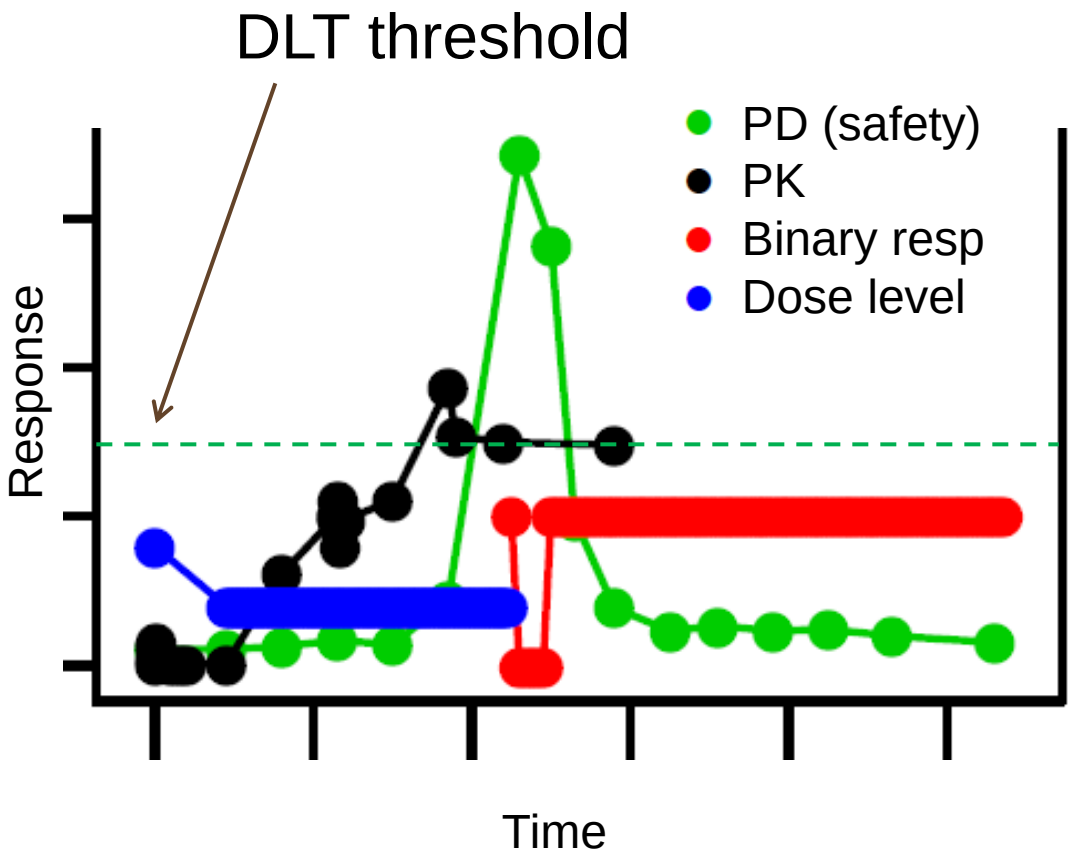
$$\theta = (\log\alpha, \log\beta)$$

reference dose

Phase I trial design at Novartis Oncology, contd

- After each patient cohort, information is derived from the posterior distribution of the model parameters, that implies posterior distribution of π
- Dose recommended for the next cohort:
  - Maximizes probability of a true DLT rate to be in a target interval
  - Probability that the true DLT rate is exceeding 0.33 is less than 25%
- This model output helps the clinical team to define the dose for the next patient cohort
- Dose escalation meeting: output of the bayesian analysis is considered together with clinical arguments, as well as **PK/PD data**

PKPD data: What do we measure?



- Repeated measurements of PK concentrations by patient
- Repeated measurements of biomarker (PD) by patient
- Covariates (typically at baseline): age, sex, race, lab values, etc.

