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Bayesian adaptive trials in Oncology drug development

Maximizing the synergy between Statisticians and Pharmacometricians

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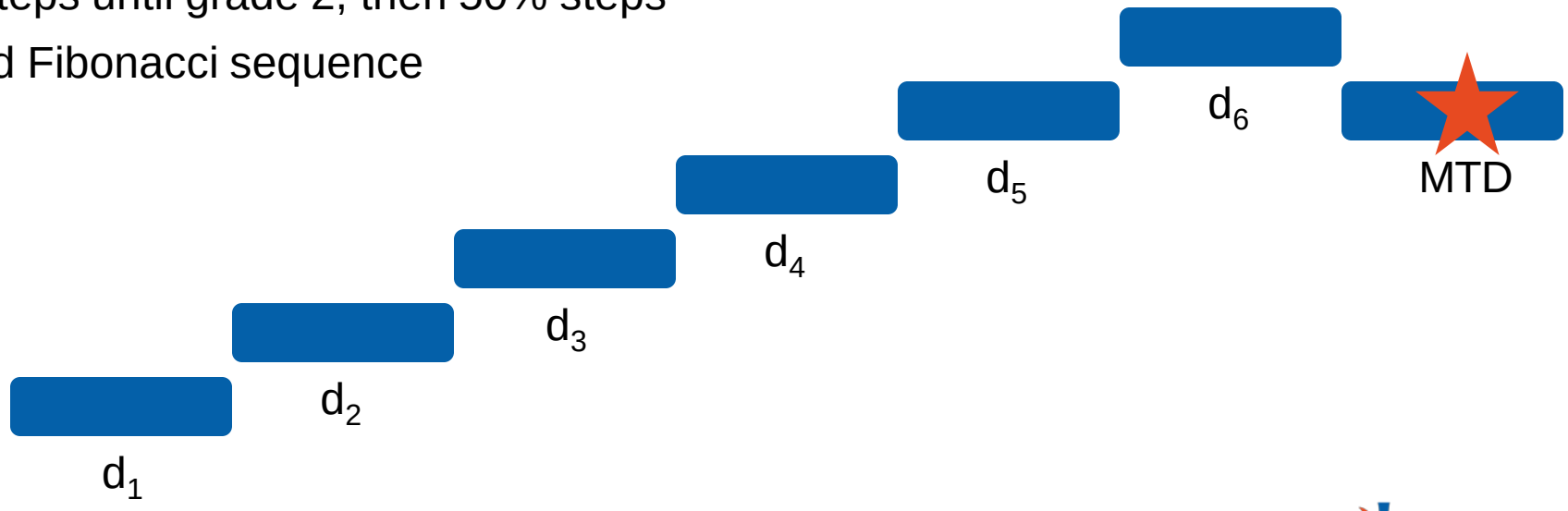
Dose escalation introduction

- Preclinical studies provide information on:
  - Starting dose (S9)
  - Estimated exposures for on- and off-target toxicity
  - Potential shape of dose-toxicity relationship
- Predefine dose levels for study
  - 100% steps until grade 2, then 50% steps
  - Modified Fibonacci sequence



Finding maximum tolerated dose

Phase I dose escalation

e.g., 3+3 design

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Dose escalation using safety

If DLT is the primary endpoint – you can still do MUCH better!

1. Model-based dose-DLT relationships
   - Bayesian logistic regression model (BLRM) (Neuenschwander 2008)
     - Incorporate mixture priors accounting for species variability
     - Allow for a variety of shape parameters reflecting uncertainty
     - Adaptive dose-levels and cohort sizes
     - Exchangeability extensions to share information across populations (Neuenschwander 2016)
   - Can be integrated with other data for weighted decision-making
2. Integrate real-time PK data into dose-safety modeling
   - Covariate in dose-DLT model (e.g., Piantadosi and Liu, 1996)
   - Hierarchical dose-exposure-DLT model (e.g., Ursino et al., 2017)
   - Indirectly into decision process (e.g., Cotterill et al., 2015)

