Tailoring dose escalation designs to early clinical development goals

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BBS seminar "Innovative model-based dose escalation designs: What next?“

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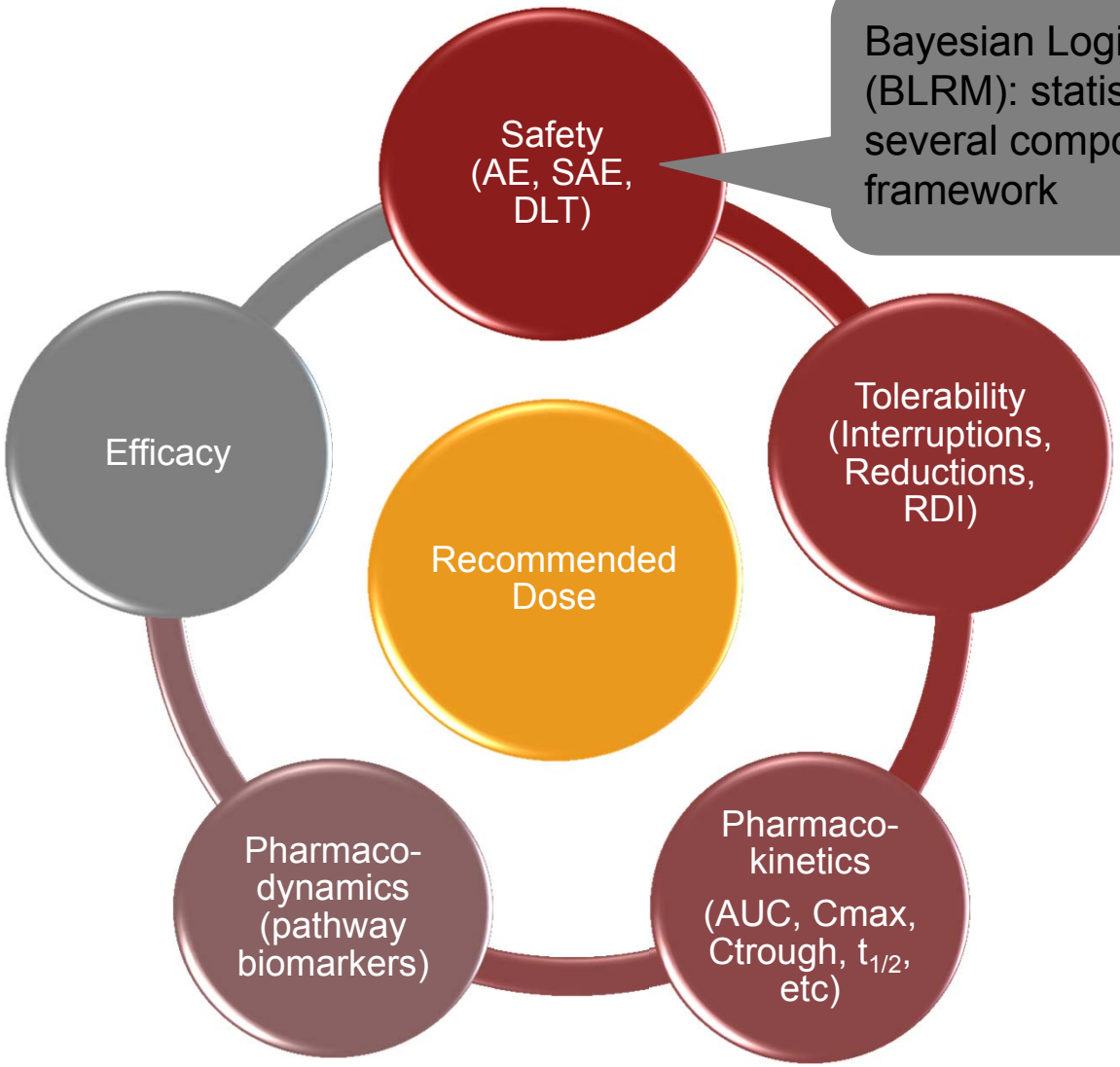
Acknowledgments

My Novartis colleagues (mainly from TCO Biostatistics and Methodology group) who over the last 10 years have continuously implemented innovative PhI dose-escalation designs and developed new methodology.

Agenda

1. Novartis's approach: learnings from the past 10 years
2. Early clinical development goals and matching designs implemented at Novartis
3. Conclusion

Integrative approach, based on totality of evidence



Bayesian Logistic Regression Model (BLRM): statistical inference is one of several components of decision-making framework

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Comprehensive analysis of Oncology Early Development trials

- Motivated by FDA's request to share experience (Feb 2016)
- Since 2006 Novartis Oncology Early Development initiated* 99 trials, out of which 79 have a dose escalation component using BLRM approach
- Analysis conducted to understand pattern of triggers that limited dose escalation increments to < 100% (DLTs, non-DLT AEs, non-toxicity reasons)
- 46 dose-escalations in scope for analysis
  - Studies completed or for which a MTD/RDE was already declared
  - 25 single agent and 21 combination (novel-novel and novel-marketed) dose-escalations

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Key findings on safety of patients

- **11% of patients experienced a DLT**
  - 2200 patients treated in 46 dose-escalations. 249 DLTs observed.
  - In simulation studies*, average observed DLT rate across a wide range of dose-DLT scenarios is around 20%.
- **7% of patients treated above MTD**
  - 18/46 (39%) dose-escalations enrolled 149 patients above MTD
  - 51 DLTs observed corresponding a pooled DLT rate of 34%
- Key safety decisions were taken in 35 trials:
  - Escalation limited by BLRM (18 trials)
  - Slow down escalation (<100%) when observing related non-DLT AEs that prevented risky escalation beyond MTD in next cohort (10/11 trials)
  - Continue to escalate safely by 100% (i.e. below MTD) despite observing related non-DLT AE's (6 trials)
- These results indicate Novartis integrative approach based on totality of evidence (which includes statistical inference) ensures safety of patients beyond what would be expected when decision only rely on DLT data

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* Neuenschwander B, Branson M, Gsponer (2008)

Added value of statistical inference component

- Bayesian design is efficient and flexible and adds value to decision making, especially when supportive data are not conclusive
- Approach can be adapted to various situations to be made protocol/drug specific in order to meet the evolving needs of early clinical development

