AEA
Analytics

Supporting oncology phase I dose-escalation trials

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Acknowledgment

- Lukas Widmer
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- Juan Gonzalez-Maffe
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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 & efficacous
- 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:

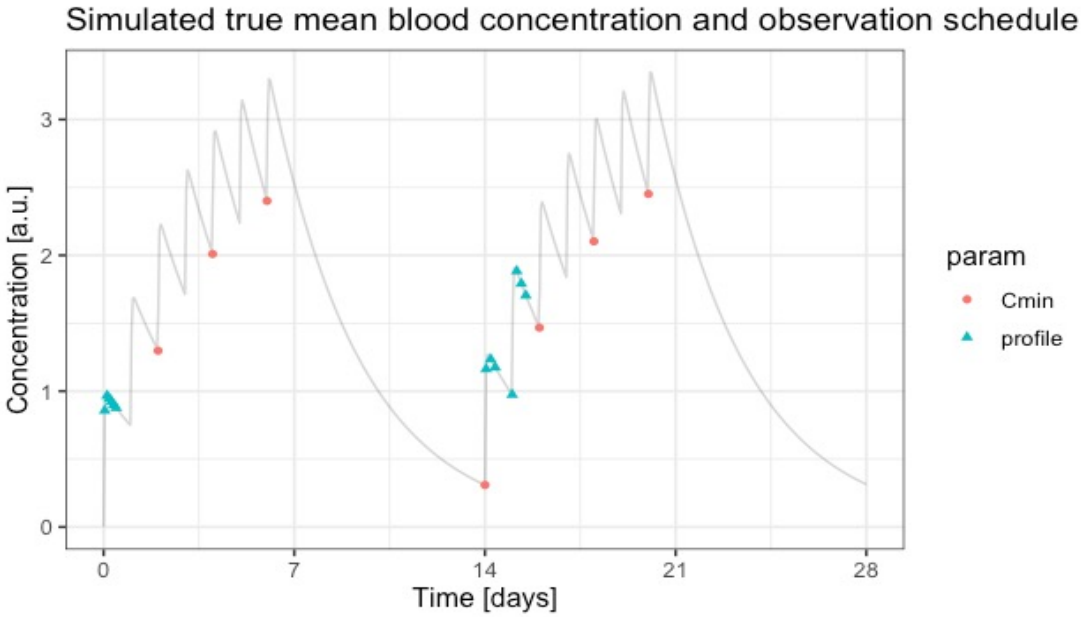
- Simplified pharmacokinetic-pharmacodynamic (PK/PD) modeling
- PK model simplified to describe steady-state kinetics only (including reaching/leaving it)
- PK model informed from individual patient non-compartemental analysis
- Coupling of simplified PK with semi-mechanistic PD models (not today)

Brief overview of common approaches in comparison

- Dose-response
  - Summarizes longitudinal PK with a single metric (total dose, dose intensity)
  - Appropiate 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 it's 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-compartement model with first order absorption (oral dosing)

cohort	patient_id	regimen_id	Dose [mg]	CL [l/h]	V [l]	N_Cmin
1	1	1	1, 1	0.12	6.25	7
1	2	1	1, 1	0.15	7.45	7
1	3	1	1, 1	0.11	8.99	7
2	4	2	2, 2	0.12	7.75	7
2	5	2	2, 2	0.07	4.56	7
2	6	2	2, 2	0.10	11.70	7
3	7	2	2, 2	0.12	7.93	7
3	8	2	2, 2	0.13	8.62	7
3	9	2	2, 2	0.08	6.45	7
4	**10**	**3**	**4, 4**	**NA**	**NA**	**3**
4	**11**	**3**	**4, 4**	**NA**	**NA**	**3**
4	**12**	**3**	**4, 4**	**NA**	**NA**	**0**