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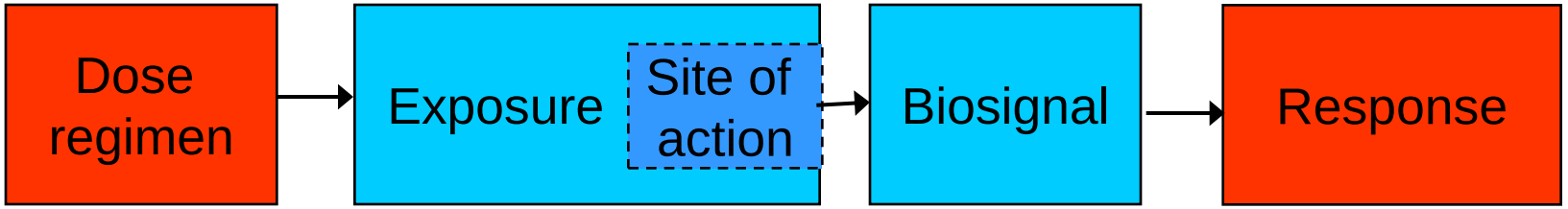
Understand the Causal Chain of Drug Action

Pharmacokinetics *Pharmacodynamics*



Dose
Dosage Interval
Route
Delivery system

PK

Biomarkers

Safety
Tolerability
Efficacy
Early Clinical Readouts

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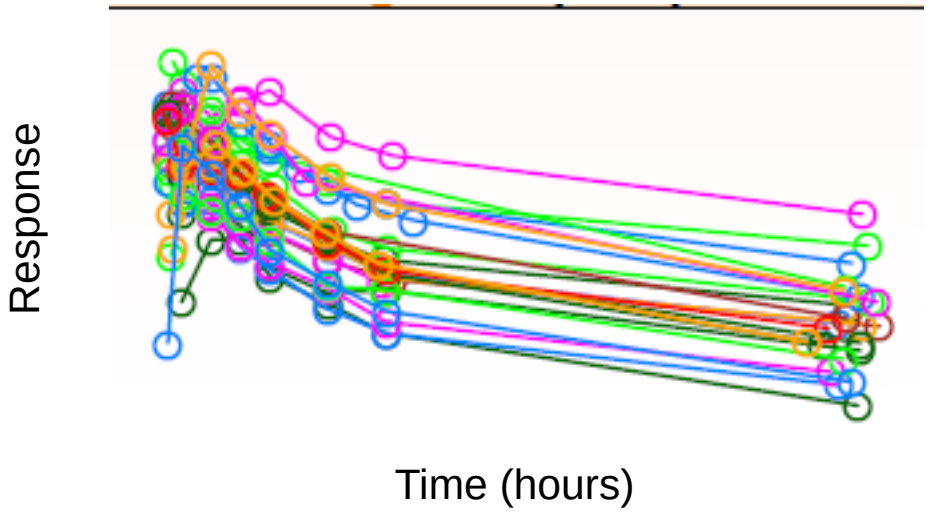
Patients are all different!

Population PK/PD model: assume some PK and PD parameters to vary between subjects



- Structural PK/PD model: system of ODEs
- Population PK/PD to determine mean, variance and covariance of PK/PD parameters of a drug within a patient population

Non-linear mixed effects models

- NLME models for parameters' estimation
- Software (frequentist setting):
  - Industry standard: NONMEM (FO, FOCE method)
  - Monolix (SAEM Method, see Samson, Mentré, Lavielle, 2007)
- Alternative:
  - Bayesian methods
  - Software is still an issue due to the difficulty of solving system of (non) linear ODEs coupled with a bayesian inference on NLME model parameters

Bayesian population PKPD

1) Models

PK $$p(y_{ij}|\theta_i, \sigma^2) \propto N(f(\theta_i; t_{ij}; D_i), \sigma^2) I(y_{ij} \in (l_{ij}, u_{ij})),$$
$$i = 1, \ldots, K, j = 1, \ldots, n_i$$

residual error variance; dosing history; concentrations or log-concentrations; structural PK model; individual-specific parameters

PD $$p(e_{ij'}|\phi_i, \theta_i, \zeta) = N(h(\phi_i; C_e), \sigma_e^2)$$

2) Distribution specifications for individual PK and PD parameters

covariate-effect; fixed effects; variance–covariance

PK $$p(\theta_i|\mu, \Omega) = \mathrm{MVN}_p(Z_i\mu, \Omega), \quad i = 1, \ldots, K$$

PD $$p(\phi_i|\psi, \Sigma) = \mathrm{MVN}_r(W_i\psi, \Sigma), \quad i = 1, \ldots, K$$