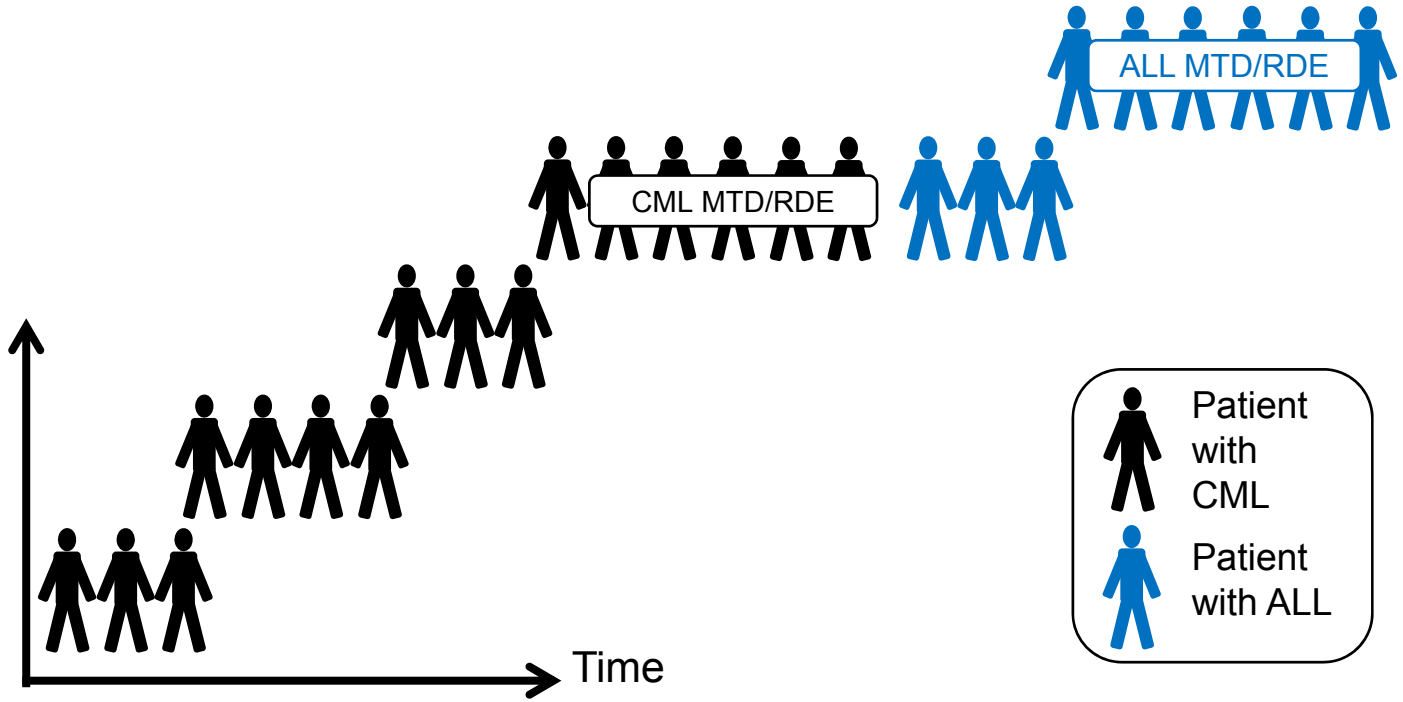
Early clinical development goals

- Complexity of trials has increased and is expected to increase further: Goal is no longer to identify s.a. MTD in unselected population.
- Single agent and many combinations treatments (e.g. dual novel-novel, triple) explored early and simultaneously, sometimes within the same trial.
- Robust integration of prior information and co-data (from relevant on-going trials) to increase efficiency. Robust information sharing within trial.
- Potential development paths are varied -> multiple combinations (‘umbrella design’) and/or multiple sub-populations (‘basket’ designs). This may includes ‘special’ designs such as ‘resistance’ trials to explore strategies to address primary/secondary resistance.
- Need to address questions around optimal regimen, formulation, food effects and drug-drug interaction potential for combinations
- Going beyond modelling of Cycle 1 DLT
  - Late-onset toxicities
  - Dose–PD/PK/clinical activity relationships

Different MTD/RDE for different indications

Establish MTD/RDE in CLL and allow further escalation in ALL since dose required to achieve clinical activity may be different to that for patients with CML

Methodology: separate BLRM for ALL incorporating data from CML

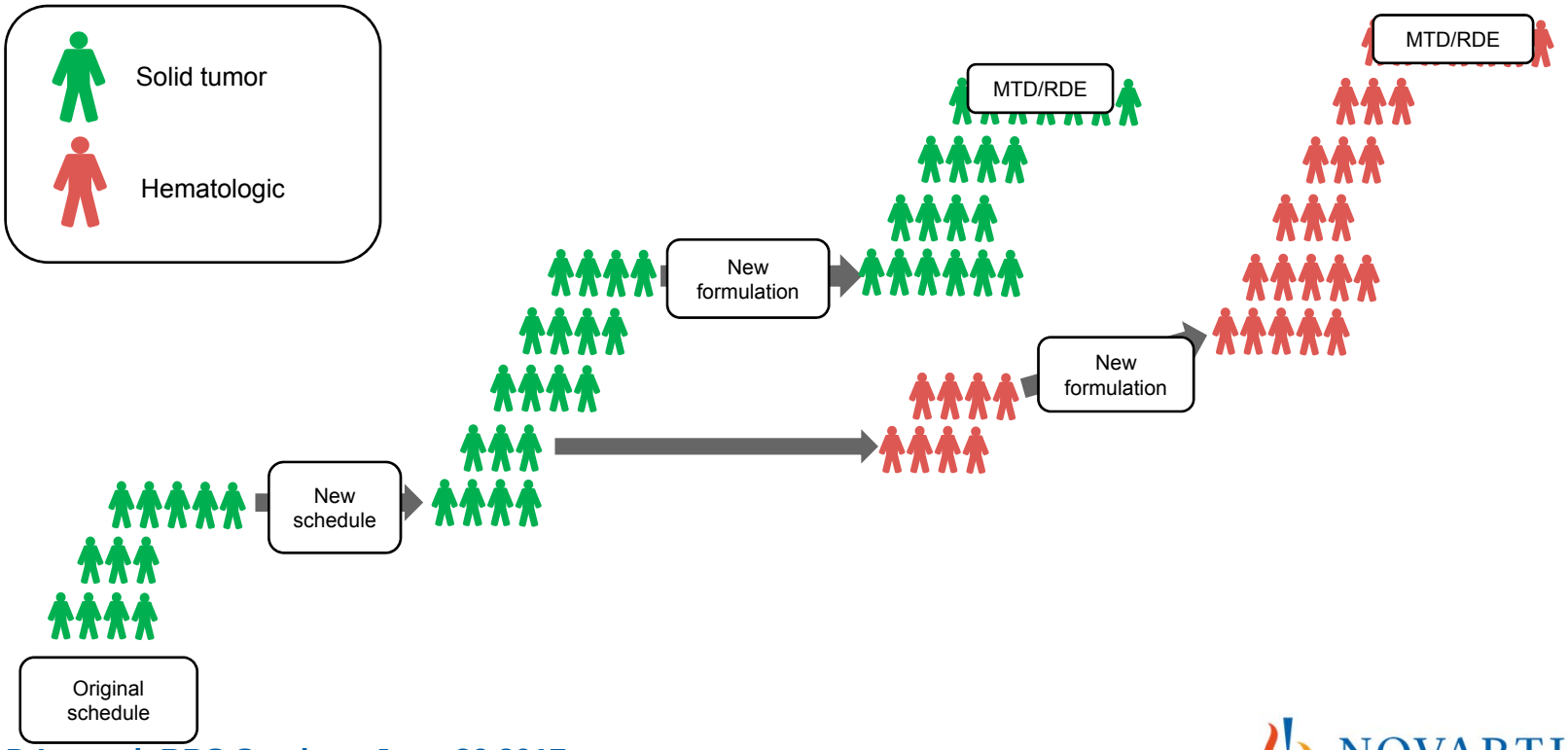


ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia

Different schedules, populations and formulations

MTD/RDE is determined separately for solid tumor and hematologic patients, using the appropriate schedule and final formulation

