

Novartis Analytics



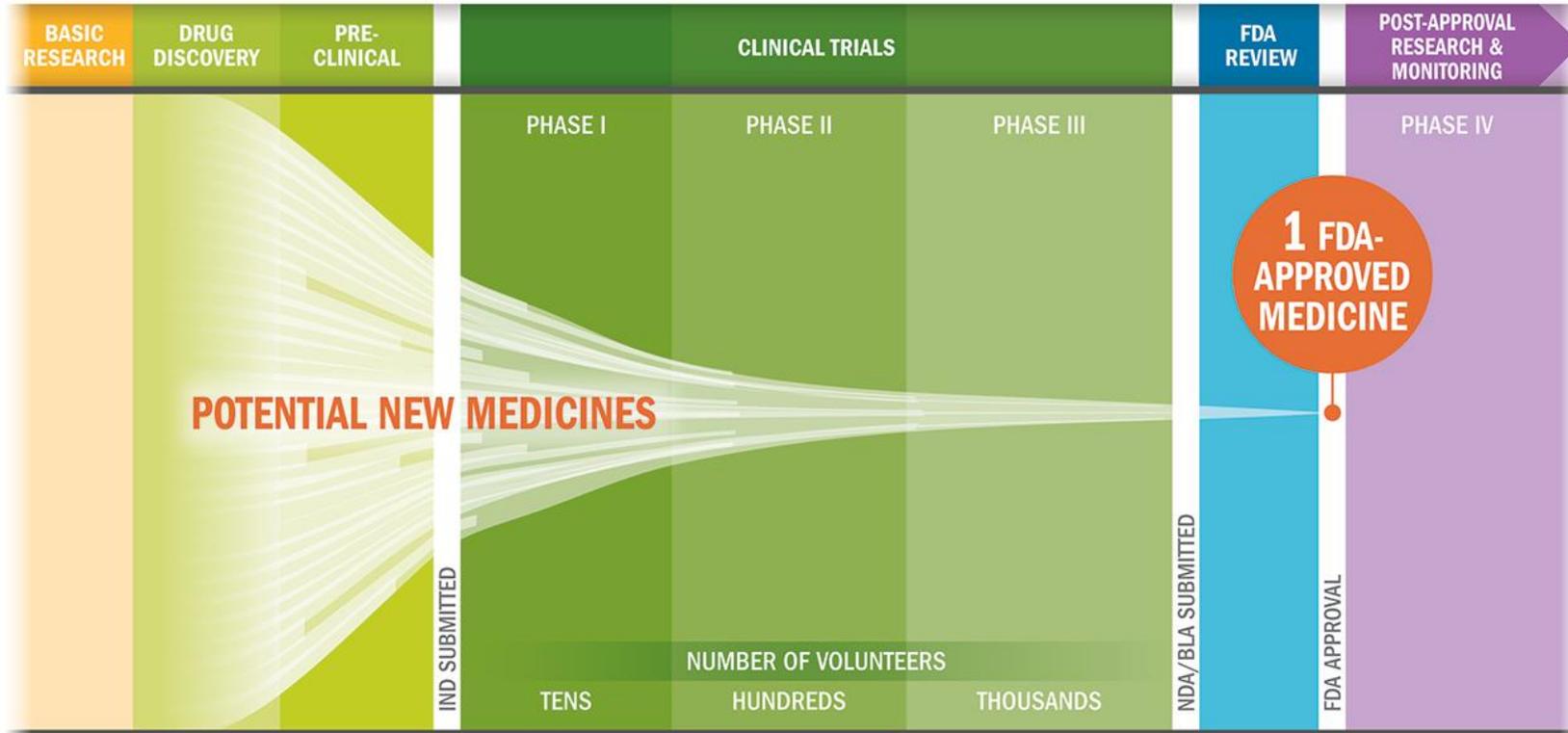
Adaptive quantitative decision making in early dose- and population-finding studies

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ASA NJ Chapter Meeting – November 2nd, 2018



THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS

From drug discovery through FDA approval, developing a new medicine takes at least 10 years on average and costs an average of \$2.6 billion.* Less than 12% of the candidate medicines that make it into Phase I clinical trials will be approved by the FDA.