3) Priors

PK $$p(\sigma^2) = \mathrm{IG}(a,b); \quad p(\mu) = \mathrm{MVN}_q(\eta, H); \quad p(\Omega) = \mathrm{IW}(R, \rho)$$

PD $$p(\zeta) = \mathscr{D}_\zeta(\xi); \quad p(\psi) = \mathrm{MVN}_s(\chi, X); \quad p(\Sigma) = \mathrm{IW}(U, v).$$

Strengthes/Caveats

- Strenghtes:
  - PK and PKPD time-course described via a mechanistic model ➔ may be used for predictions
  - Fixed AND random effects are estimated
  - Various alternative dose/dose regimens can be evaluated w.r.t. their PK/safety/efficacy profiles
- Caveates:
  - Not always evident what a particular model structure should be and what is a meaning of a compartment (exception: PBPK models)
  - Identifiability issues
  - Data heterogeneous/sparse ➔ difficult to fit a NLME model
  - Time-consuming
  - Priors on PK (PD) parameters in Bayesian setting?

Goal: move PKPD modeling into a learning phase

- Traditionally, PKPD modeling is used to support submission dossier (confirmatory phase)
- Too late to make an impact on the decision making re. drug development
- By performing modeling early in the program, we can:
  - Avoid treating patients at unnecessary low (high) doses
  - Reduce total number of patients
  - Help with dose selection/justification
  - Detect subpopulations with better response to treatment
  - Synthetize information available in various trials and in the literature

➔ Optimized drug development process

The idea is not new, but rarely used in practice

- Piantadosi and Liu (1996) acknowledged the fact that incorporation of PK data into the dose escalation trial design could potentially improve efficiency and accuracy of the studies
- This is especially the case in a presence of a high inter-patient variability, and also when the drug has a complicated PK profile (often the case in Oncology)
- Piantadosi and Liu considered an extension of a Continual Reassessment Method (CRM) approach by including PK information into the dose-escalation process

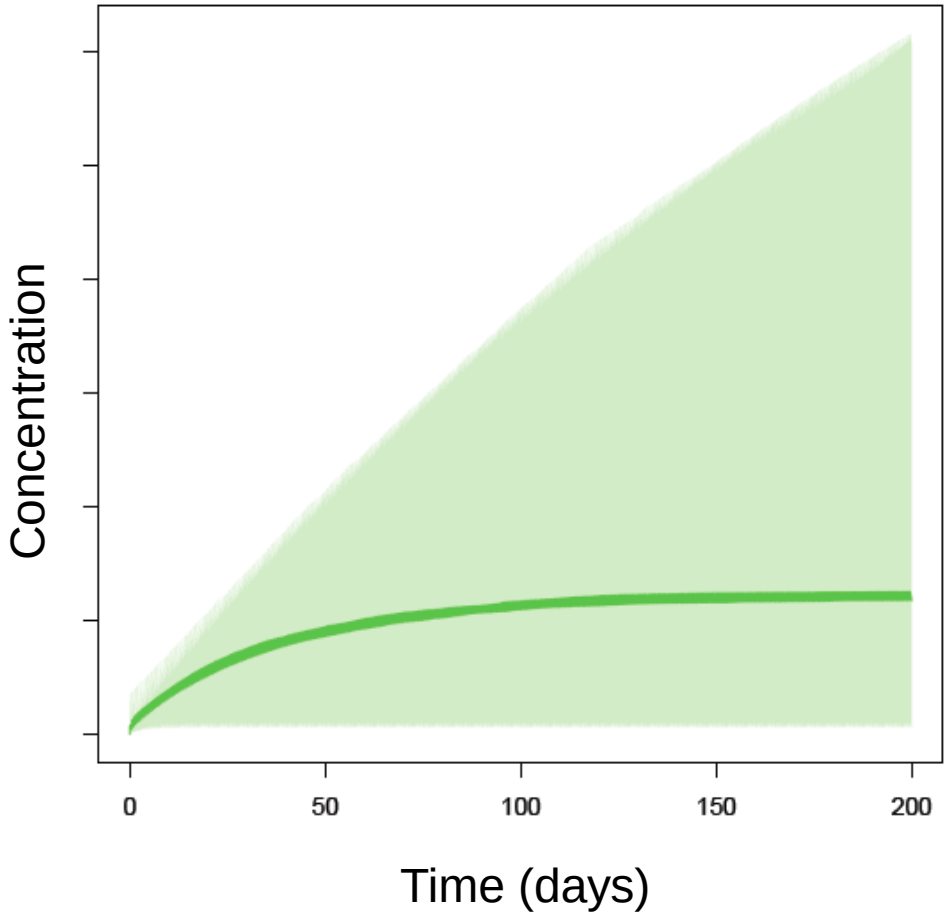
$$\text{logit}(p) = \beta_0 - \beta_1 \times \text{dose} - \beta_2 \times \Delta_{\text{AUC}}$$