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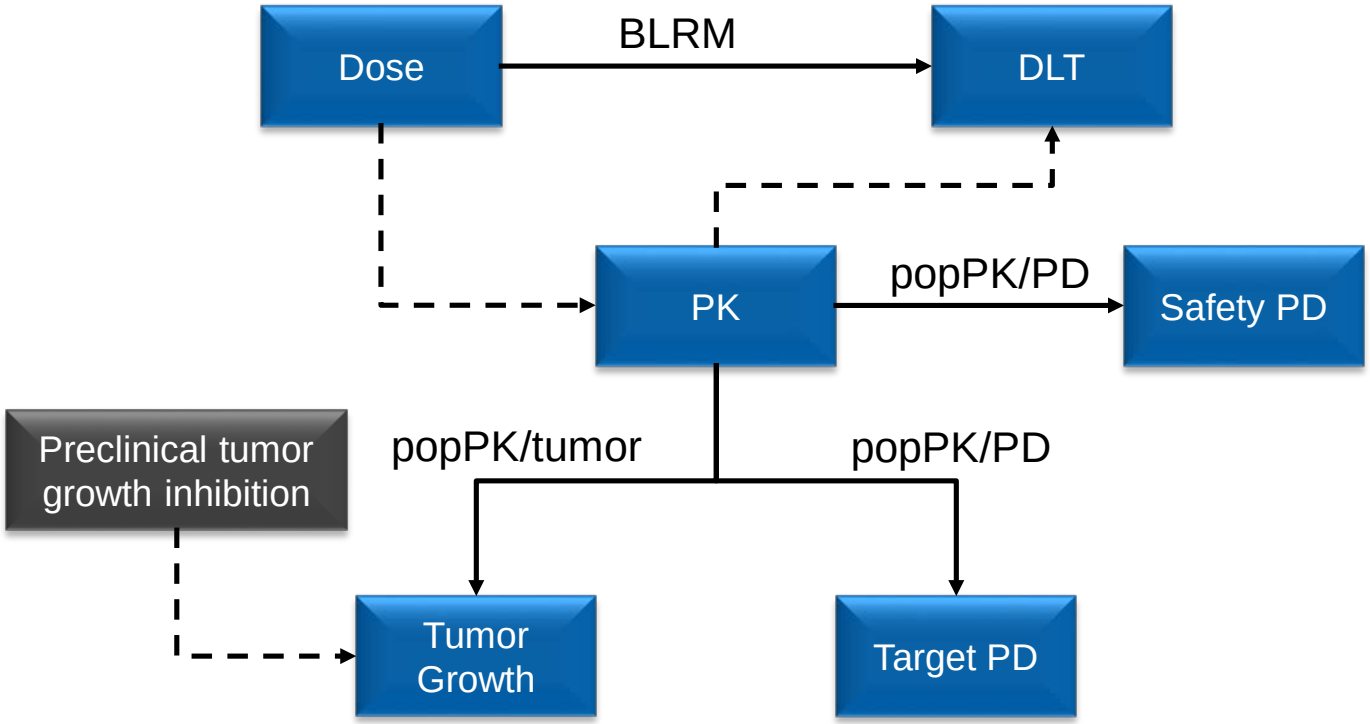
What if we use all data to guide dose recommendations?

Integrated modeling approach drives dose selection



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QD data
10 mg 1 pt, 0 DLT
20 mg 2 pts, 0 DLT
40 mg 2 pts, 0 DLT
60 mg 3 pts, 0 DLT
100 mg 3 pts, 0 DLT
200 mg 4 pts, 0 DLT

Dose → BLRM → DLT

Mouse MTD ~ 100 mg QD
Dog MTD ~ 350 mg QD

Preclinical species variability

At most 100% per protocol

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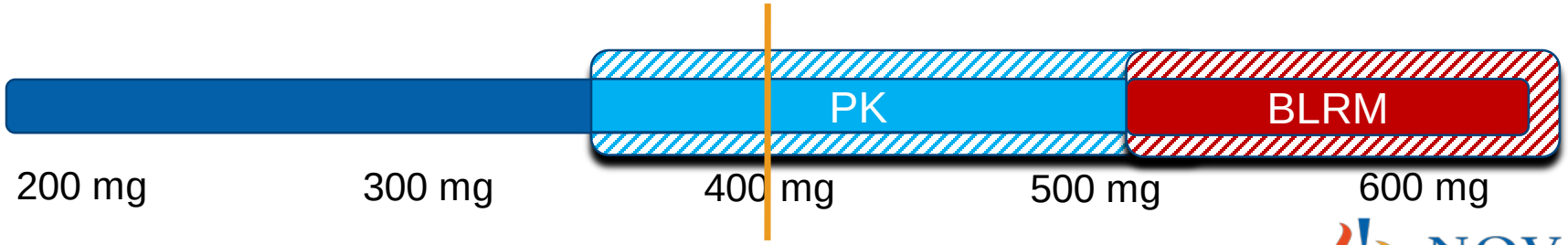
PK

