Supporting oncology phase I dose-escalation trials

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Acknowledgment

- Lukas Widmer
- Lada Markovtsova
- Juan Gonzalez-Maffe
- Melodie Monod
- Paul Bürkner
Phase I dose-escalation trials in oncology

- Basic design:
  - Enroll small cohorts of (late-stage) cancer patients (N=3-6) at a candidate dosing level
  - Monitor patient cohort for ~1 cycle (4 weeks)
  - Decrease (~1/2x) / repeat same / increase dose (~2x) for next cohort
  - Iterate until a recommended dose is found – sufficiently safe & efficacious

- Trial design to find a maximum tolerated dose (MTD) are ideal for cytotoxic treatments for which efficacy and safety follow one another closely

- Novel treatments differ!
  - In many instances, longer-term tolerability must be warranted
  - Timing of dosing is critical (e.g. ramp-up of dose to avoid cytotoxic reaction of body)

- FDA project Optimus challenges current standard paradigm
Supporting ongoing dose escalation

Goal:
Explore dose regimen – response relationships in order to guide dose escalation decisions

Challenges:
- Small sample size
- Limited data availability while trial runs, in particular for latest patient cohort
- Missing/unclean data

Proposed solution:
- Simplified pharmacokinetic-pharmacodynamic (PK/PD) modeling
- PK model simplified to describe steady-state kinetics only (including reaching/leaving it)
- PK model informed from individual patient non-compartmental analysis
- Coupling of simplified PK with semi-mechanistic PD models (not today)
Brief overview of common approaches in comparison

- **Dose-response**
  - Summarizes longitudinal PK with a single metric (total dose, dose intensity)
  - Appropriate to characterize relationships in steady-state

- **K-PD**
  - Utilizes full dosing history, but no PK data at all
  - Neglects between-subject variability in PK model, but characterizes drug exposure over time

- **Simplified PK proposed here**
  - Utilizes full dosing history and *NCA estimates of key PK model parameters*
  - Accounts for *individual subject PK* and characterizes drug exposure over time
  - Simplification approach assumes linear PK and restricts reliability to *steady-state and its vicinity*

- **Full PK/PD model**
  - Best modeling approach, but can be demanding to fit along with ongoing trial
Simulated example trial scenario

- **Treatment**
  - 1 week dosing + 1 week no dosing
  - Constant dose 1, 2, 4, 8 mg
  - 4 weeks cycle

- **Using PK as outcome for simplification here:** Cmin, the concentration just before next dosing

- **Objectives for investigation**
  - Can we describe drug concentration in and around steady-state?
  - Is the sparse data sufficient to inform simplified PK model based on NCA estimates?
  - How to handle missing data accordingly.
Simulated data scenario

- **Data scenario**
  - 4 cohorts of patients
  - 3 patients per cohort
  - Partially observed data in cohort 4

- **Clearance and volume** sampled from multi-variate normal

- **PK model used is a 1-compartment model with first order absorption (oral dosing)**

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### Formula:

\[
obs_y | mi() \sim pk_conc(logFrel, \log Ka, \log Cl, \log V, \text{obs}_\text{time}, \text{dose}_\text{time}, \text{dose}_\text{amt}, \\
\text{dose}_\text{addl}, \text{dose}_\text{tau})
\]

#### LogFrel

\[
\log Frel \sim 1
\]

#### LogKa

\[
\log Ka \sim 1
\]

#### LogCl

\[
\log Cl \sim 0 + mi(nca_1Cl, \text{patient}_id)
\]

#### LogV

\[
\log V \sim 0 + mi(nca_1V, \text{patient}_id)
\]

#### Nca_1Cl

\[
nca_1Cl | mi() + \text{subset}(ref\_cmin) + \text{index(patient}_id) \sim 1
\]

#### Nca_1V

\[
nca_1V | mi() + \text{subset}(ref\_cmin) + \text{index(patient}_id) \sim 1
\]

- Modeling multiple outcomes per patient while using 1 NCA estimate per patient
- \text{pk}_\text{conc} is a non-linear function provided to \text{brms}
- \text{mi()} allows for missing data in outcome and model parameters
- Missing parameters are imputed with uncertainty in context of full model
- Imputation model for clearance & volume is learned from all observed data
brms model run

## Formula:
\[ \text{obs}_x | \text{mi()} \sim \text{pk_conc(logFrel, logKa, logCl, logV, obs_time, dose_time, dose_amt, dose_addl, dose_tau)} \]

### Population-Level Effects:

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### Family Specific Parameters:

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### Draws were sampled using sample(hmc). For each parameter, Bulk_ESS and Tail_ESS are effective sample size measures, and Rhat is the potential scale reduction factor on split chains (at convergence, Rhat = 1).
Model check for cohort 1 & 2

Posterior predictive check $C_{\text{min}}$ (dose standardized)
All observed data cohort 1 & 2
Model check for cohort 3 & partially observed cohort 4

Posterior predictive check Cmin (dose standardized)

Observed 3. cohort & partially observed 4. cohort
Phase I dose-escalation trials in oncology explore dose regimen – response relationships and require constant reassessment of dosing amount and timing.

Dose-escalation decisions rely on small sample sizes, limited data availability and unbalanced allocation to dosing regimens.

Proposal to utilize a simplified PK model:
- Goal is to describe steady state kinetics including reaching and leaving steady-state.
- Formulated on basis of nominal time and non-compartmental analysis (NCA) estimates as these are readily available during a running trial.
- Allow for missing data of outcome and/or NCA inputs.
- Accounts for individual level patient PK.

Simulated development prototype promising, but there is a lot to be done…
Thank you
References


brms model prior

### Formula: `obs_y | mi() ~ pk_conc(logFrel, logKa, logCl, logV, obs_time, dose_time, dose_amt, dose_addl, dose_tau)`

### priors

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Recovery of true model parameters

Population level parameters
True value + 50% / 90% CrIs

Variance component parameters
True value + 50% / 90% CrIs