When and how PKPD modeling is to support the decision making

1. Complex/unexpected PK
2. Heterogeneity in the patients' population
3. We want to target a specific subgroup of patients (i.e. disease, ethnicity, etc.)
4. Evaluation of alternative dose regimens
5. Justification of dose selection for future trials

1. Complex/unexpected PK

- Phase 1 Oncology trial
- At early stage of the trial, PopPK/PD model:
  - predicted very long half-life and time to steady-state of a drug
  - predicted higher probability of DLT event at lower dose compared to prior believe
- Protocol was augmented to include more frequent monitoring for DLTs during first 3 cycles



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2. Heterogeneity in the patients' population

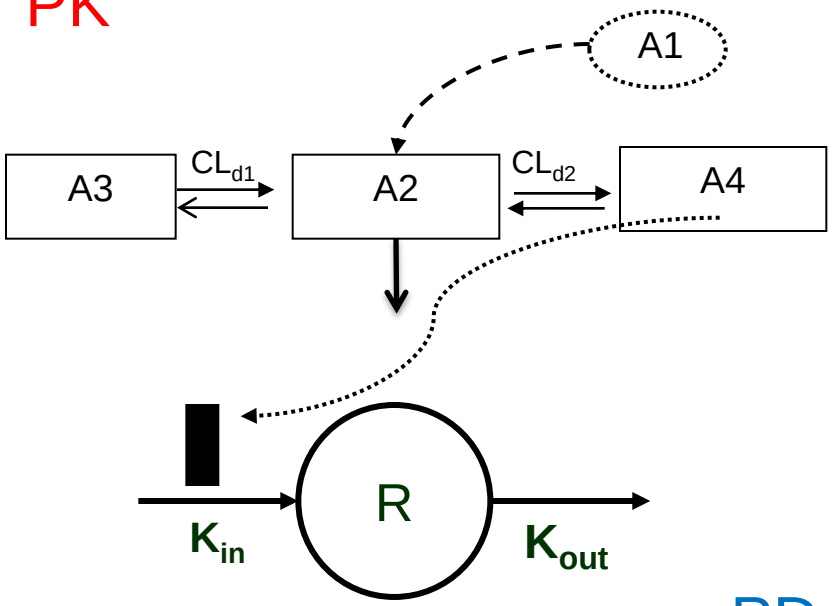
Myelosuppression example

- Phase I/II trial: myelosuppression as a main DLT (number of blood cells falls below certain threshold)
- Standard analyses to examine relationship btw probability of a DLT as explained by AUC failed
- Indirect response PKPD model was used to model the time-course of the biomarker:
  - Dose intake leads to drop in the number of the blood cells
  - After certain time without drug intake, back to baseline
  - Baseline values for blood cells numbers and tumor type are strongly driving the time-course of PD ➔ should be taken into account when calculating probailities of a DLT

2. Heterogeneity in the patients' population

Myelosuppression example

PK



$$\begin{cases} \frac{dA_1}{dt} = -k_a A_1, \\ \frac{dA_2}{dt} = k_a A_1 - K_{23}A_2 - K_{24}A_2 + K_{32}A_3 + K_{42}A_4 - \frac{CL}{V_2}A_2, \\ \frac{dA_3}{dt} = K_{23}A_2 - K_{32}A_3, \\ \frac{dA_4}{dt} = K_{24}A_2 - K_{42}A_4; \end{cases}$$

$$A_1 = Dose, A_2 = A_3 = A_4 = 0, t = 0$$

PD

$$\frac{dR}{dt} = k_{in} \cdot \left(1 - \frac{\mathrm{Im}\,ax \cdot C_{Drug}}{IC_{50} + C_{Drug}}\right) - k_{out} \cdot R$$

$$\frac{dR}{dt} = 0, t = 0$$

- I_{max}= Maximal effect
- I_{50} = Effect at half of I_{max}
- K_{in} = Zero order production rate
- K_{out} = First order turn over rate
- R = Response