AUC increases proportionally
Estimated AUC@400 mg exceeds
Dog MTD exposure, 350 mg is OK



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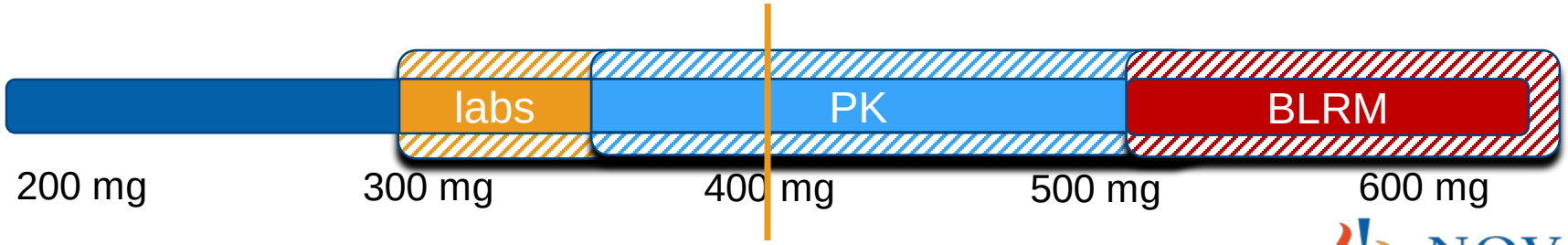
PK → popPK/PD → Safety PD

popPK-platelet model estimates P(gr 3 thrombocytopenia) > 25% at doses above 300 mg given lab data