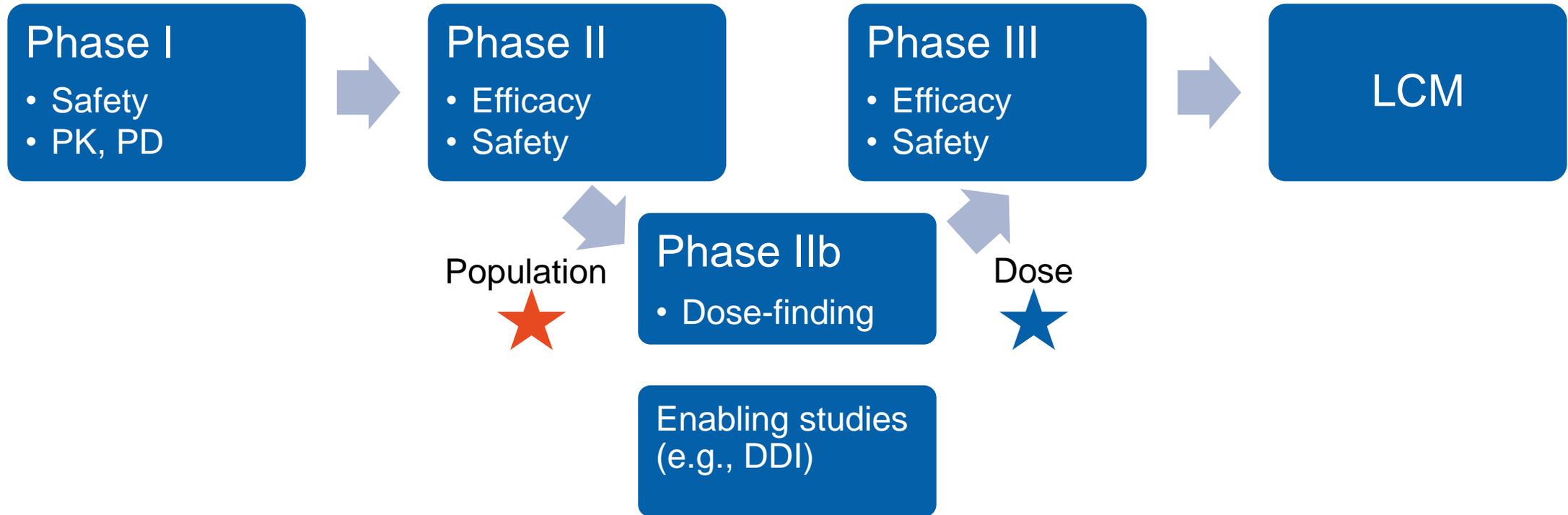


Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

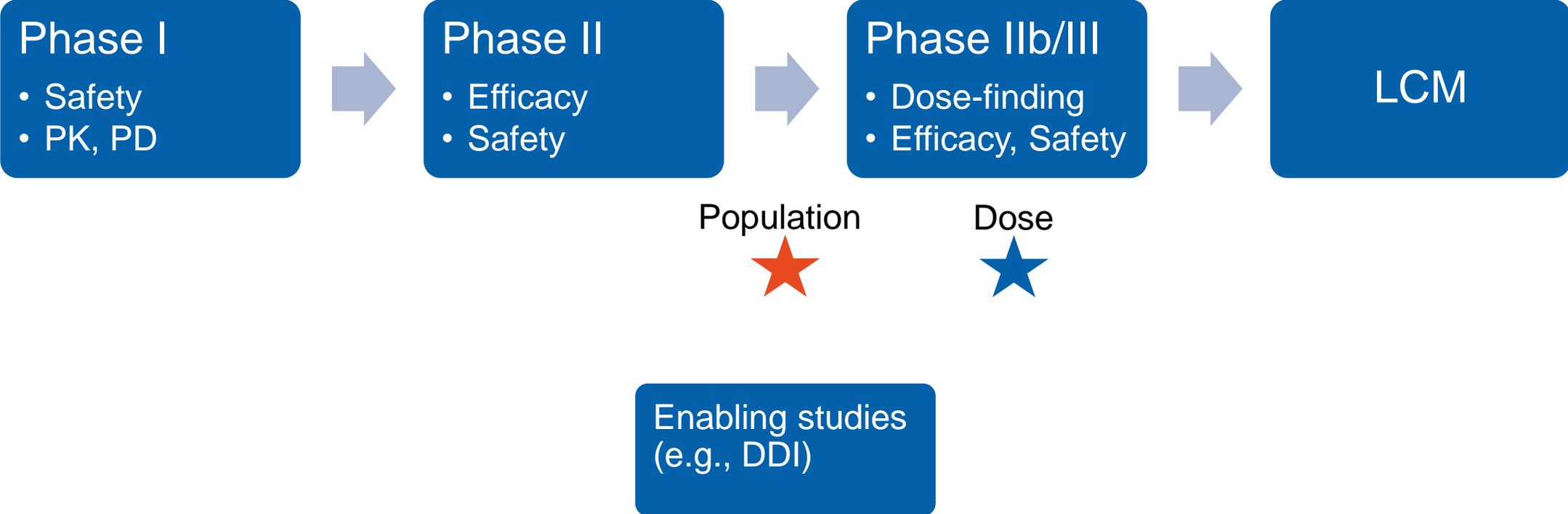
* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be \$2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

Source: PhRMA adaptation based on Tufts Center for the Study of Drug Development (CSDD) Briefing: "Cost of Developing a New Drug," Nov. 2014. Tufts CSDD & School of Medicine., and US FDA Infographic, "Drug Approval Process," <http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM284393.pdf> (accessed Jan. 20, 2015).