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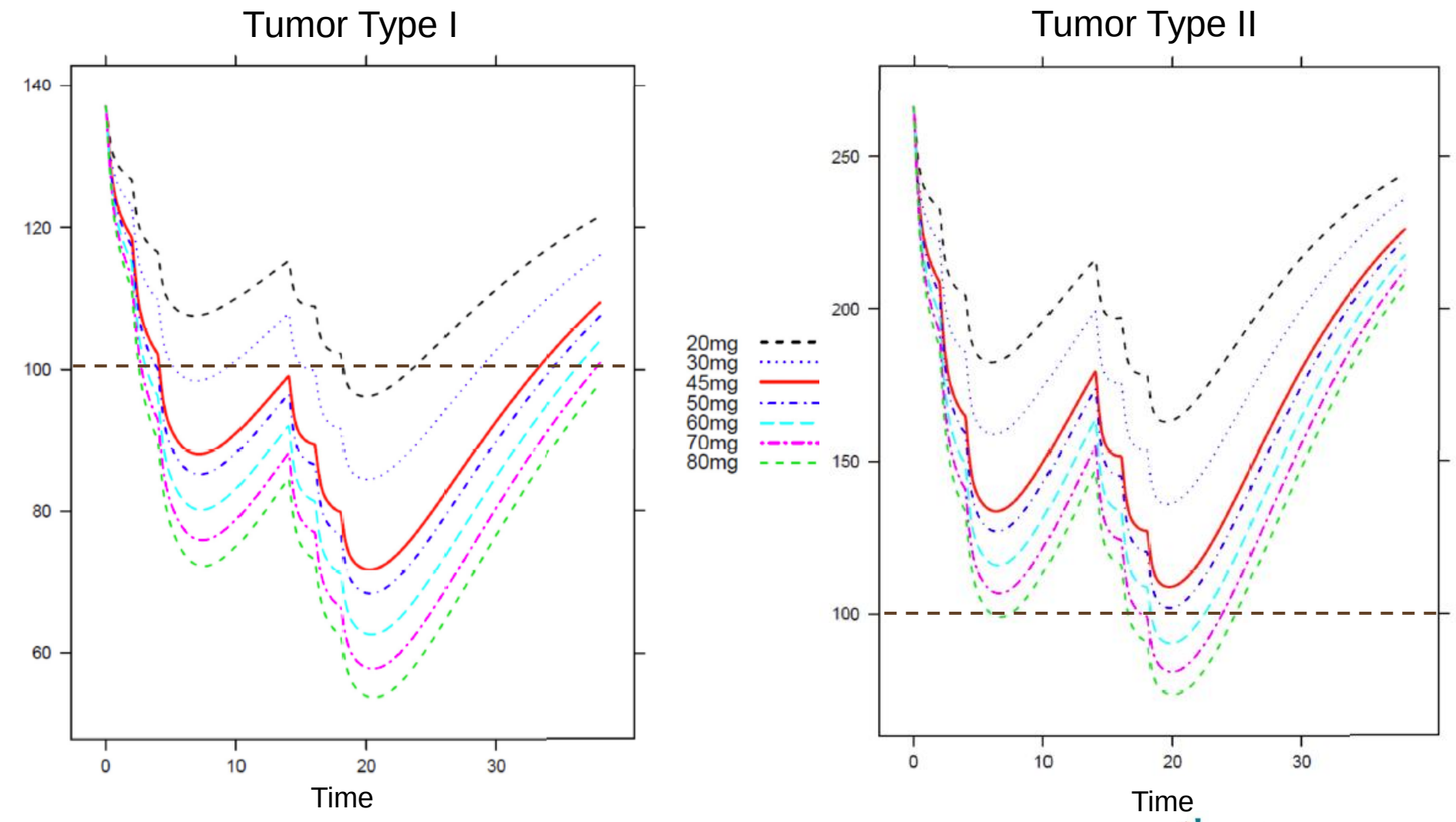
2. Heterogeneity in the patients' population