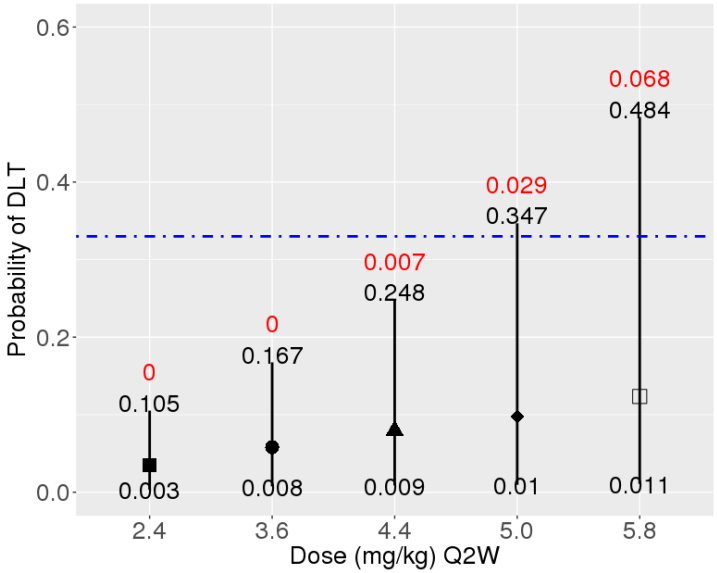


At most 100% per protocol

Potential to augment decision making using PK/PD

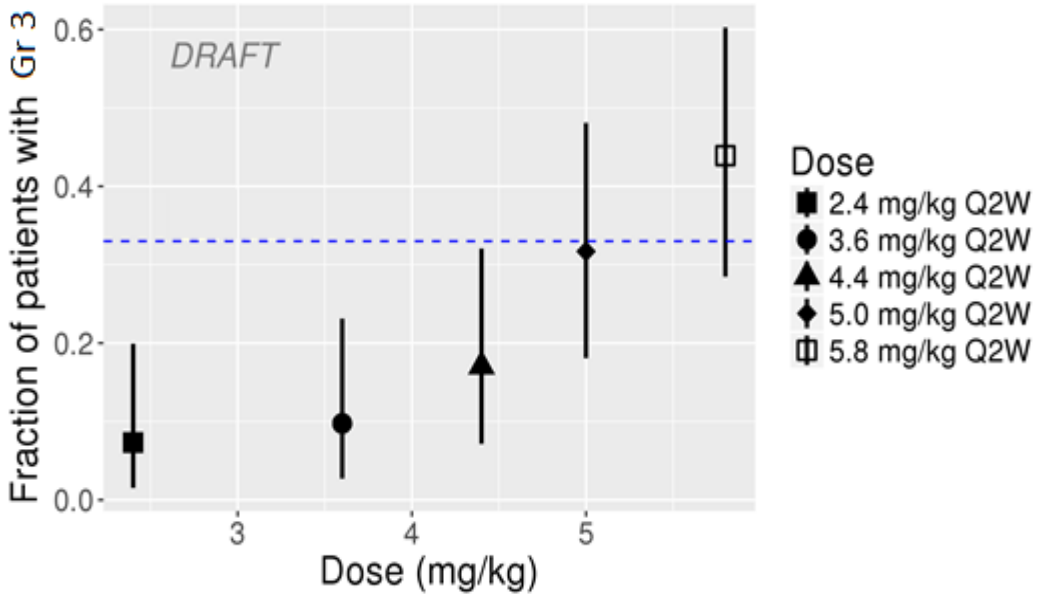
- Example: data available for doses up to 4.4 mg/kg
  - BLRM reflects low risk given no observed DLT
  - Semi mechanistic PKPD model predicts potential increased risk of thrombocytopenia at higher doses based on all platelet and exposure data