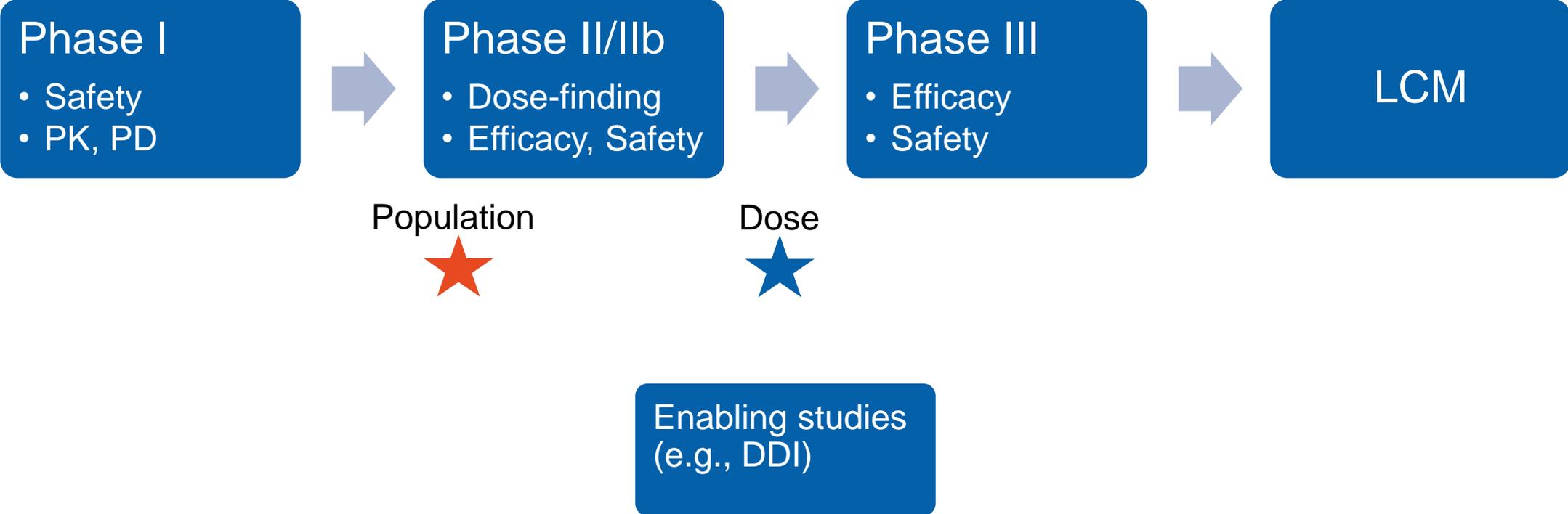
The development paradigm



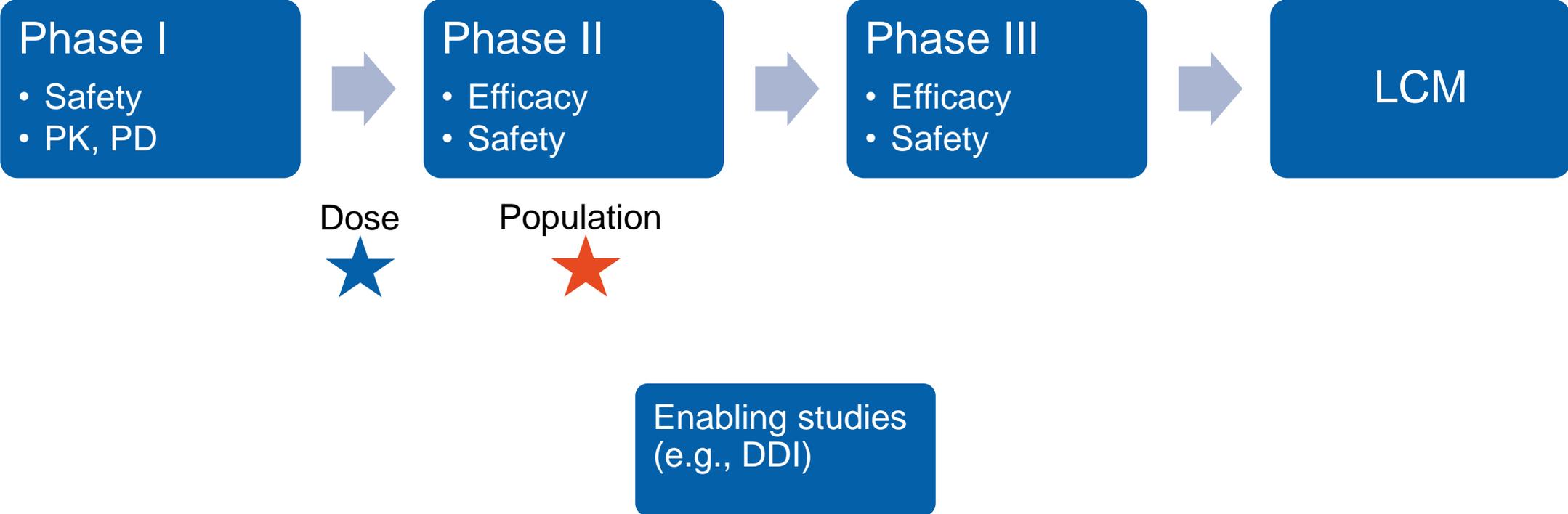
The development paradigm



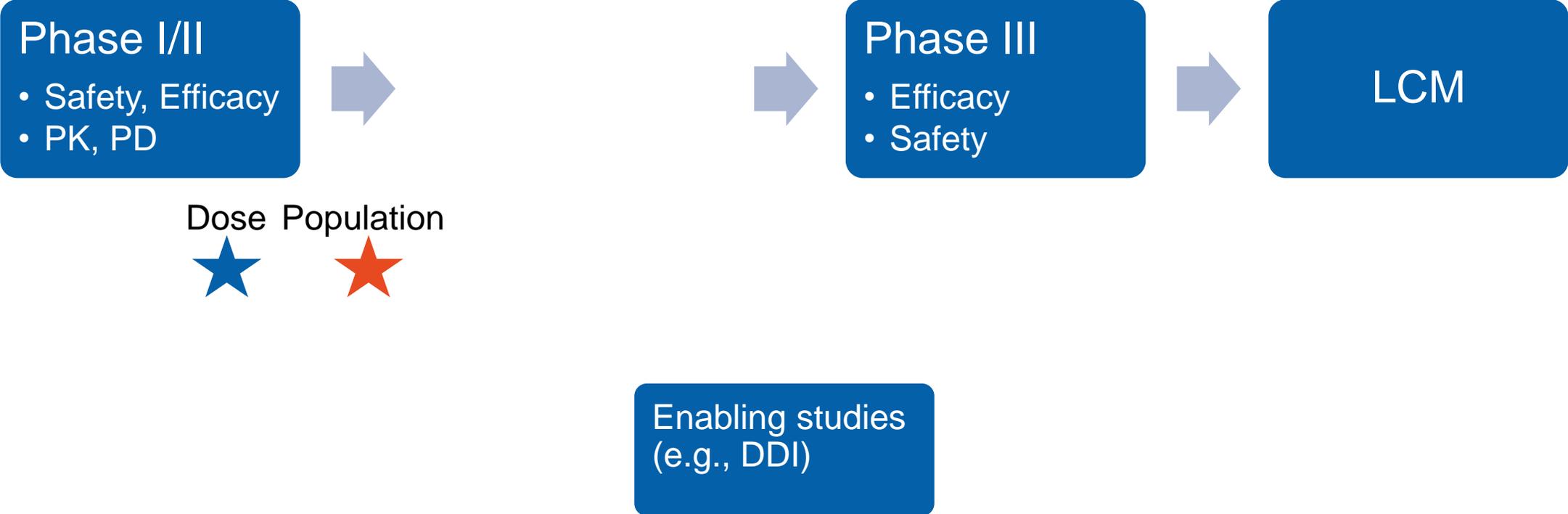
The development paradigm



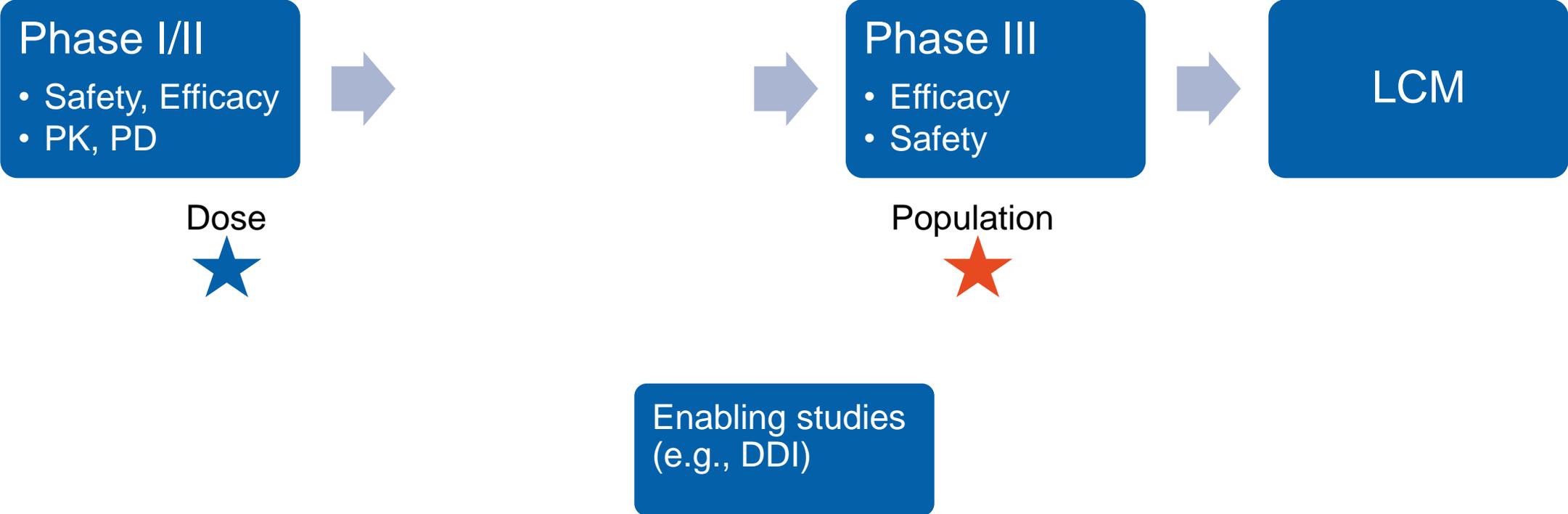
The development paradigm



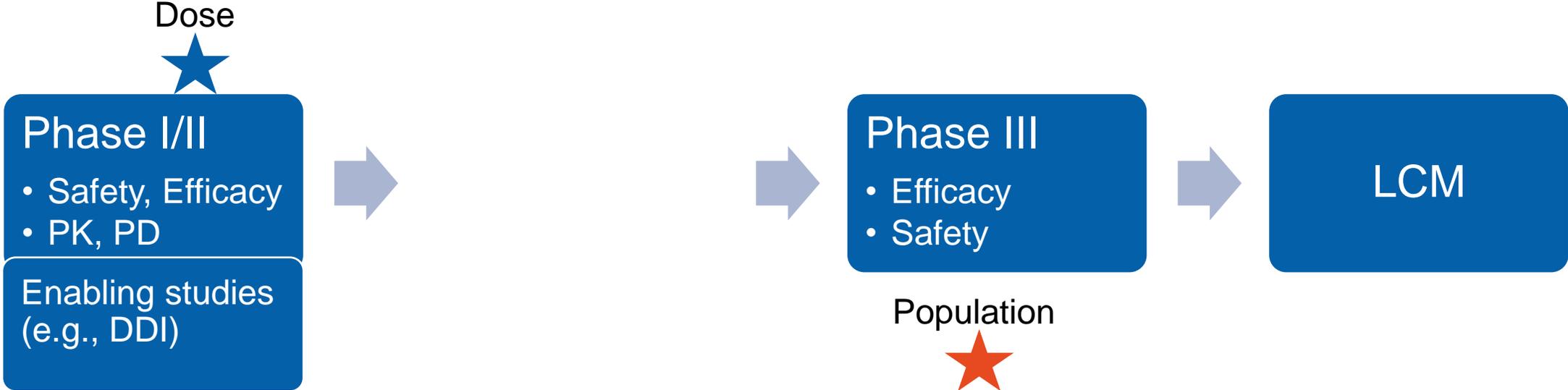
The development paradigm



The development paradigm



The development paradigm