Myelosuppression example



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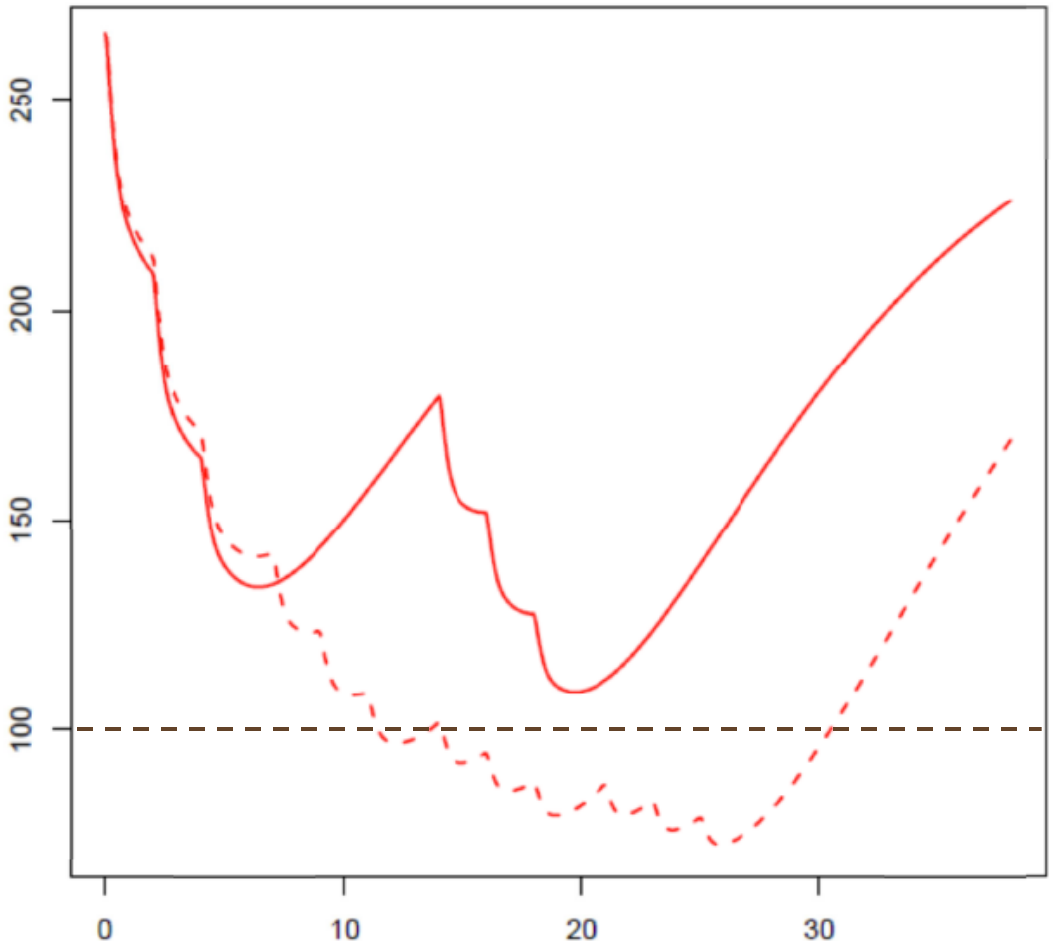
3. Evaluation of an alternative dose/regimen

- Evaluation of an alternative dose regimen
- Interested to reduce probability of a DLT, while maintaining same efficacy
- Simulations from a PKPD myelosuppression model showed that QoW regimen would have better safety profile, while maintaining comparable level of exposure



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4. Subgroups' stratification

Japanese trial example

- Developing drugs targeting specific subpopulations as a part of a global development program has become one of the main priorities for the majority of pharmaceutical companies
- Ethnicity sensitivity is one of the examples where we would like to get advantage of leveraging knowledge btw. global and local populations
- Development in Japan is cost and time consuming, due to the uncertain impact of ethnic differences on pharmacokinetics and drug responses ➔ alternatives to existing methods should be developed