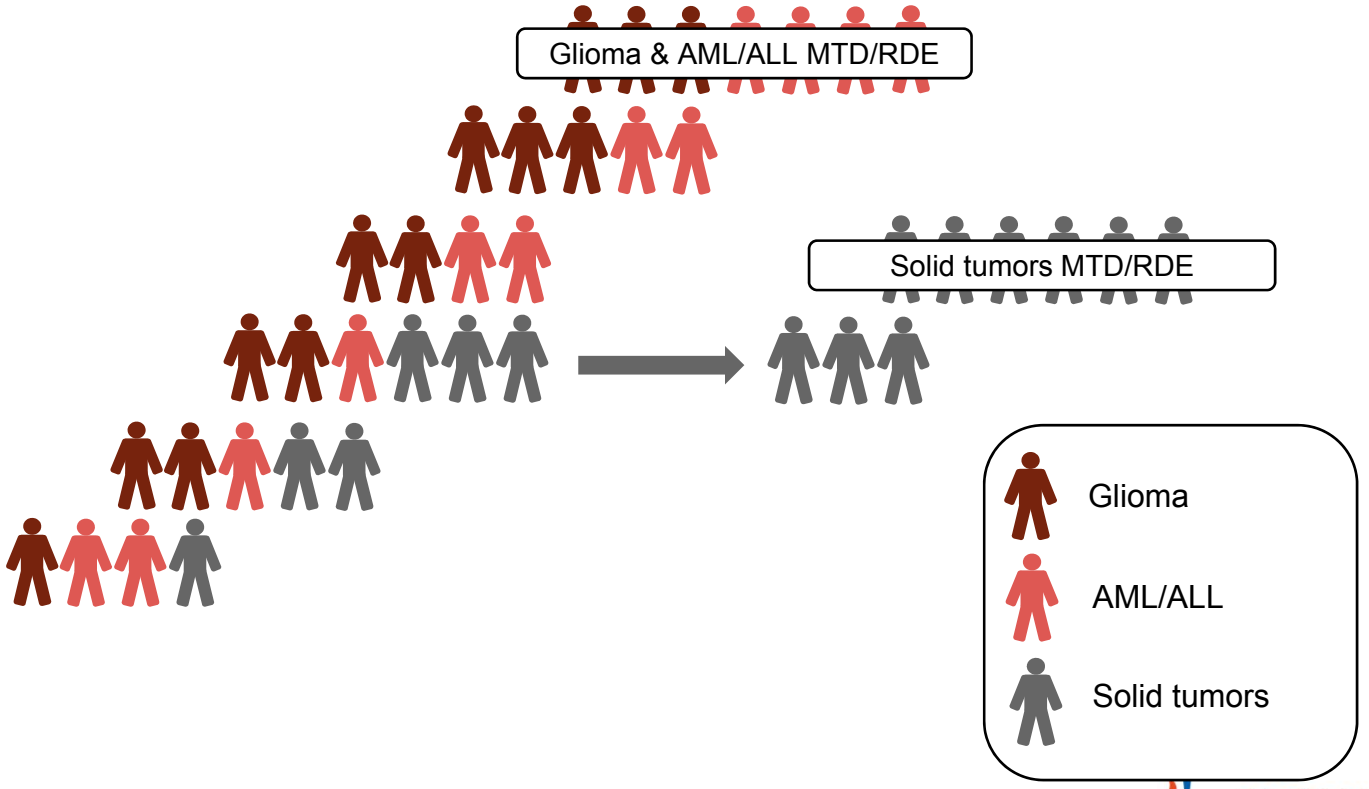
Methodology: different DLT definitions, separate BLRM for hematologic patients incorporating data from solid tumor patients



Allowing for different MTD/RDE for different indications

If evidence emerges that indications have different dose–DLT relationships, then the dose–DLT relationship for each indication may be explored separately

Methodology: hierarchical version of BLRM informed by between-indication heterogeneity observed in DLT data (EXNEX: tailored exchangeability)



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AML, acute myeloid leukemia.

EXNEX: Tailored Exchangeability*

- Bayesian hierarchical model used to combine information across different strata
- Exchangeability (EX) allows sharing of information across strata and leads to shrinkage of estimates towards a common mean → compromise between no pooling and complete pooling
- What if there are one or several strata that are dissimilar from the rest?
- EXNEX is an extension/robustification of EX, which allows for exchangeability/non-exchangeability.