brms model setup

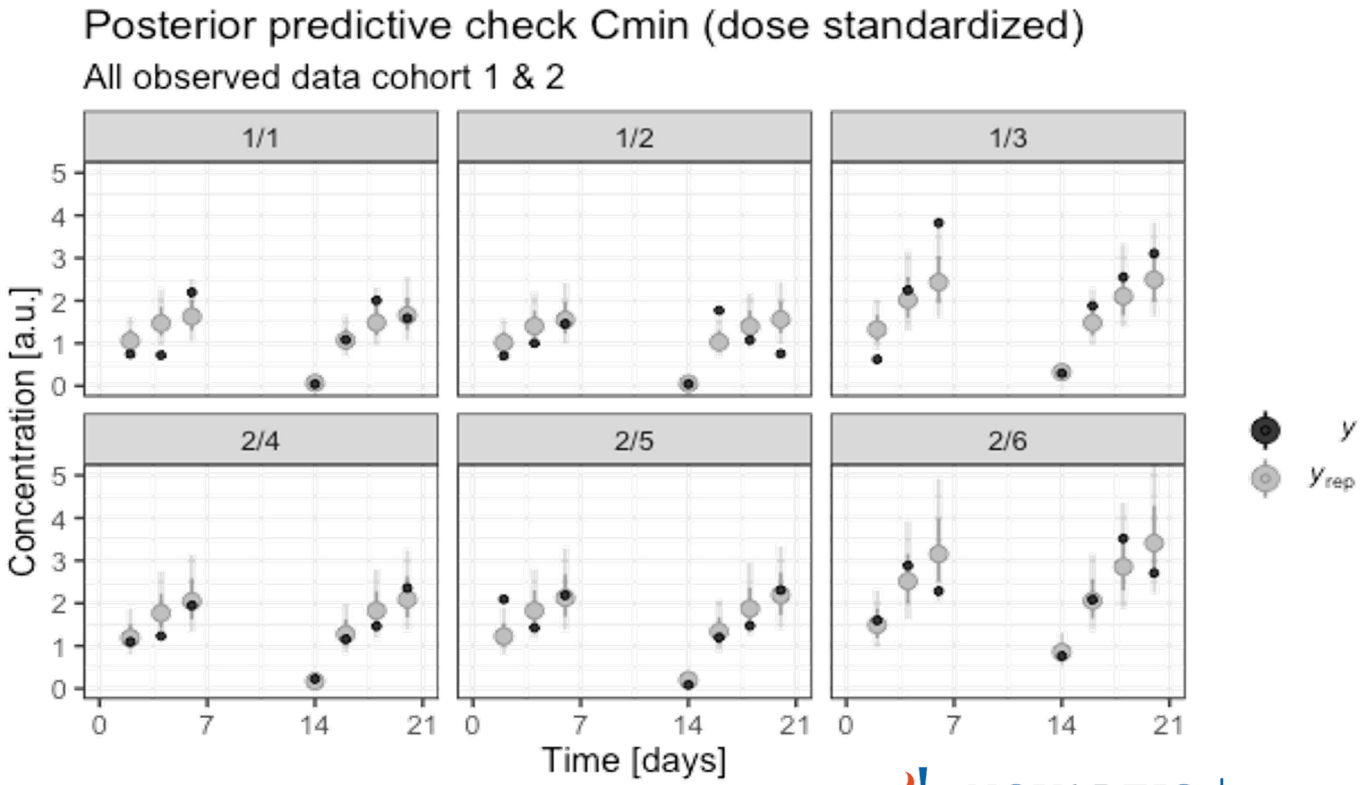
```
## Formula: obs_y | mi() ~ pk_conc(logFrel, logKa, logCl, logV, obs_time, dose_time, dose_amt,
dose_addl, dose_tau)
##          logFrel ~ 1
##          logKa ~ 1
##          logCl ~ 0 + mi(nca_lCl, patient_id)
##          logV ~ 0 + mi(nca_lV, patient_id)
##          nca_lCl | mi() + subset(ref_cmin) + index(patient_id) ~ 1
##          nca_lV | mi() + subset(ref_cmin) + index(patient_id) ~ 1
```

- Modeling multiple outcomes per patient while using 1 NCA estimate per patient
- `pk_conc` is a non-linear function provided to brms
- **`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