a) BLRM



Risk of overdose at each dose level is displayed in red

b) PKPD-thrombocytopenia



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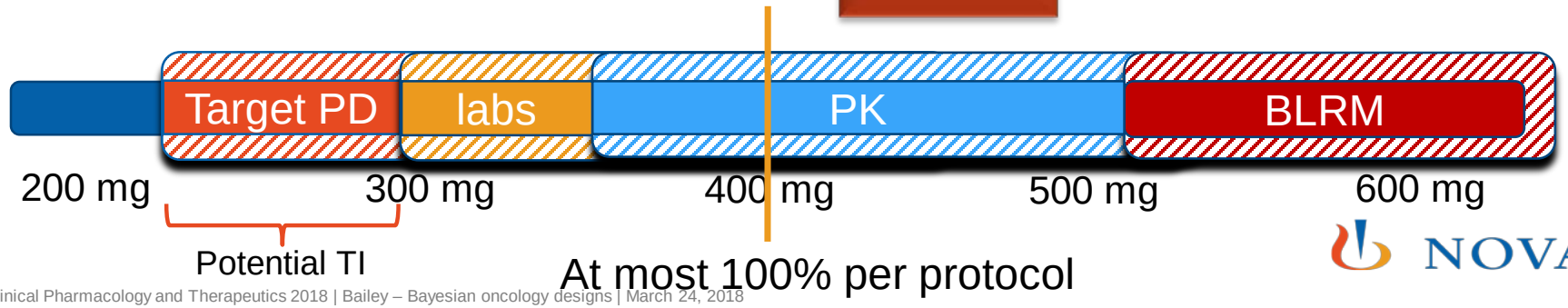
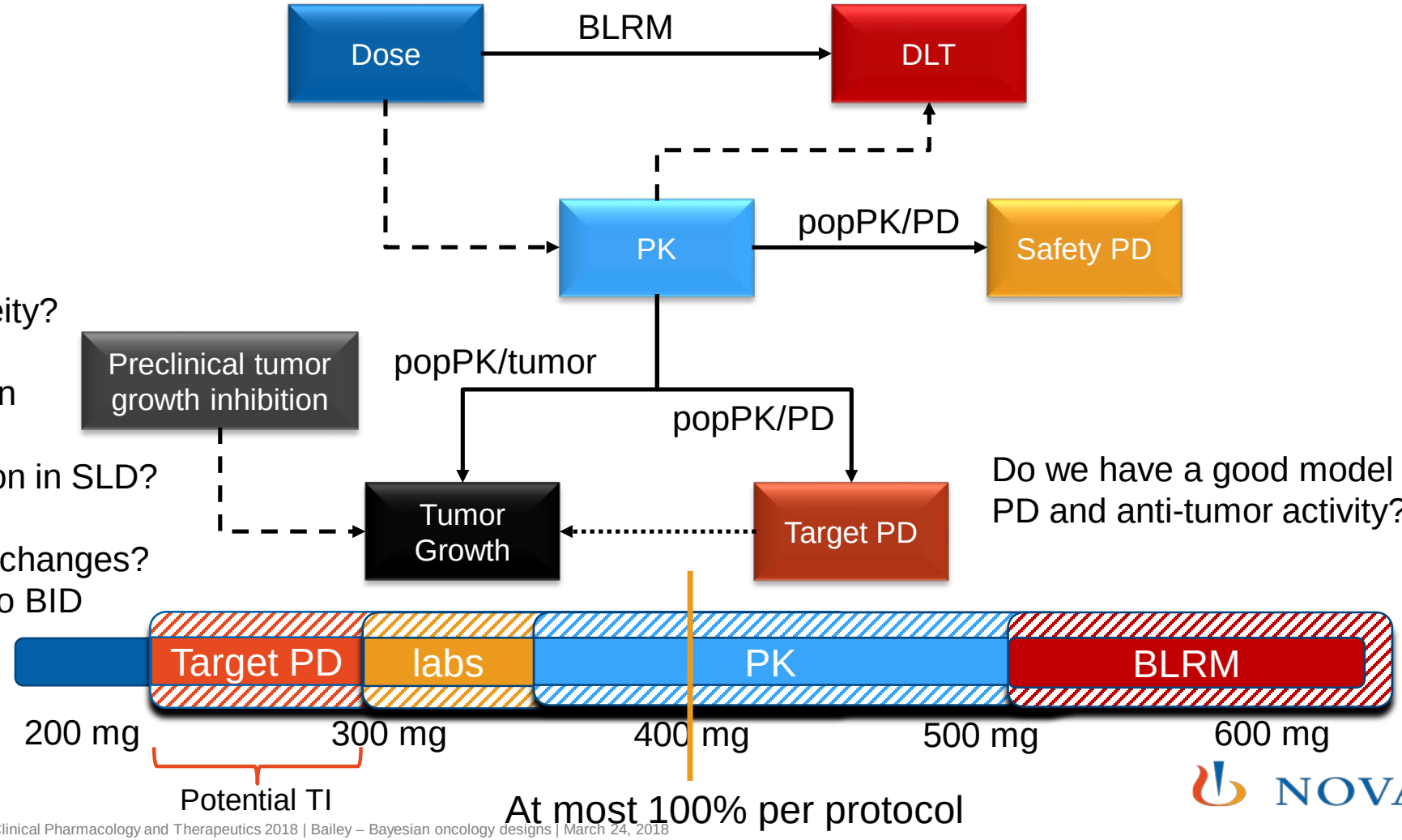
P(gr 3 thrombocytopenia) > 25% at
doses above 300 mg given lab data