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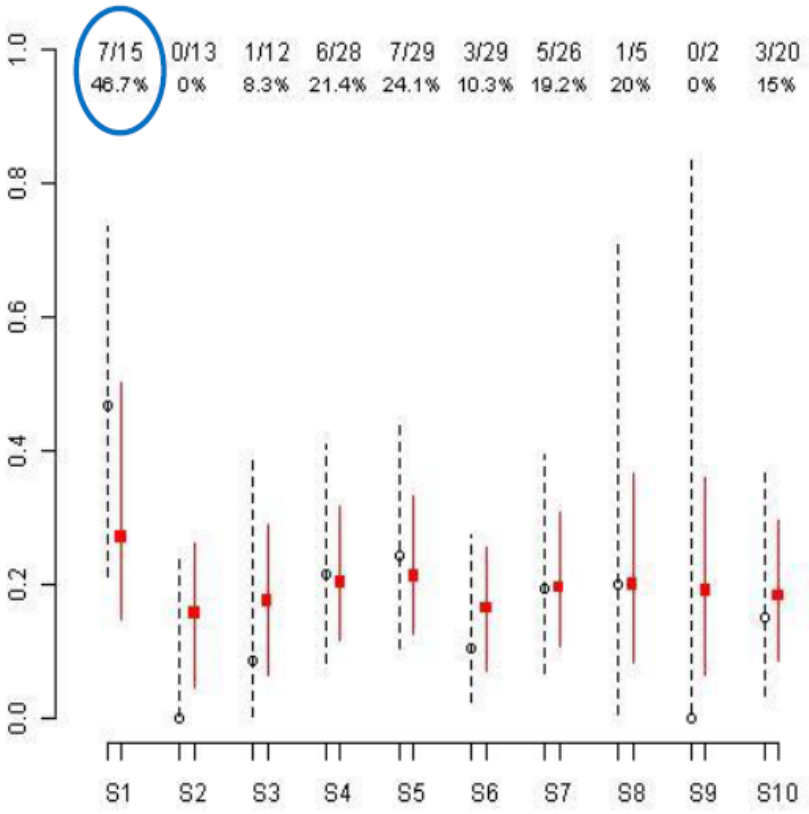
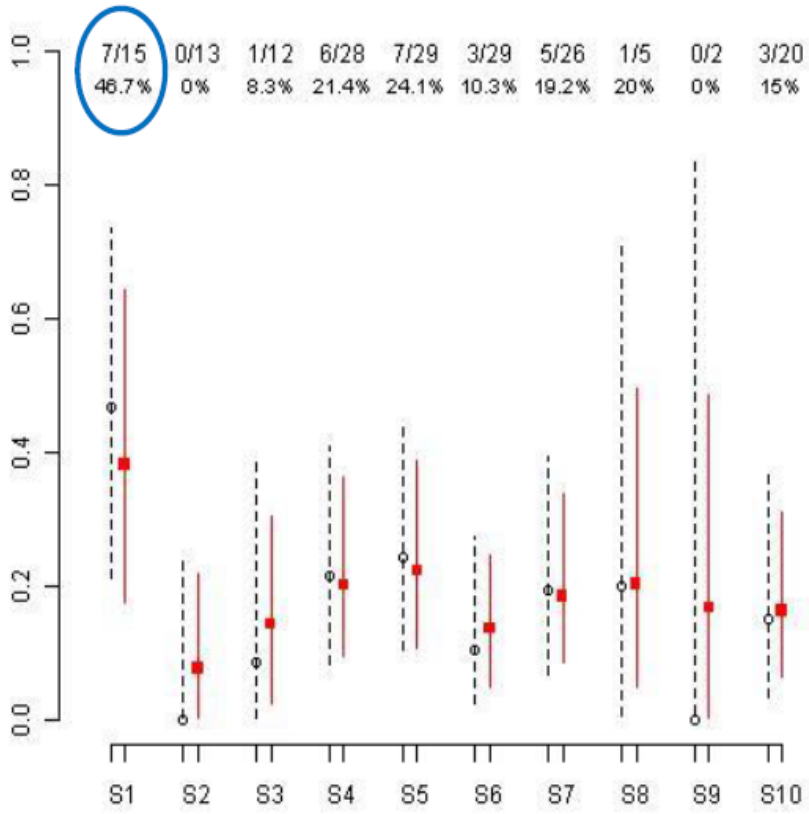
* Neuenschwander, Wandel, Roychoudhury, Bailey (2015)

Example of EXNEX analysis

- - - (stratified) — *EX: Left Panel, EXNEX: Right Panel*





EX: fairly strong borrowing.
Too much shrinkage for subtype1?

EXNEX: borrowing for 2-10
Type 1 similar to stratified analysis!

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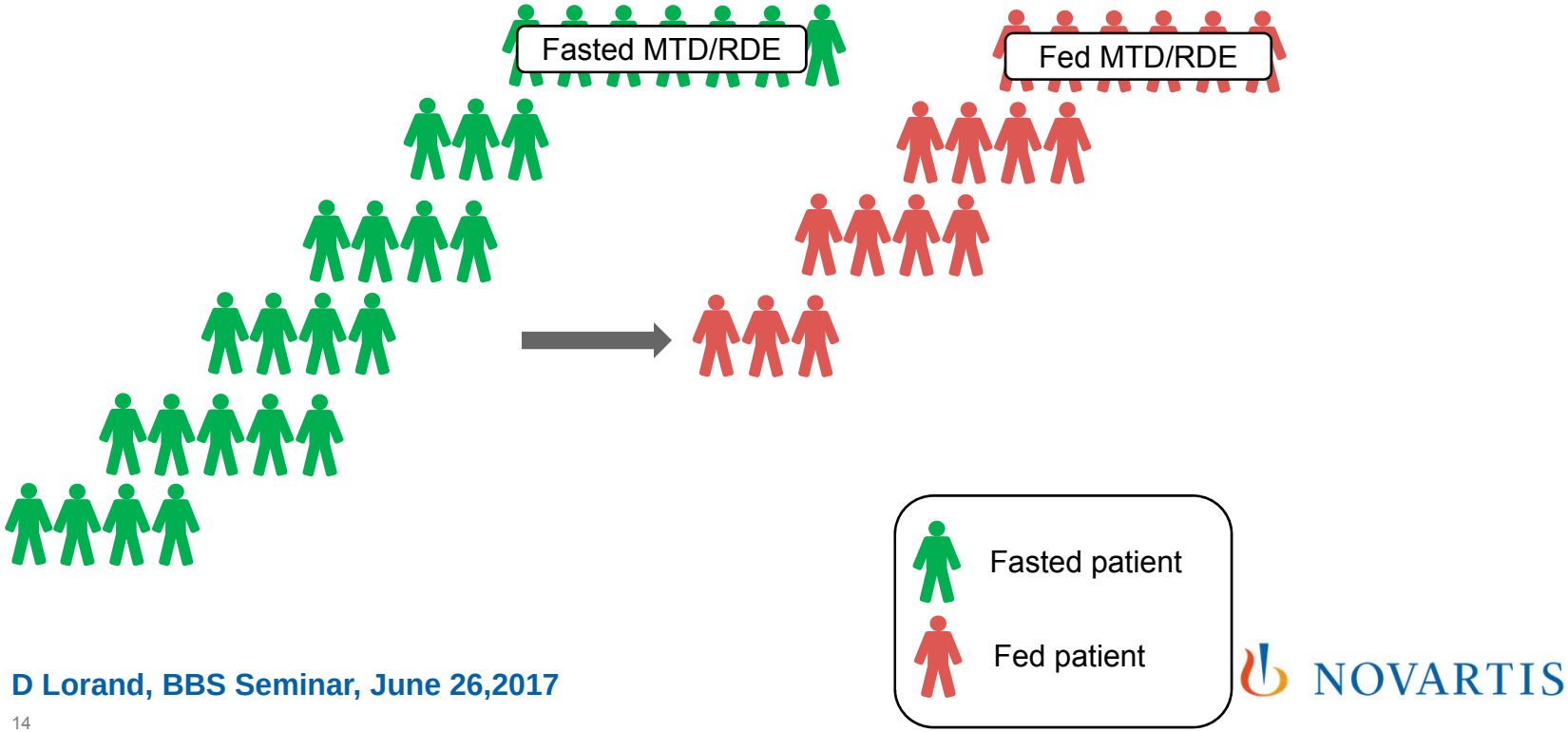
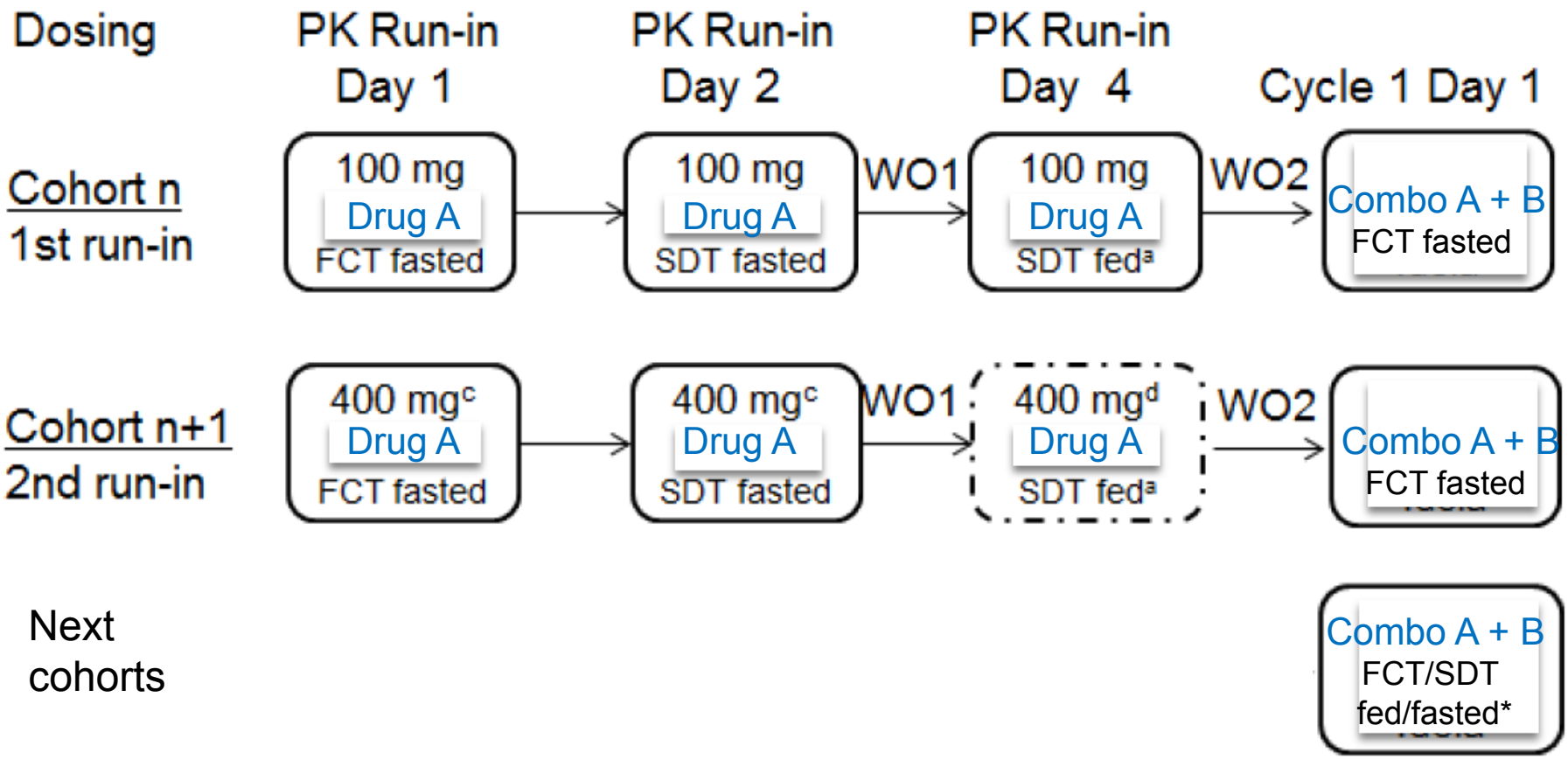
Different MTD/RDE for fasted and fed dosing