Early Oncology Development

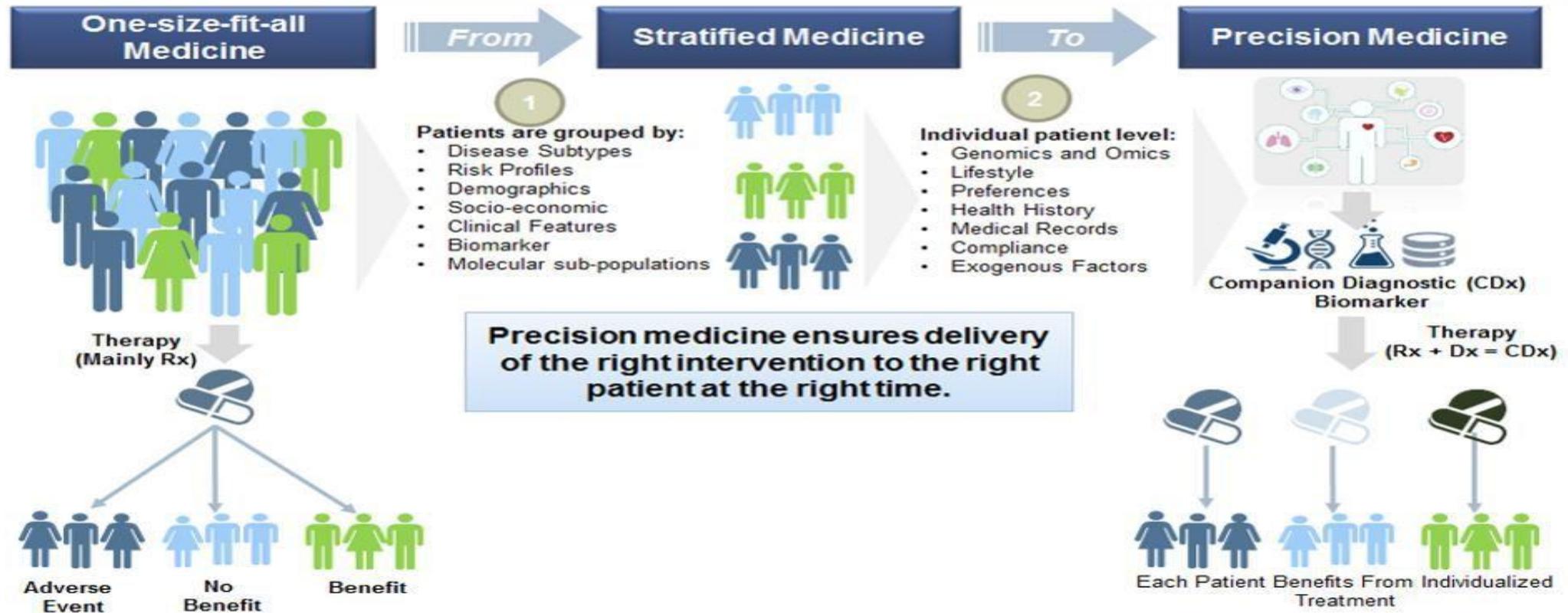
The changing world of oncology medicines

Paradigm shift towards precision medicine

(Source: Frost & Sullivan -Figure 1: New Paradigm Shift in Treatment)

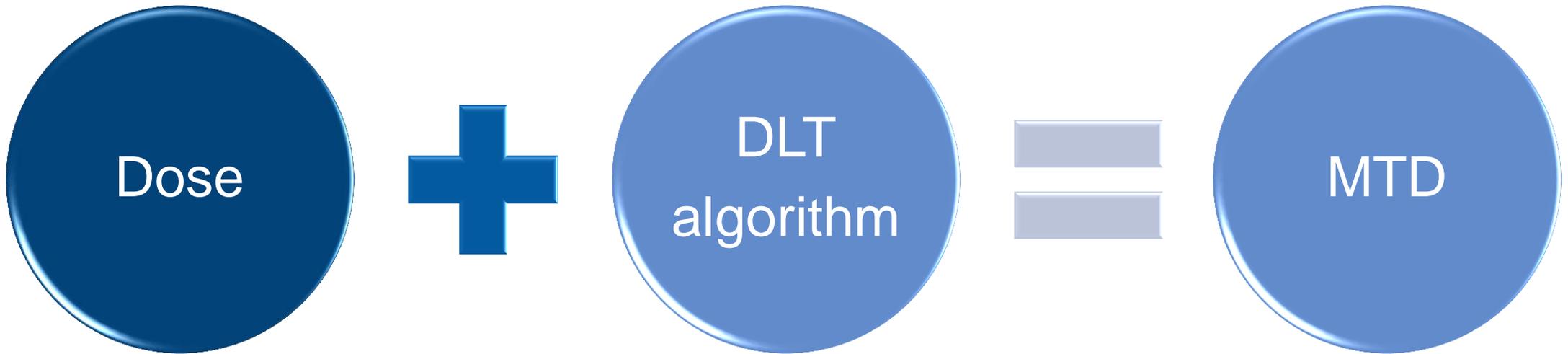
New Paradigm Shift in Treatment

Transitioning From the 'one-size-fits-all' to 'precision medicine' model with multi-level patient stratification.



