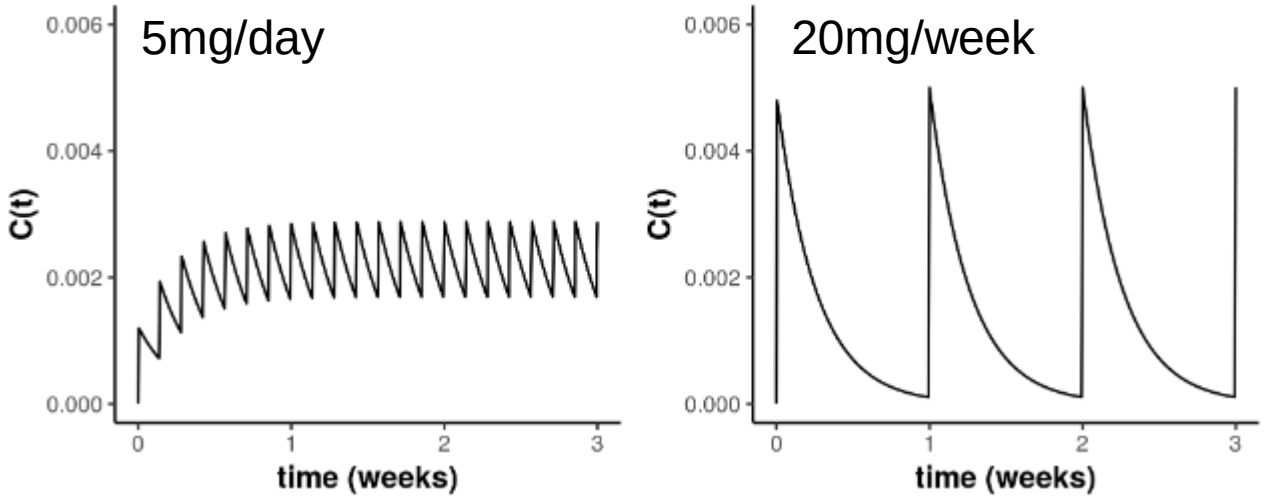
Advanced Exploratory Analytics, Analytics



Model-based extrapolation between dosing regimens

Varying regimens in oncology Phase I dose-escalation trials

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Basel, EFSPI Workshop
25th September 2018

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Acknowledgements

- Burak Kürsad Günhan
- Tim Friede
- Abdelkader Seroutou

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Oncology Phase I Dose-Escalation

- Disease severity mandates efficacy maximization
- Aim is to find maximum tolerated dose (MTD)
- Adaptive trial design
  - Sequential enrollment of small cohorts of 3-6 patients
  - Treatment for 1 cycle
  - Assessment of cycle 1 trial data once cycle 1 completes
  - Dose of next cohort must ensure patient safety
- Challenges for statistical approaches
  - Data sparsity
  - (Drug combinations)
  - Only consideration of a dose escalation... Dose regimens??

Everolimus Example

- Phase Ib dose-escalation in small-cell lung cancer

  Besse B, Heist RS, Papadmitrakopoulou VA, et al. A phase ib dose-escalation study of everolimus combined with cisplatin and etoposide as first-line therapy in patients with extensive-stage small-cell lung cancer. Ann Oncol. 2014

- Explored two regimens
  - Daily dosing: 2.5 mg/day, 5.0 mg/day
  - Weekly dosing: 20 mg/week, 30 mg/week
- Each regimen analyzed separately
- MTD declared for daily 2.5 mg

Regimen	Dose [mg/admin]	N	DLT
daily	2.5	4	2
daily	5.0	6	3
weekly	20.0	5	0
weekly	30.0	13	4

Bayesian Logistic Regression Model (BLRM)

- Statistical model
  - Data: # of patients with DLT r_i per cohort with n_i patients at dose d_i
  - Binomial likelihood with DLT probability $\pi_i(d_i)$
  - Logit-link regression: intercept, positive slope with $\log\left(\frac{d_i}{d^*}\right)$
- Escalation with overdose control (EWOC)

$$P(\pi(d) \geq 0.33) < 0.25$$

- Regimens out of scope
- Ad-hoc limitations
  - Need for down-weighting ⇔ efficiency loss
  - 2-step approach leads to one BLRM per regimen

Regimen	Dose [mg/admin]	Dose [mg/day]	N	DLT
daily	2.5	2.50	4	2
daily	5.0	5.00	6	3
weekly	20.0	20/7 =2.86	5	0
weekly	30.0	30/7 =4.29	13	4