popPK/PD → Target PD

P(achieve target BM change) > 90%
at doses > 240 mg QD

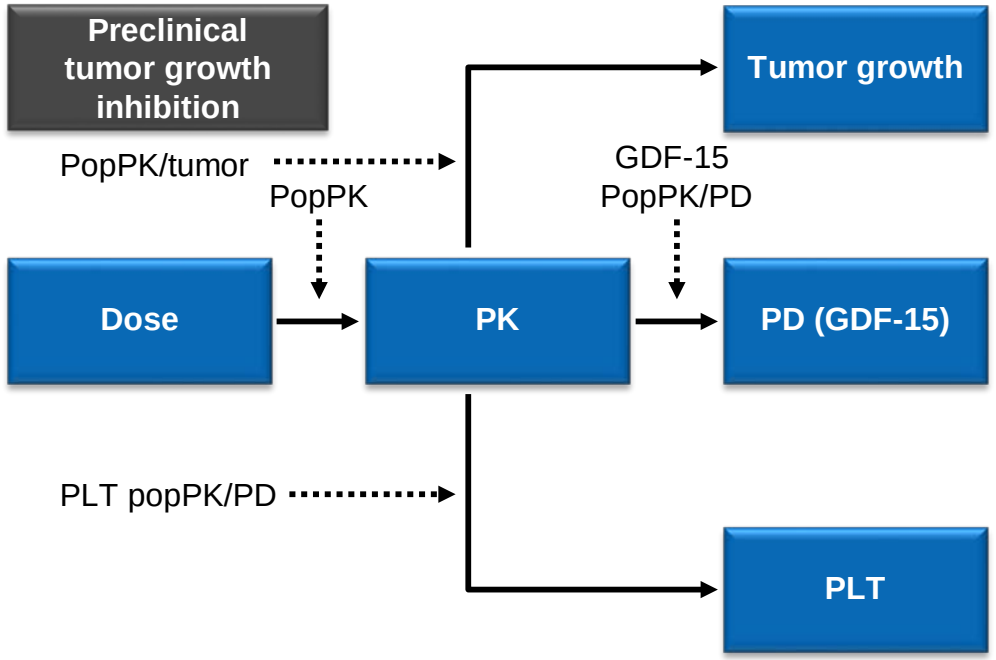


Integrated modeling approach drives dose selection



Integrated modeling approach drives dose selection

- Refer to Meille et al. (2017) at AACR
  - Provided an overview of an integrated modeling approach to address choice of dose and schedule supported by multiple PopPK/PD models
  - Safety supported by Bayesian logistic regression model with MAP sharing across regimens (Neuenschwander et al., 2008 and 2010)



Establishing a therapeutic window from within phase I - challenges

- Mixed patient populations (e.g., advanced solid tumors)
  - Need to enrich disease sub-groups at one or more dose levels
- Variability within a patient population
  - Baseline prognostic risk factors for both safety (e.g., laboratory markers) and early progression (e.g., immune-environment)
- Model-based approaches are particularly useful to support combination strategy
  - Integrate preclinical synergistic modeling
    - Therapeutic window may shift from single-agent exposures
  - Incorporate real-time PK-DDI and PK/PD modeling
- Identification of a therapeutic window uses a holistic understanding of all the data

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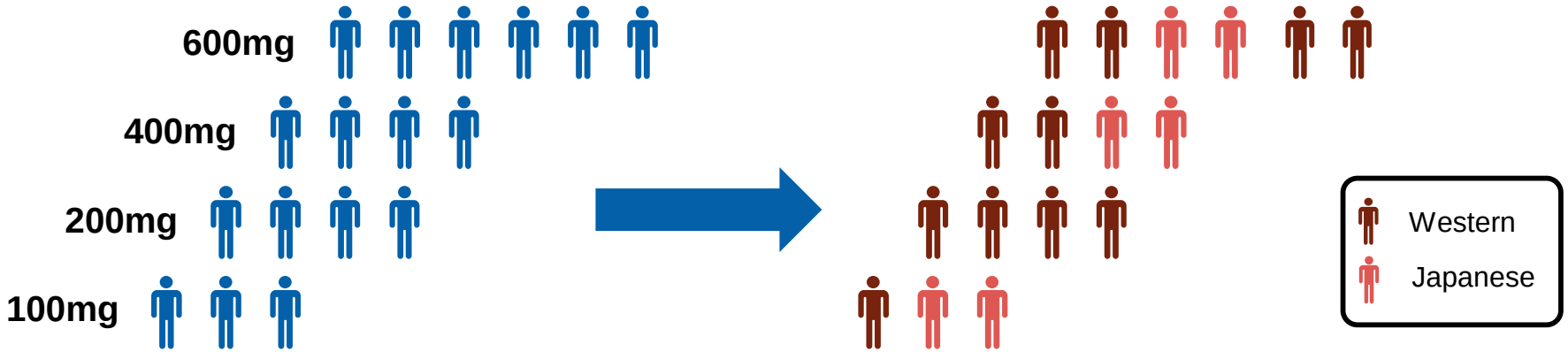
Regional exchangeability in dose-escalation



- Assume the potential for similarity (EX) and then seek to see if there is evidence of a difference (NEX)
  - Ethnic sensitivity can be in:
    - Dose-Exposure, Exposure-Safety, Exposure-Activity and more...
  - Supplement dose-safety with additional (pop)PK, (pop)PK/PD, E-R modeling and explore across phase I/II