Finding a maximum tolerated dose

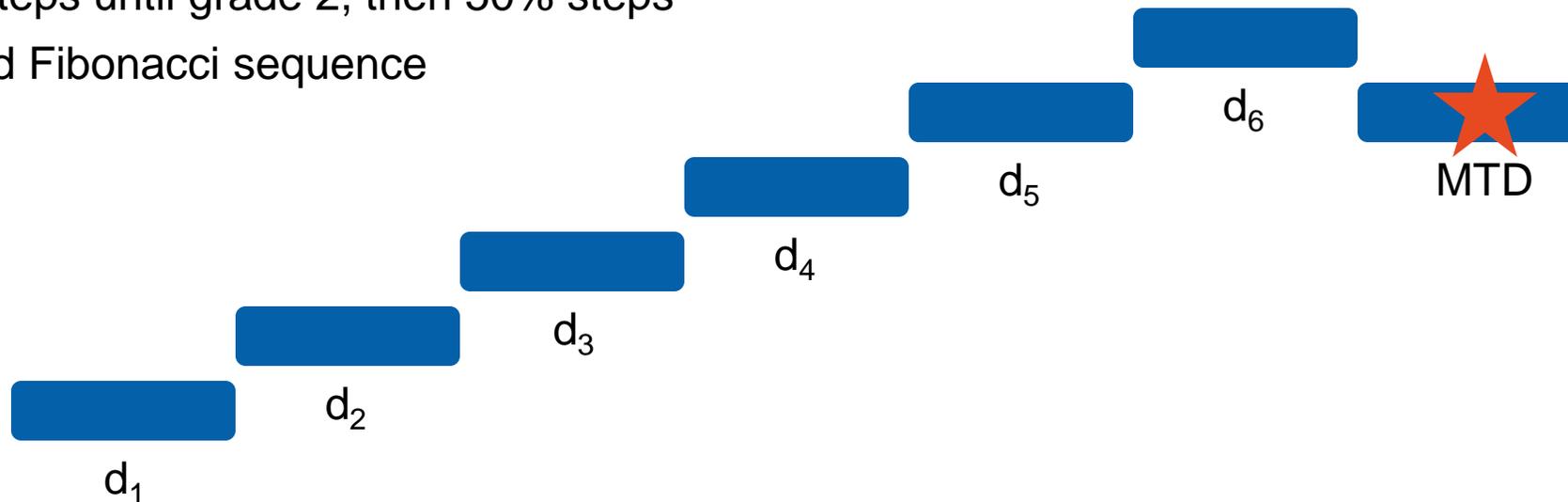
Phase I dose escalation



e.g., 3+3 design

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



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)

Moving from dose-escalation to dose-finding paradigm

- From preclinical studies we have data on
 - Exposures related to tumor stasis and regression
 - PK/PD modeling of target engagement
 - Physiological models for PD or lab changes related to potential adverse events
- Non-safety primary endpoints
 - Need to increase data across multiple “relevant” doses
 - Use simulation to understand value of additional PK/PD data
 - Do more to understand signal-to-noise ratio
 - Preclinical modeling or cross-program analyses to support selection of best endpoints/time-points to use
 - Single agent responses may not be seen so we need to assess activity through proof-of-mechanism

What if we use all data to guide dose recommendations?

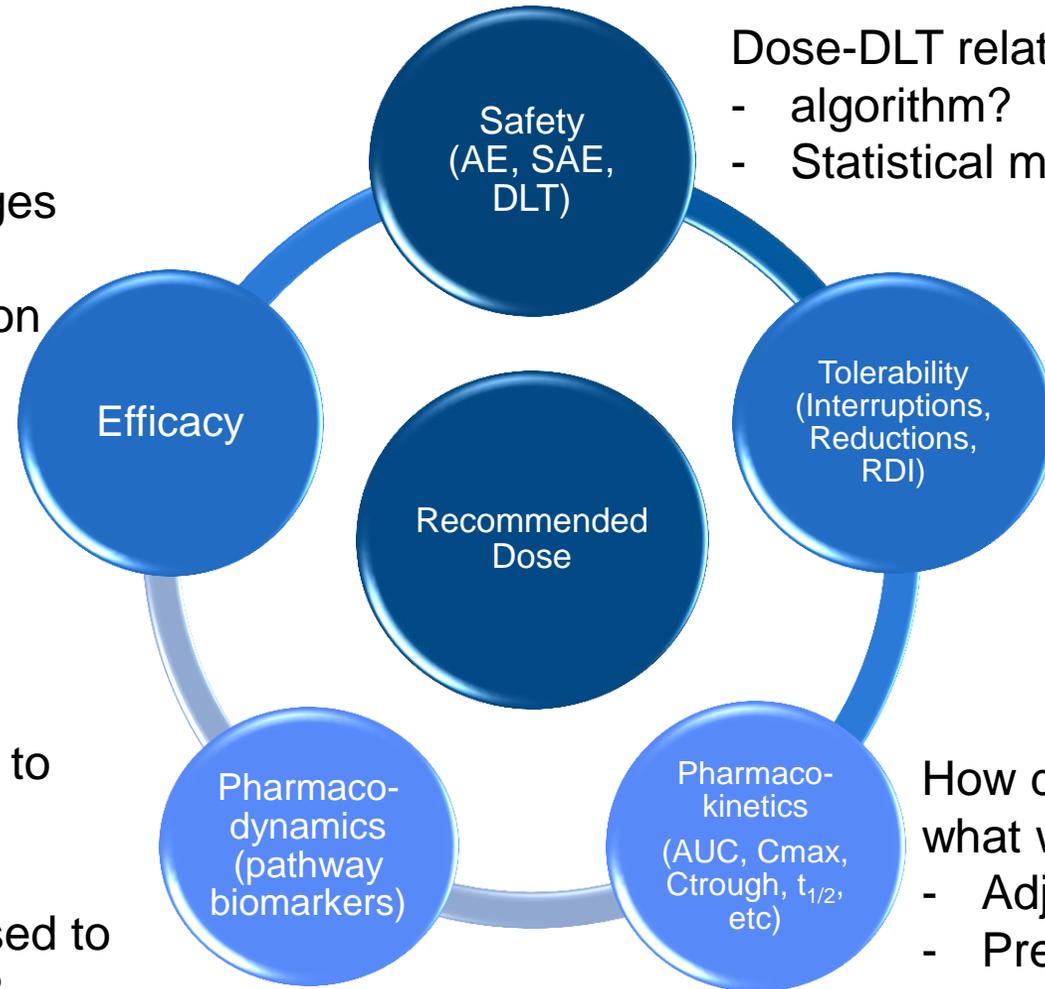
Dose-PK-PD-response

- Do we see desired PD changes leading to clinical response?
- Can we identify sub-population to enrich?

Prediction of impact due to a change in regimen?

How does this data compare to what we predicted/hoped?

- Target engagement?
- In-stream PK/PD being used to guide alternate regimens?



Dose-DLT relationship

- algorithm?
- Statistical model?