Does not replace a formal food effect study, but allows for an preliminary assessment of clinically relevant food effect with PK food-effect sub study

Methodology: flexible BLRM for determination of a different MTD/RDE for fasted and fed regimen if appropriate (re-scaling based on relative bioavailability estimated from food-effect PK (sub)study)



Example of design with PK sub-study

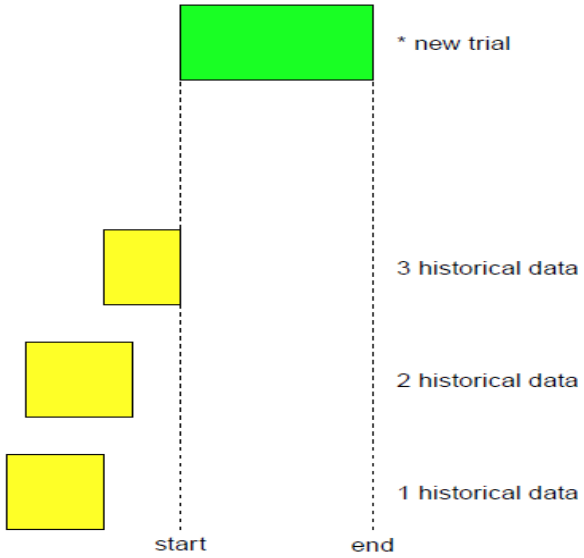


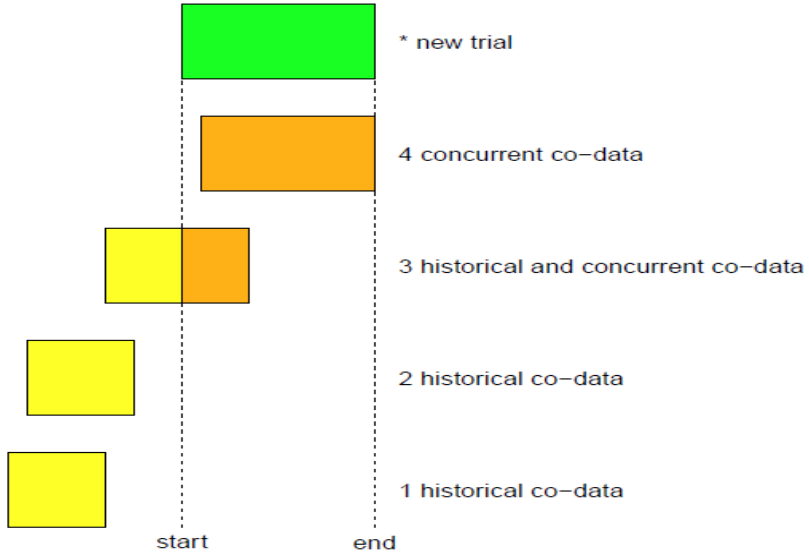
* Decision also driven by additional data from Drug A s.a. study

Integration of co-data* (from relevant on-going trials)

- actual trial
- + 3 trials with historical *co-data*

- ...trial 3 is ongoing...
- and trial 4 hasn't started yet
- → concurrent *co-data*





Example of application: dose-escalation of a combination while s.a. dose-escalation trials are still on-going

Methodology: Meta-Analytic-Combined (MAC) approach is a meta-analysis of all co-data and current trial data