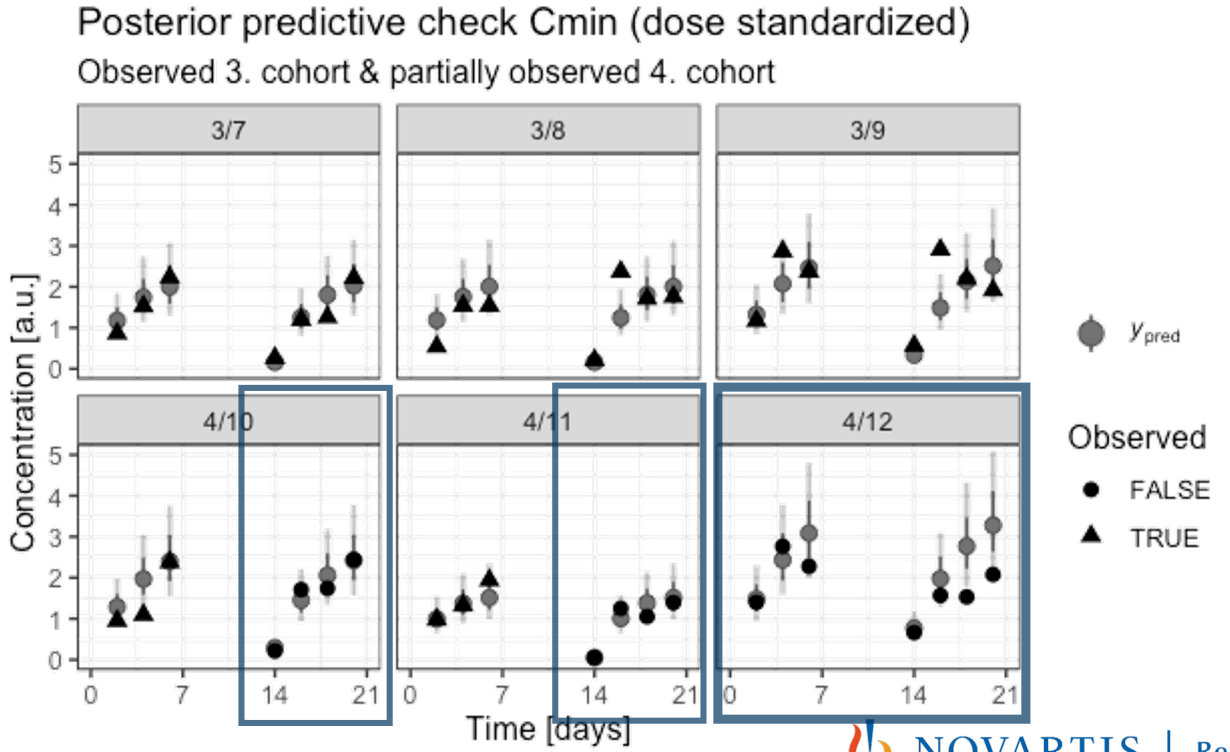
brms model run

```
## Formula: obs_y | mi() ~ pk_conc(logFrel, logKa, logCl, logV, obs_time, dose_time, dose_amt, dose_addl, dose_tau)
##          logFrel ~ 1
##          logKa ~ 1
##          logCl ~ 0 + mi(nca_lCl, patient_id)
##          logV ~ 0 + mi(nca_lV, patient_id)
##          nca_lCl | mi() + subset(ref_cmin) + index(patient_id) ~ 1
##          nca_lV | mi() + subset(ref_cmin) + index(patient_id) ~ 1
##    Data: pk_obs (Number of observations: 84)
##   Draws: 4 chains, each with iter = 2000; warmup = 1000; thin = 1;
##          total post-warmup draws = 4000
##
## Population-Level Effects:
##                                Estimate Est.Error l-95% CI u-95% CI Rhat Bulk_ESS Tail_ESS
## ncalCl_Intercept                  -2.28      0.11    -2.49    -2.06 1.00     5905     2858
## ncalV_Intercept                    1.97      0.08     1.81     2.13 1.00     5257     2799
## obsy_logFrel_Intercept             0.00      0.00     0.00     0.00   NA       NA       NA
## obsy_logKa_Intercept               0.69      0.00     0.69     0.69   NA       NA       NA
## obsy_logCl_minca_lClpatient_id     1.00      0.00     1.00     1.00   NA       NA       NA
## obsy_logV_minca_lVpatient_id       1.00      0.00     1.00     1.00   NA       NA       NA
##
## Family Specific Parameters:
##              Estimate Est.Error l-95% CI u-95% CI Rhat Bulk_ESS Tail_ESS
## sigma_obsy       0.34      0.03     0.29     0.41 1.00     4346     3010
## sigma_ncalCl     0.36      0.08     0.24     0.56 1.00     6124     2840
## sigma_ncalV      0.27      0.07     0.18     0.43 1.00     5574     2819
##
## 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



Model check for cohort 3 & partially observed cohort 4



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Summary

- 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-compartemental analysis (NCA) estimates as these are readily available during a running trial
  - Allow for missing data of outcome and/or NCA inputs
  - Accounts for individal level patient PK
- Simulated development prototype promising, but there is a lot to be done…

Thank you

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References

- Jacqmin, P., Snoeck, E., van Schaick, E. A., Gieschke, R., Pillai, P., Steimer, J. L., & Girard, P. (2007). Modelling response time profiles in the absence of drug concentrations: Definition and performance evaluation of the K-PD model. *Journal of Pharmacokinetics and Pharmacodynamics*, *34*(1), 57–85. https://doi.org/10.1007/s10928-006-9035-z
- Günhan, B. K., Weber, S., & Friede, T. (2020). A Bayesian time-to-event pharmacokinetic model for phase I dose-escalation trials with multiple schedules. *Statistics in Medicine*, *39*(27), 3986–4000. https://doi.org/10.1002/sim.8703
- Bürkner, P.-C. (2017). brms: An R Package for Bayesian Multilevel Models Using Stan. *Journal of Statistical Software*, *80*(1). https://doi.org/10.18637/jss.v080.i01

brms model prior

```
## Formula: obs_y | mi() ~ pk_conc(logFrel, logKa, logCl, logV, obs_time, dose_time,
dose_amt, dose_addl, dose_tau)
##          logFrel ~ 1
##          logKa ~ 1
##          logCl ~ 0 + mi(nca_lCl, patient_id)
##          logV ~ 0 + mi(nca_lV, patient_id)
##          nca_lCl | mi() + subset(ref_cmin) + index(patient_id) ~ 1
##          nca_lV | mi() + subset(ref_cmin) + index(patient_id) ~ 1
```

prior	class	resp	nlpar
normal(0, log(10)/1.64)	Intercept	ncalCl	
normal(0, log(10)/1.64)	Intercept	ncalV	
constant(log_frel)	b	obsy	logFrel
constant(log_ka)	b	obsy	logKa
constant(1)	b	obsy	logCl
constant(1)	b	obsy	logV
normal(0, 1)	sigma	obsy	
normal(0, 0.5)	sigma	ncalCl	
normal(0, 0.5)	sigma	ncalV	

Recovery of true model parameters