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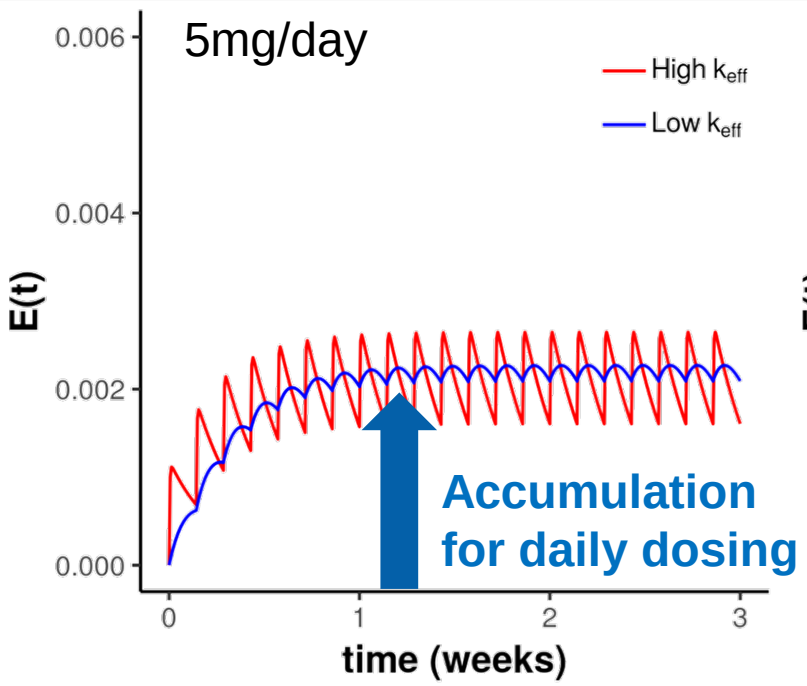
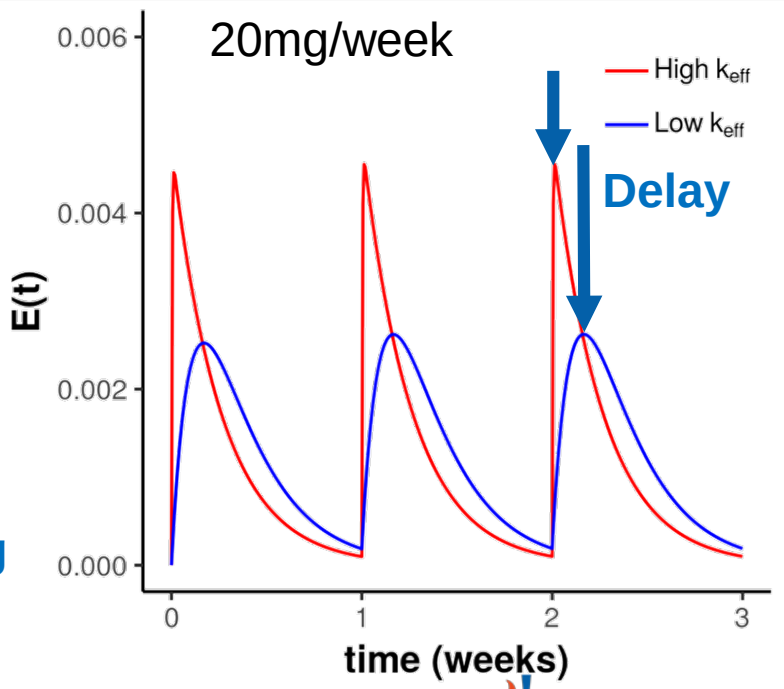
Time to event pharmacokinetic model (TITE-PK)

- Time to first event model using an *exposure metric*
- Exposure metric based on drug *pharmaco**kinetics***
- Use of planned regimen and known PK parameters