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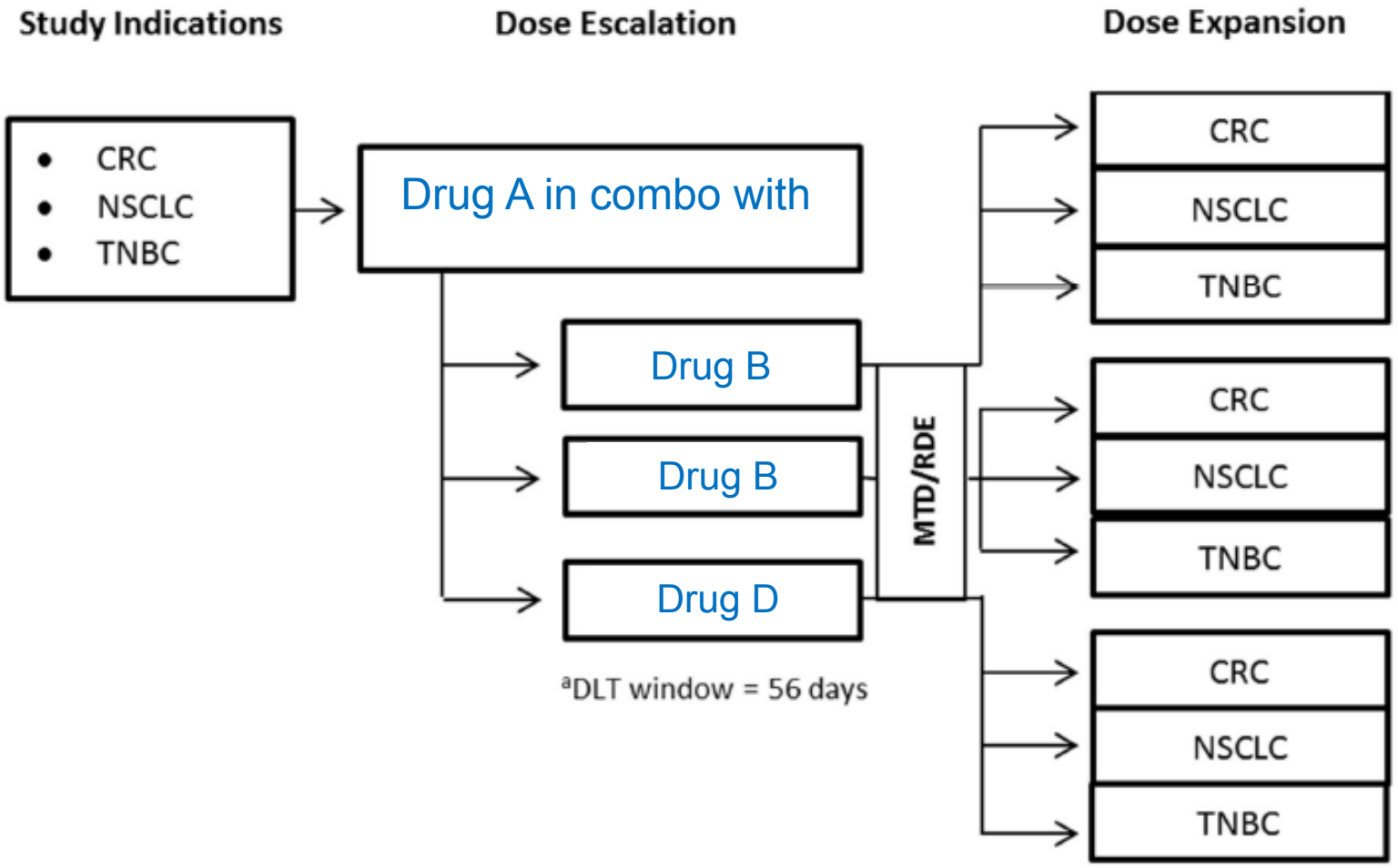
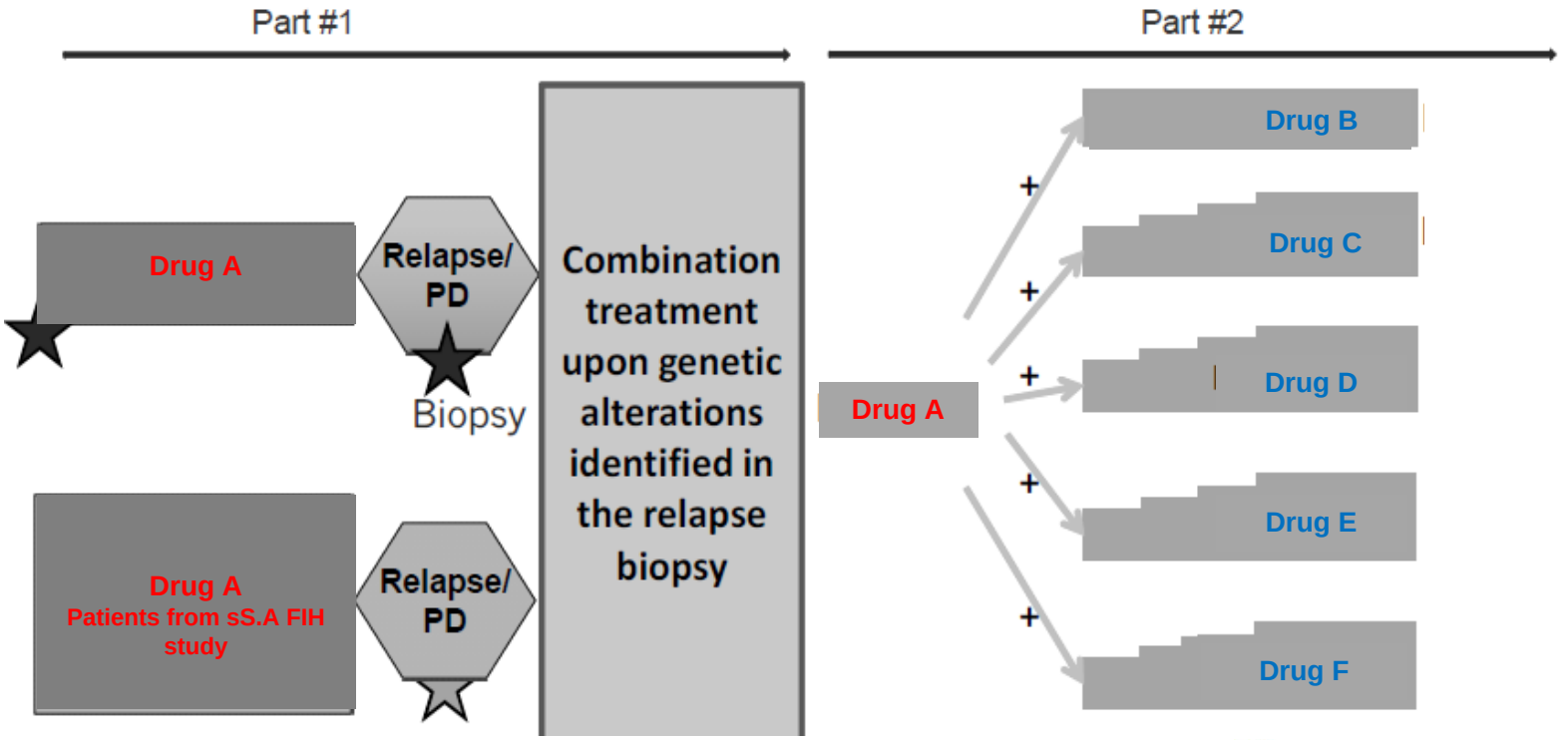
* Neuenschwander, Roychoudhury, Schmidli (2016)