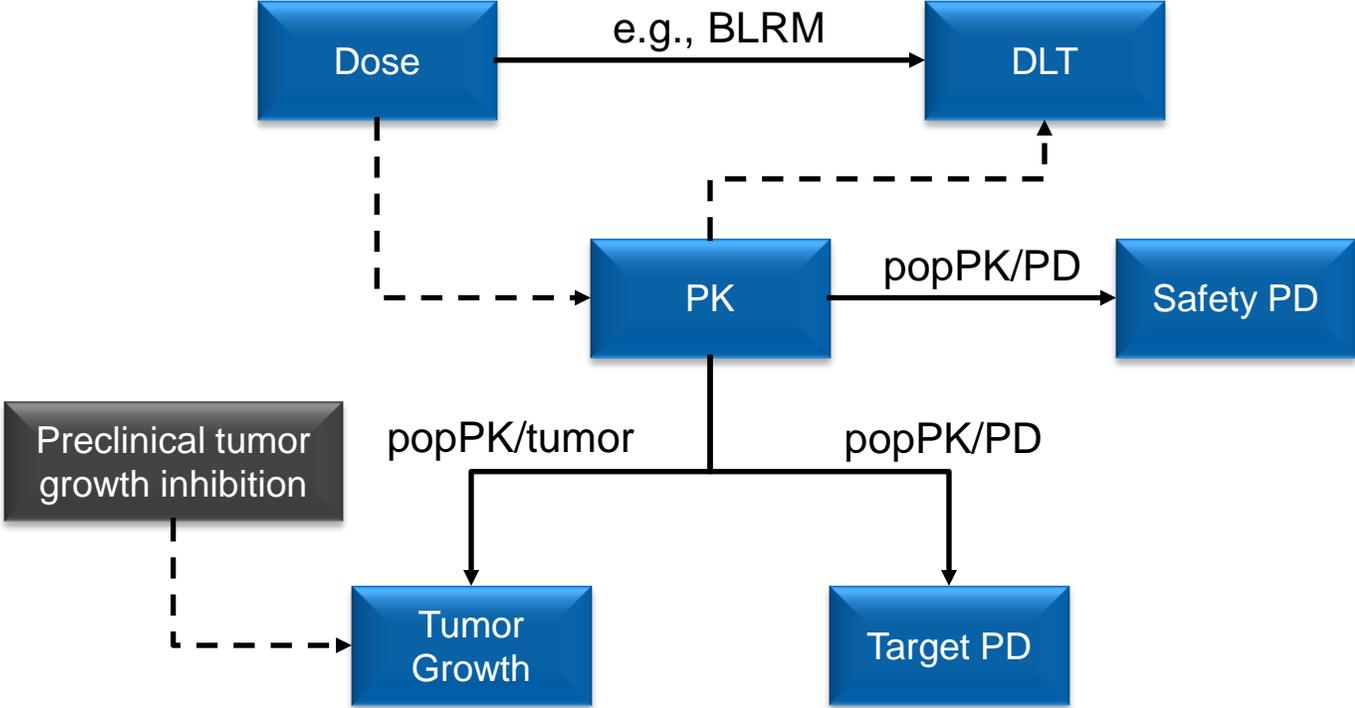
Lower-grade AE

- Frequency, impact
- Time-to-onset
- Event-free rate

How does this data compare to what we predicted/hoped?

- Adjust escalation scheme in-stream?
- Predictions under new regimens?

Integrated modeling approach drives dose selection



Integrated modeling approach drives dose selection

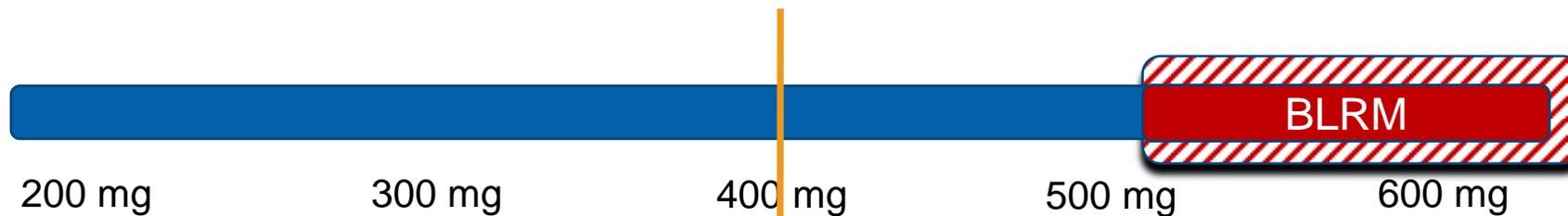
Mouse MTD ~ 100 mg QD
Dog MTD ~ 350 mg QD