TITE-PK model
Time-varying Poisson process

- Hazard at time t proportional to exposure metric $E(t)$

$$\boldsymbol{h(t) = \beta\, E(t)}$$

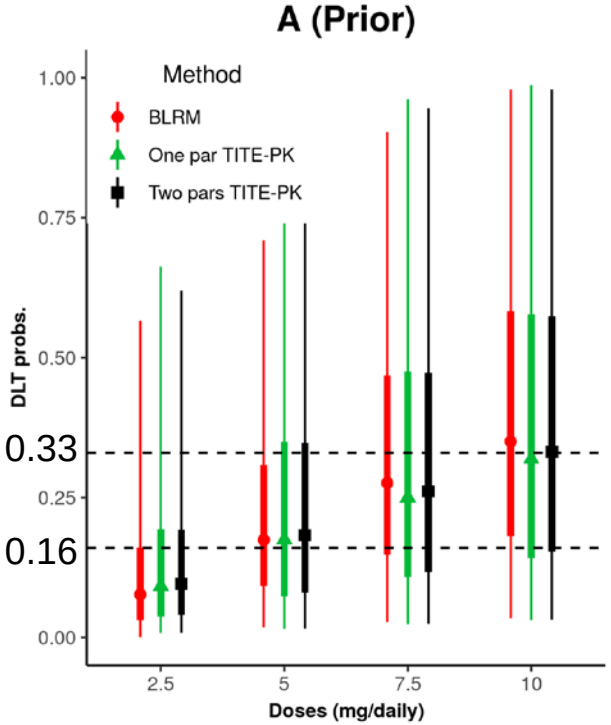
$$H(t) = \int_0^t h(t')\, dt' = \beta\, \mathrm{AUC}_E(t)$$

$$S(t) = P(T > t) = \exp\big(-H(t)\big)$$

- Follow-up until time t^* end of cycle 1
- Dosing regimen
  - Dose d
  - Frequency of dosing f
- EWOC metric *for cycle 1 of a regimen*

$$P(T \le t^* | d, f) = 1 - P(T > t^* | d, f)$$
$$= 1 - S(t^* | d, f)$$

Everolimus Daily Regimen Reanalysis Daily->Weekly Switch



- All models have matched priors
- Posteriors with daily data
- Posteriors with daily+weekly data

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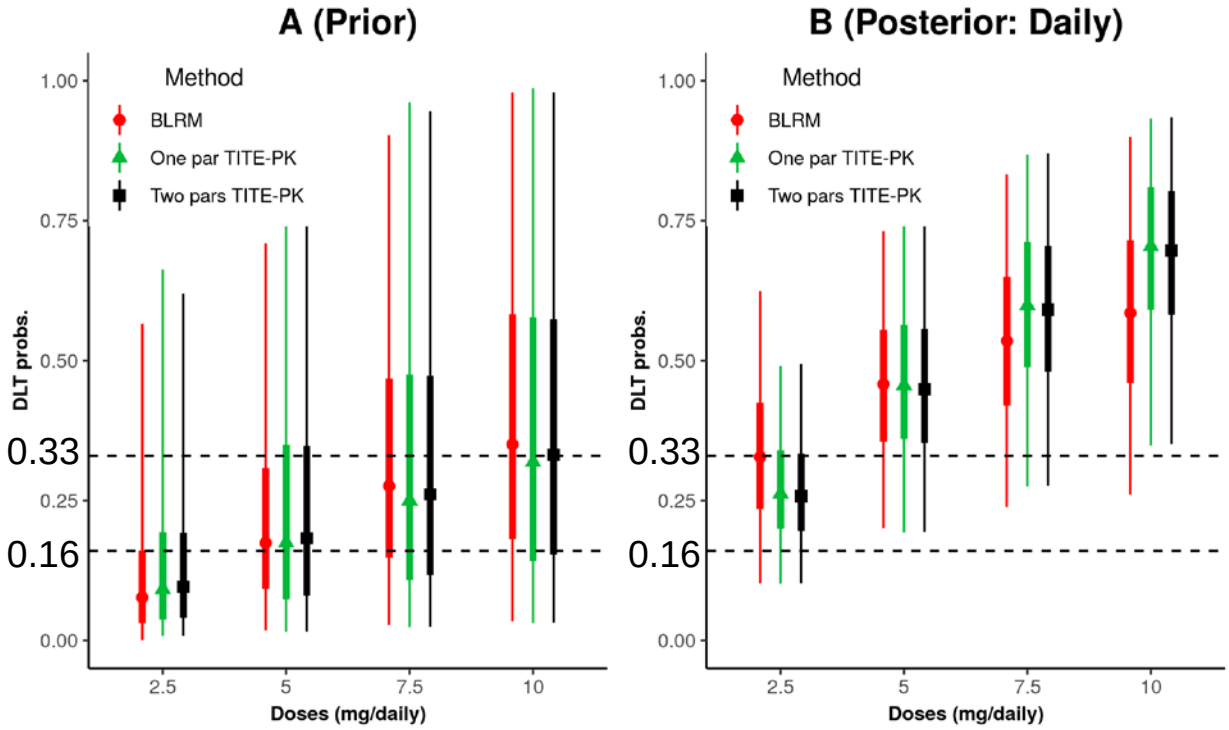
Everolimus Daily Regimen Reanalysis Daily->Weekly Switch