Multiple combinations, multiple indications



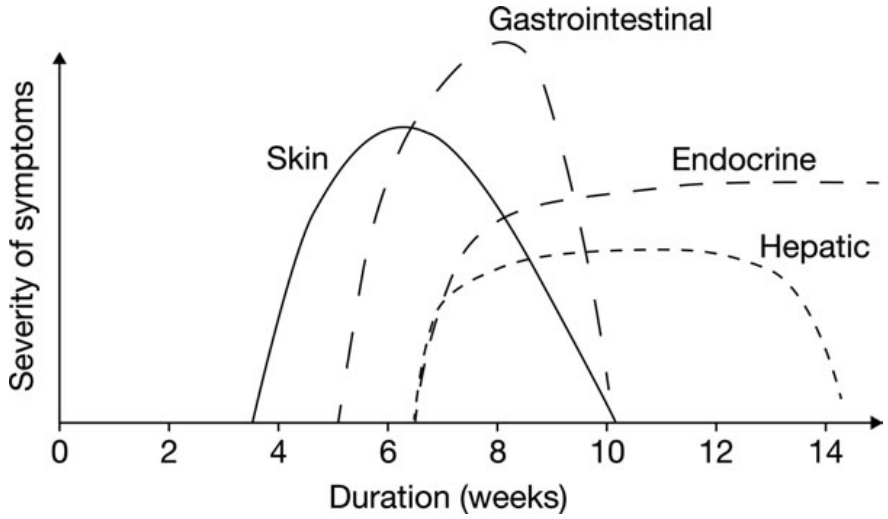
‘Resistance’ design

- Can progression with Drug A be reversed upon addition of another targeted agent?
  → Bayesian analysis of ORR for each escalation arm
- Patients progress quickly and rapid escalation (including intra-patient escalation after 1st cycle) allowed using BLRM methodology (one model for each arm)
- Trial conduct is challenging, e.g. screening prior entering Part 2

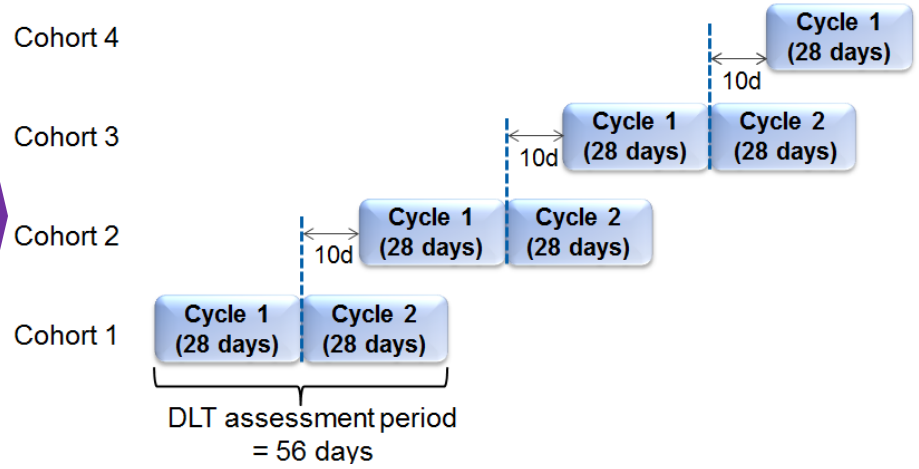


Incorporating late-onset toxicities

Example of late onset of irAE



Efficient dose-escalation scheme



- Efficient dose-escalation scheme supported by a 'by- cycle' BLRM from which cumulative risk is derived
- A dose will not be tested in the Cycle 2 before having being studied successfully in Cycle 1. Any dose in Cycle 2 is always equal to or lower than the dose used in Cycle 1.

Incorporating Bayesian modeling of PK data (PK) in decision making*

- Leverage PK information gained from single-agent trials as well as preclinical knowledge on PK DDI to learn faster about DDI in patients
- Combine outputs from Bayesian modeling of dose–DLT and dose–exposure relationships to identify dose with acceptable safety and optimal exposure of both agents
- Implemented in trials where PK DDI was anticipated at design stage and observed during the conduct of the trials
- Other applications/opportunities
  - Used for a single agent where the co-primary goal (along with assessing safety) was to match the exposure from a competing drug
  - Integration of preclinical information for better characterization of the PK model at early stage of dose-escalation and for efficient and optimal dose selection. Bayesian mechanism-based (rather than empirical) PK model.

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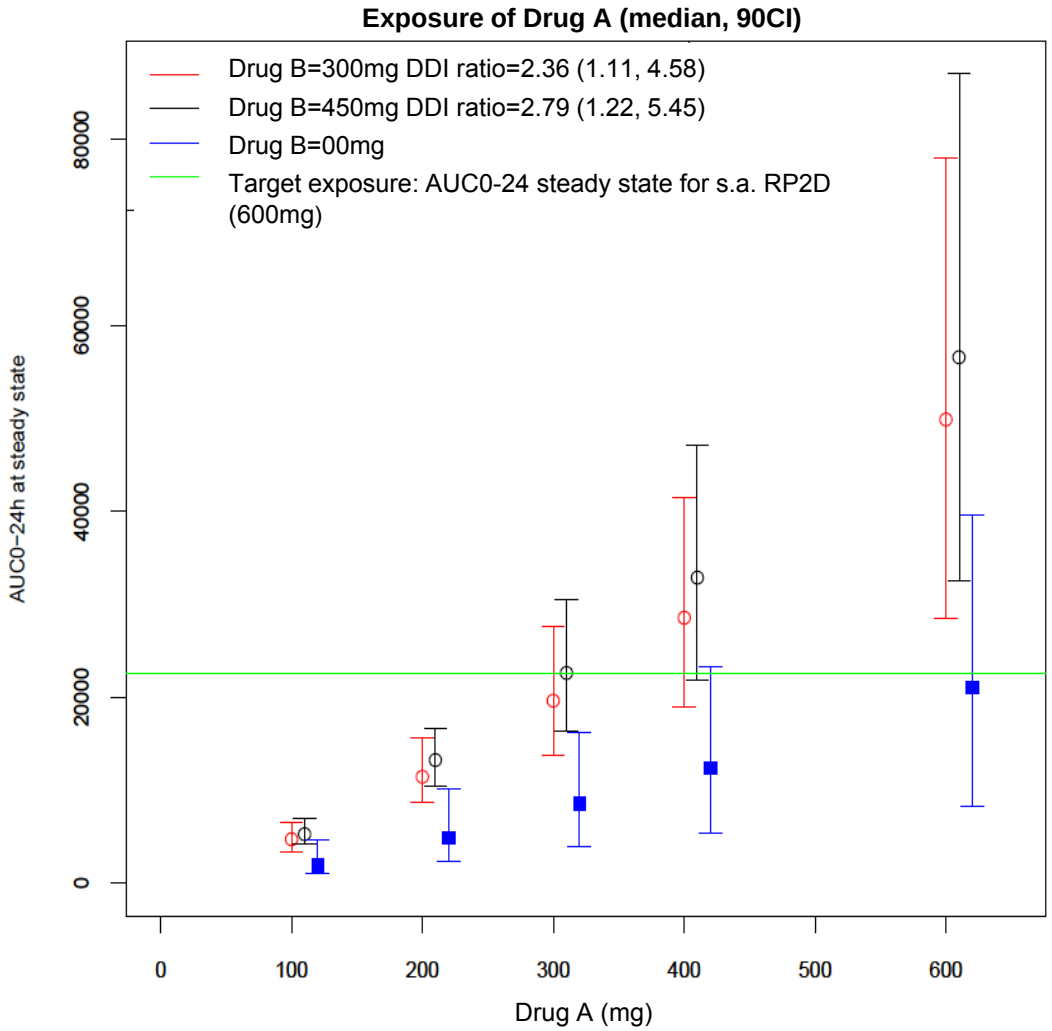
* Presented at BBS Seminar (April 2015), Cotterill, Lorand, Wang, Jaki (2015)