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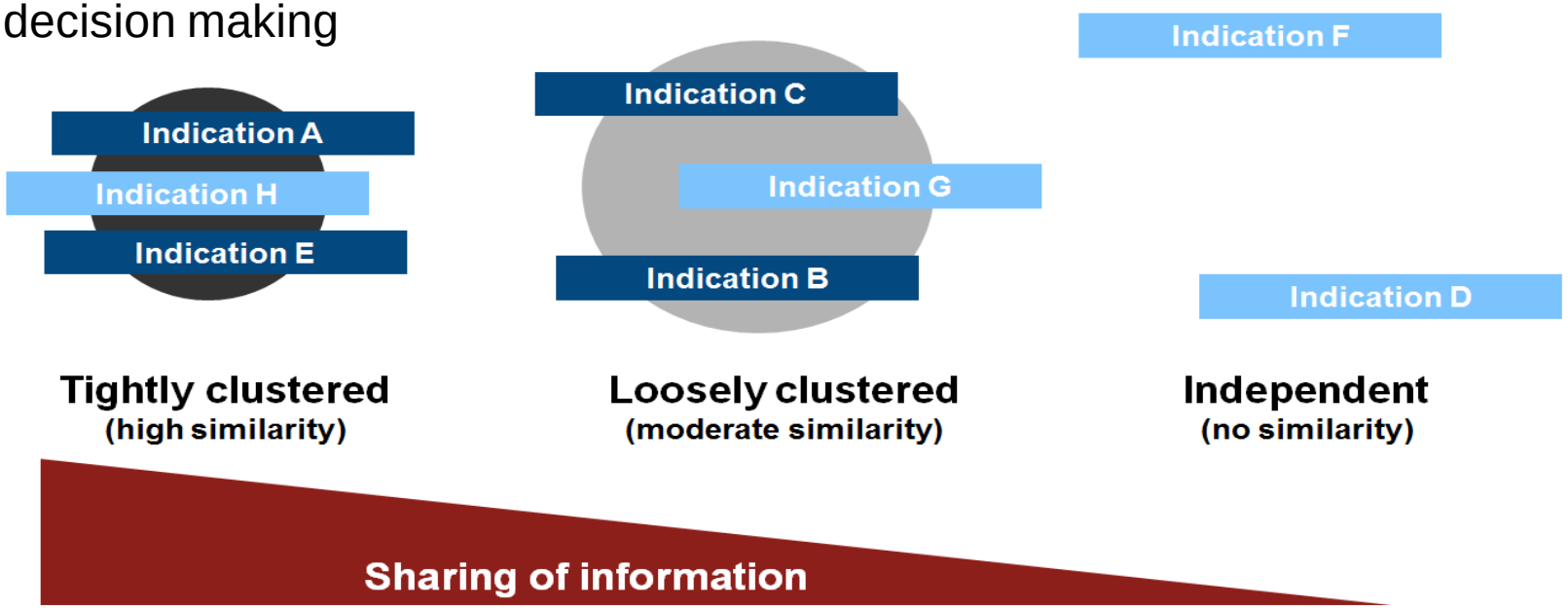
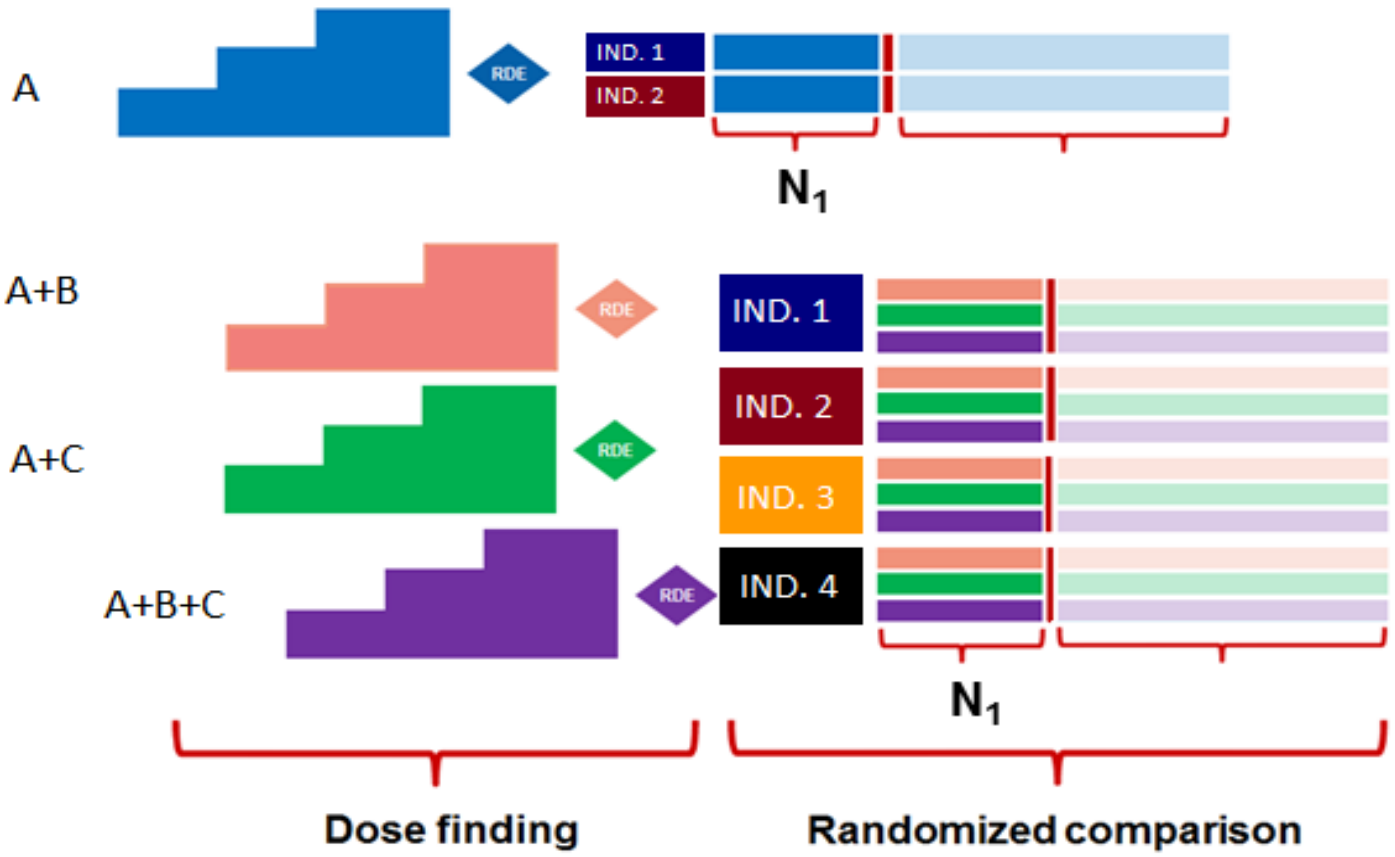
Exchangeability in dose-expansions