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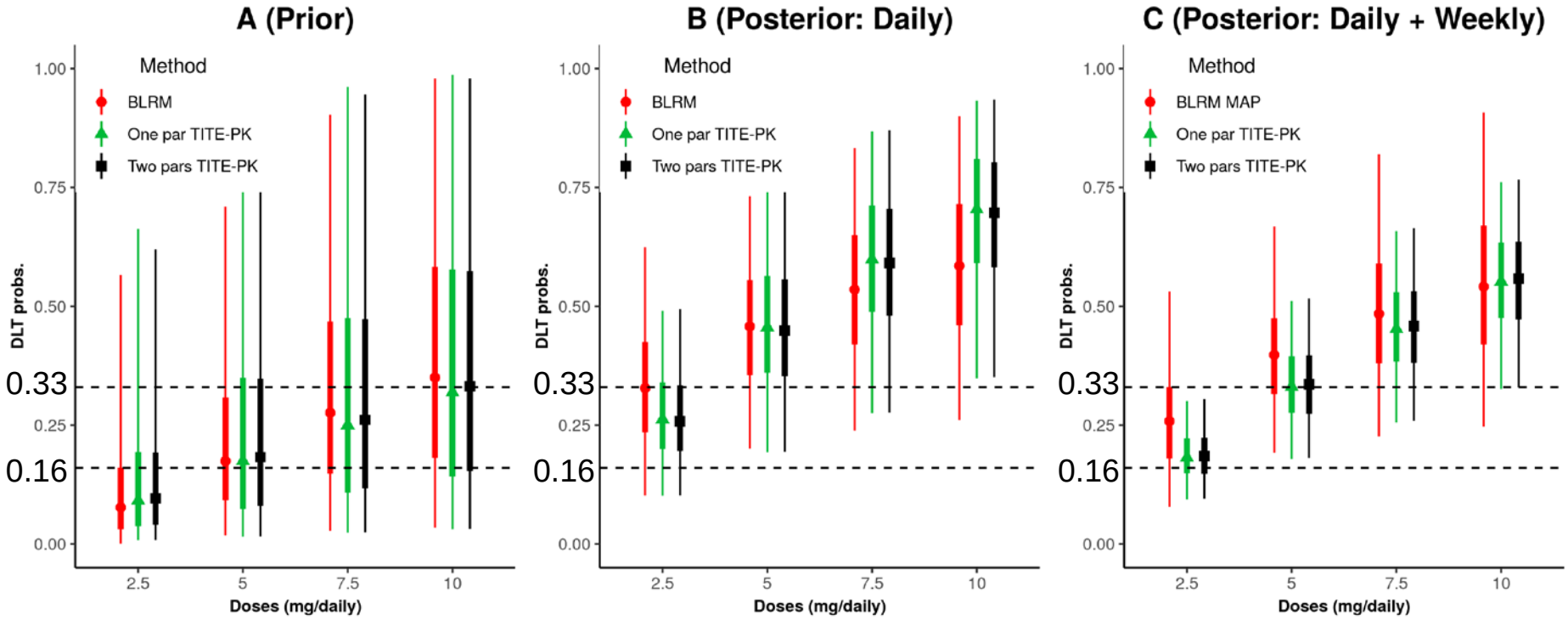

- All models have matched priors
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Conclusions

- Model based extrapolation
  - Enables more efficient use of trial data
  - Potentially enhances available historical data (collected under different regimens)
  - Requires assumptions here: Pharmacokinetic principles
- Advantages of TITE-PK
  - No more need for ad-hoc approaches used to combine different dosing regimens ⇔ easier to apply + greater statistical efficiency
  - Greater flexibility for escalation trials
  - Coherent (single-model) dose-toxicity model for multiple regimens
  - Operationally feasible

Thank you

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- Besse B, Heist RS, Papadmitrakopoulou VA, et al. A phase ib dose-escalation study of everolimus combined with cisplatin and etoposide as first-line therapy in patients with extensive-stage small-cell lung cancer. Ann Oncol. 2014;25(2):505-511. doi:10.1093/annonc/mdt535.
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