Preclinical
species variability



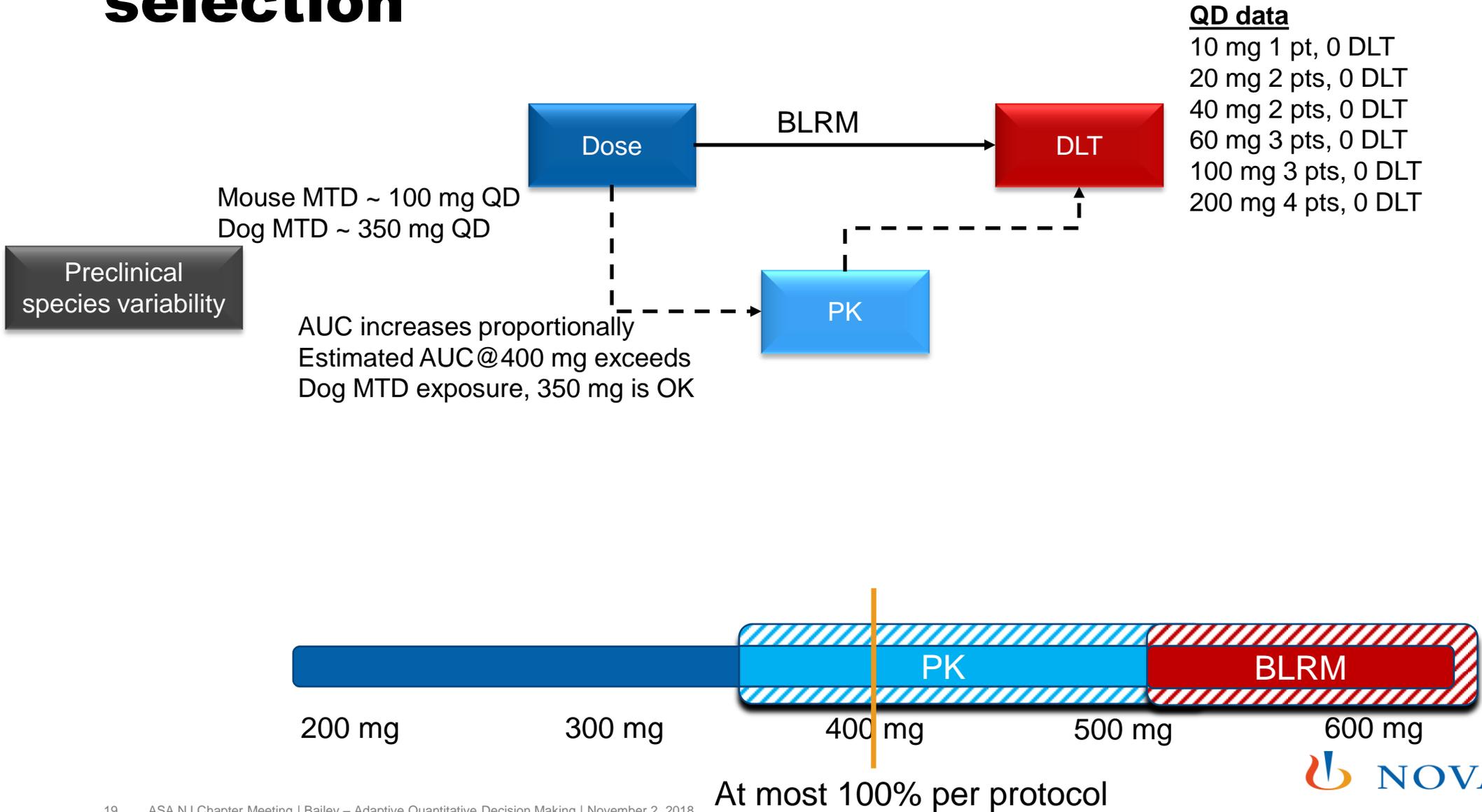
QD data

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

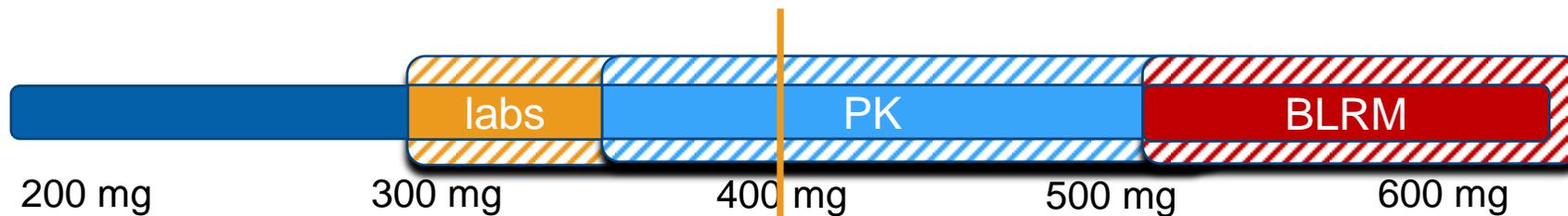
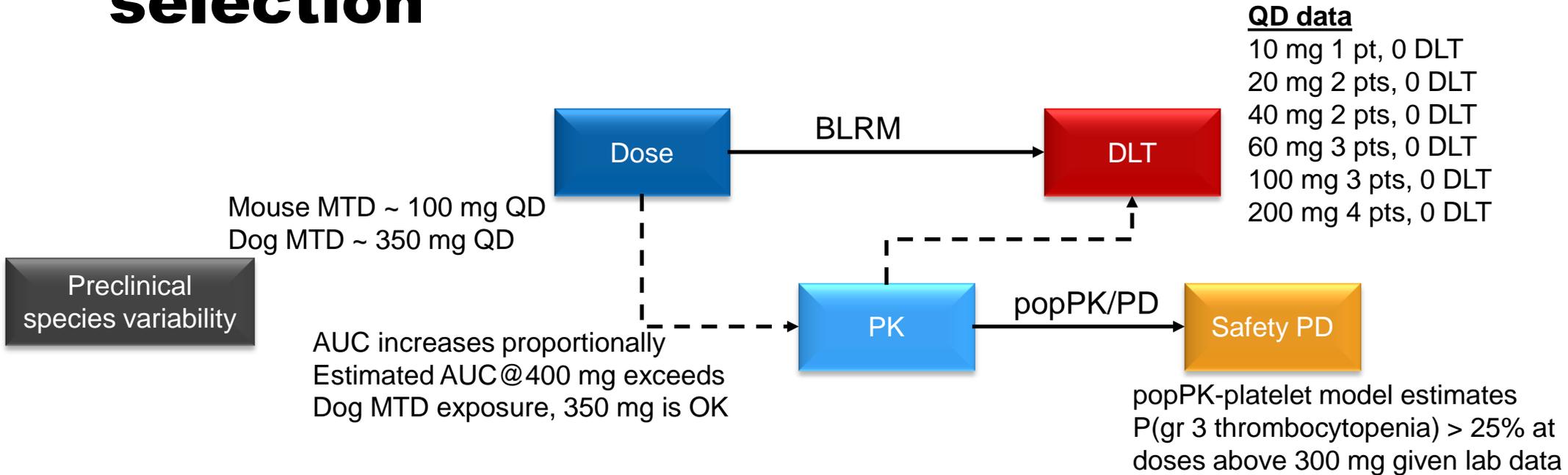


At most 100% per protocol

Integrated modeling approach drives dose selection



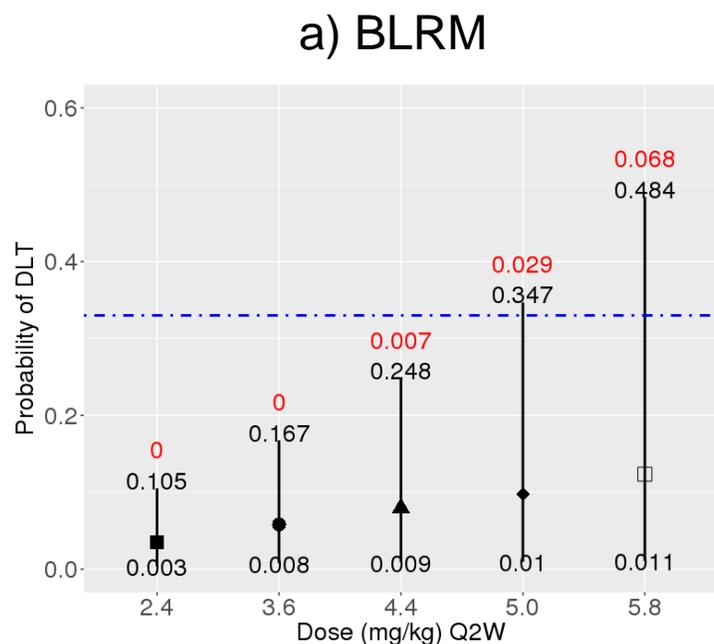
Integrated modeling approach drives dose selection