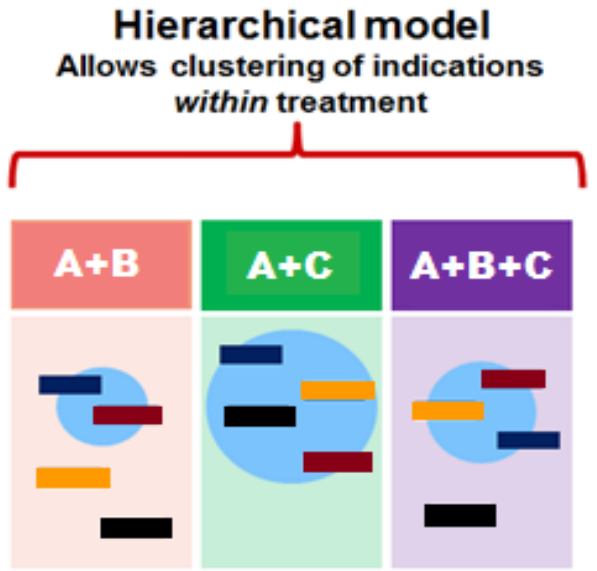
- Model based approach facilitates decision making
  - For example: stopping indications for **Futility**
- Borrowing of information within ‘clusters’ can increase accuracy of estimation of treatment effect
  - **Better** decision making



Multiple combinations in one protocol

On what endpoint should we cluster?





Conclusions

- Can’t forget safety but..
- We have had to move beyond the “more-is-better” mindset and must be smarter in designing and running dose-finding studies
- Complementary modeling approaches can be used to support decision making while safety risks are controlled
- Need to make better use of methodologies to deal with indirect comparisons when addressing patient heterogeneity and non-contemporary data
- May need to study more than one dose level or regimen within phase II or pivotal studies

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Thank you

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