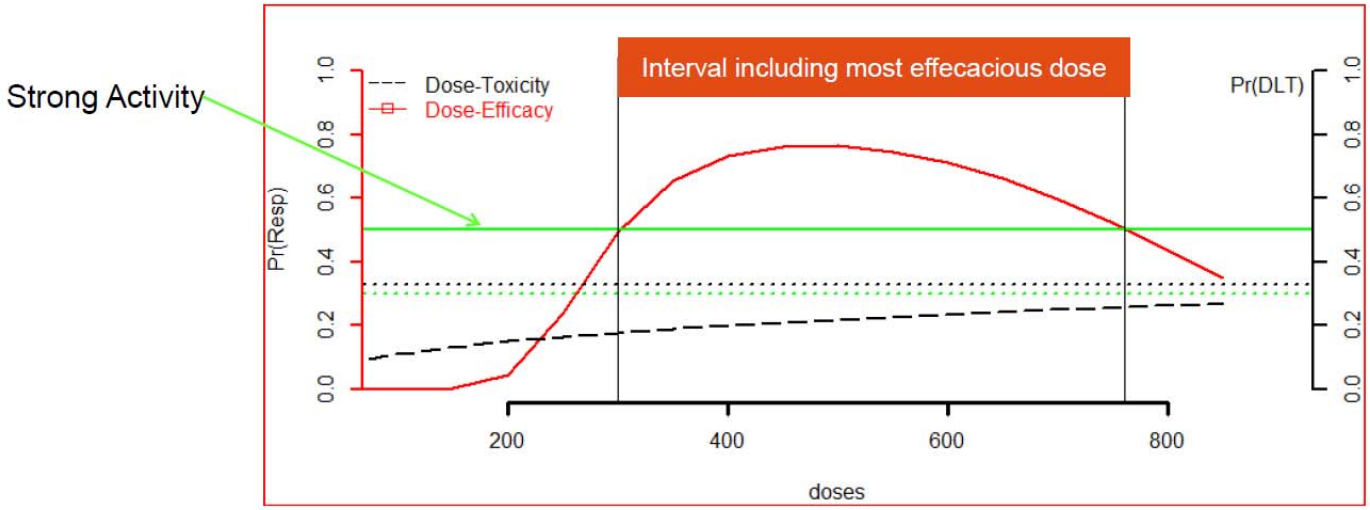
Model estimates from an on-going trial



- Drug A exposure expected to increase when combined with Drug B
  - Drug A: time dependent inhibitor (TDI) of CYP3A4
  - Drug B: primarily metabolized by CYP3A4 and is also TDI of CYP3A4
- 27 patients treated
- 8 cohorts across 4 dose-combinations (100-300mg for Drug A and 300-450mg for Drug B)
- No DLT observed
- Model-based estimation of exposure and DDI ratio were key for decisions

Incorporating Bayesian modeling of PD or clinical efficacy*

- Similar to PK application but different model
- BLRM + Bayesian model for dose-activity relationship + modelling of association structure using cross-ratio model (Dale 1986)



- Other opportunities: (Bayesian) mechanism-based PD model leveraging preclinical and literature information, e.g. model receptor occupancy for anti-body drug to inform escalation decision (bigger escalation jump from low starting dose up to pre-defined level and then smaller escalation steps to explore therapeutic range).

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* Aout, Seroutou (2017)

Conclusion

- Complexity of PhI dose-escalation trials has increased and is expected to increase further – dealing with complexity has become the routine
- Trials need to address early and simultaneously multiple aspects of early development
- This leads to opportunities to implement innovative designs requiring novel and efficient statistical methodology
- Availability of good surrogate endpoints for clinical activity may lead to next major evolution in the designs:
  - Today: limitations remain for such endpoints to influence decisions (endpoints not known or not well understood, no reliable assay available, operational challenges for real-time sample and data analyses)
  - Tomorrow: more data for better understood endpoints will be available. This will increase the need to statistical inference and quantitative decision making

References

- Aout, A, Seroutou, A. (2017). Joint Modelling of efficacy and Toxicity in oncology Phase I dose escalation studies. In preparation
- Cotterill, A., Lorand, D., Wang, J. and Jaki, T. (2015), A practical design for a dual-agent dose-escalation trial that incorporates pharmacokinetic data. Statist. Med., doi: 10.1002/sim.6482.
- Dale, JR. (1986). Global Cross-ratio Models for Bivariate, Discrete, Ordered Responses. Biometrics. 42, 909-917
- Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Statistics in Medicine 2008; 27:2420–2439.
- Neuenschwander B, Matano A, Tang Z, Roychoudhury S, Wandel S and Bailey S: A Bayesian Industry Approach to Phase I Combination Trials in Oncology in Zhao W and Yang H. Statistical Methods in Drug Combination Studies. Chapman & Hall/CRC, 2014.
- Neuenschwander, B., Wandel,S., Roychoudhury, S., and Bailey, S. (2015), “Robust Exchangeability-Nonexchangeability Designs for Early Phase Oncology Trials With Multiple Strata,” Pharmaceutical Statistics, 15, 123–134
- Beat Neuenschwander, Satrajit Roychoudhury & Heinz Schmidli (2016) On the Use of Co-Data in Clinical Trials, Statistics in Biopharmaceutical Research, 8:3, 345-354, DOI: 10.1080/19466315.2016.1174149
- Schmidli H, Gsteiger S, Roychoudhury S, O’Hegan A, Spiegelhalter D, and Neuenschwander B (2014), Robust Meta-Analytic-Predictive Priors in Clinical Trials with Historical Control Information. Biometrics 70:1023-1032