4. Subgroups' stratification, contd

Japanese trial example

- Bayesian model-based trial design by Neunschwander et al.
- PKPD model could be used:
  - To select prior distributions
  - To help with a better guess for a starting dose
- Reassessment of the probability of toxicity for Japanese population based on PK metrics:

$$\text{dose d} \xrightarrow{\text{PK model}} \text{PK params } \theta \longrightarrow AUC(d,\theta) \xrightarrow{\text{DLT model}} \pi_\theta(d)$$

- Reassessment of the probability of toxicity for Japanese population based on PKPD modeling

4. Subgroups' stratification, contd

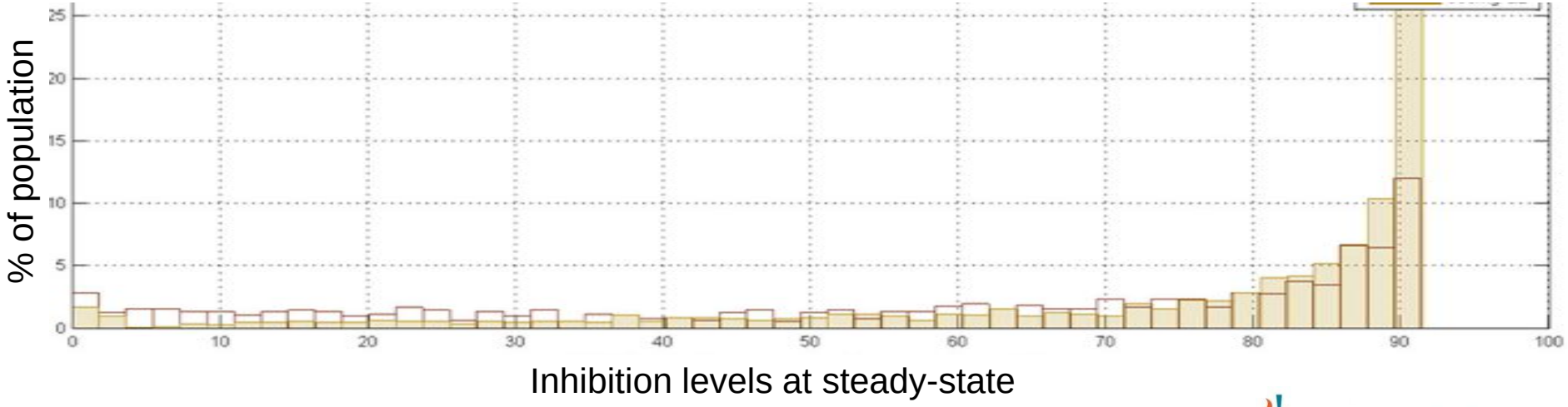
Japanese trial example

- In an ongoing Japanese trial, DLTs were observed at dose levels that were lower compared to an MTD established in Western population
- Sample size is low
- Is there any systematic differencies btw. Japanese and Western?
- Analysis:
  - popPK with Japan as a covariate: large differencies btw two populations
  - PKPD: DLTs are driven by peack concentrations

➔ higher risk of getting a DLT event for a Japanese patient as compared to a Western patient at the same dose level

5. Justification of dose selection for future trials

- Based on the outcomes of a phase I trial, 2 dose levels were selected for a phase II pivotal trial
- FDA challenged us: is there a dose-response w.r.t. efficacy?
- PopPK model used to simulate conc distributions
- Bayesian PKPD Emax model to predict inhibition of a certain pathway under «conservative» scenario
- Simulated patients' distributions of inhibition levels by dose showed differentiation btw two doses, especially at higher inhibition levels



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Summary 1

- We advocate in favour of applying population PKPD modeling techniques early in drug development
- We exploied adavantages and feasibility of performing PKPD modelling to support Phase I/II trial design in Oncology on several concrete examples
- Based on the experience so far, the main advantages are:
  - Description of a time-course of a dose-exposure-biomarker relationship depending on dosing history and individual patient characterisitcs
  - Able to predict response in hypothetical populations for various dose regimens
  - Analyses are adjusted as new data become available

Summary 2

- Modeling could be very challenging:
  - Lack of knowledge of the mechanism of action of a new drug
  - Data are very sparse
  - Involves alot of assumptions
  - Lot of simulations are required
  - Timing issues
- Collaboration and clear communication btw different line functions assigned to a project (clinicians, biostatisticians, clinical pharmacology, biomarker, etc.) is essential in order the approach works successfully and integrated into the decision making process

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