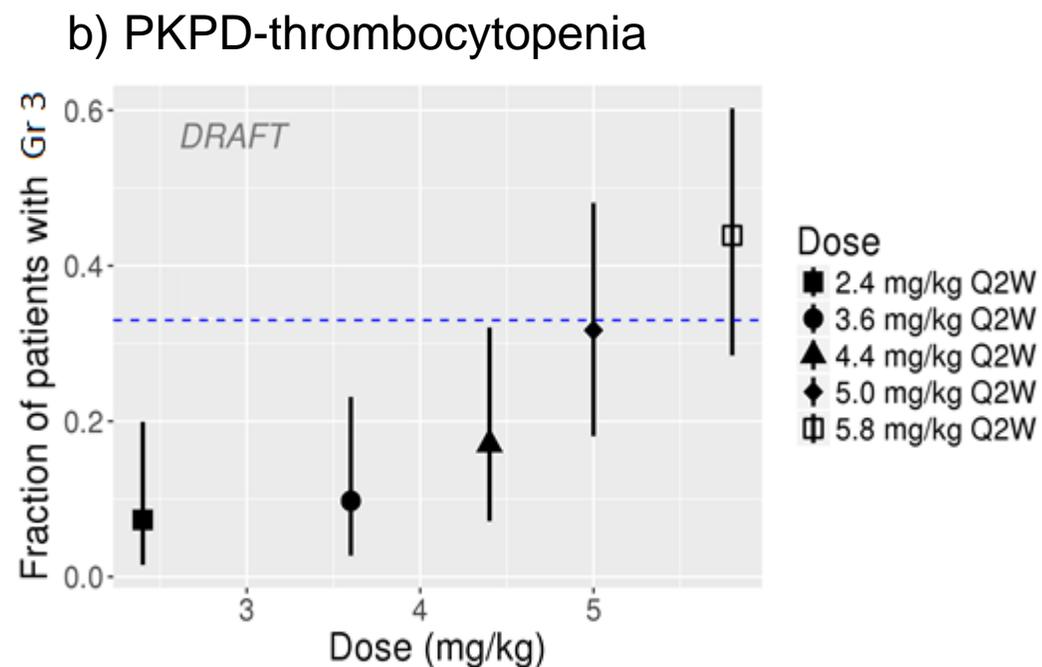
At most 100% per protocol

Potential to augment decision making using PK/PD

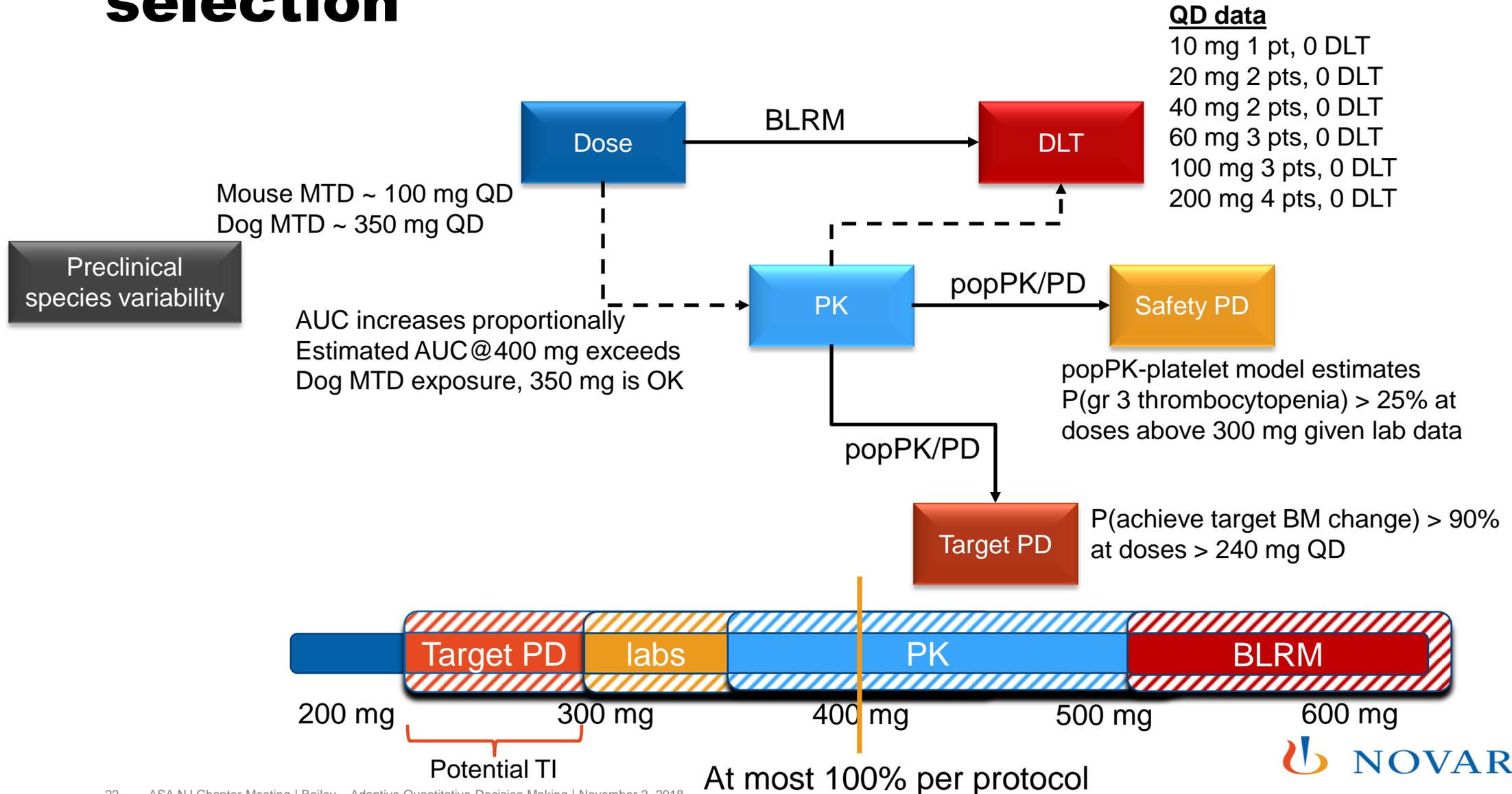
- Example: data available for doses up to 4.4 mg/kg
 - BLRM reflects low risk given no observed DLT
 - Semi mechanistic PKPD model predicts potential increased risk of thrombocytopenia at higher doses based on all platelet and exposure data



Risk of overdose at each dose level is displayed in red

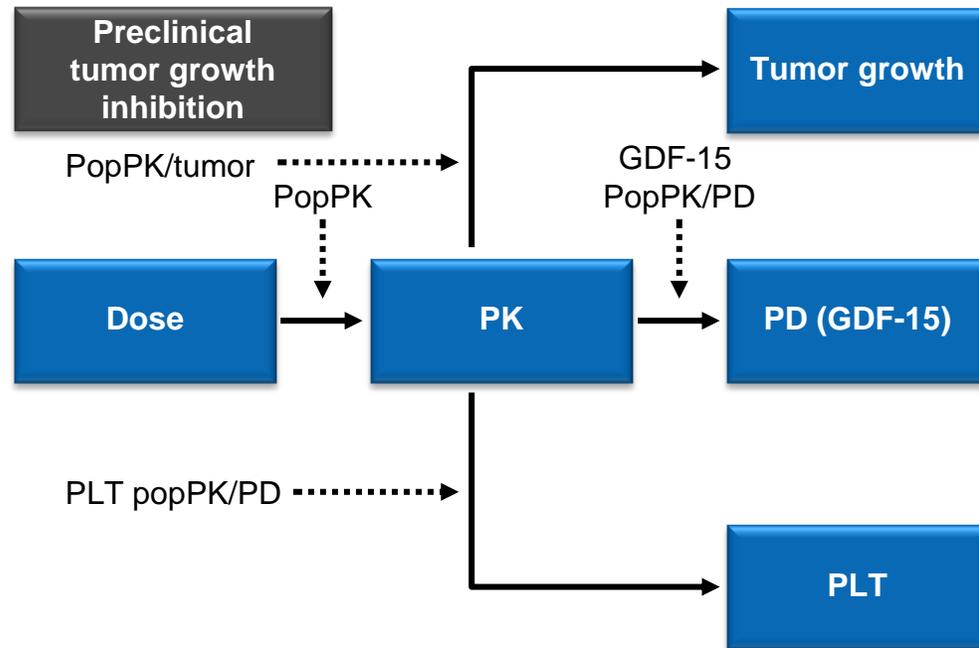


Integrated modeling approach drives dose selection



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)

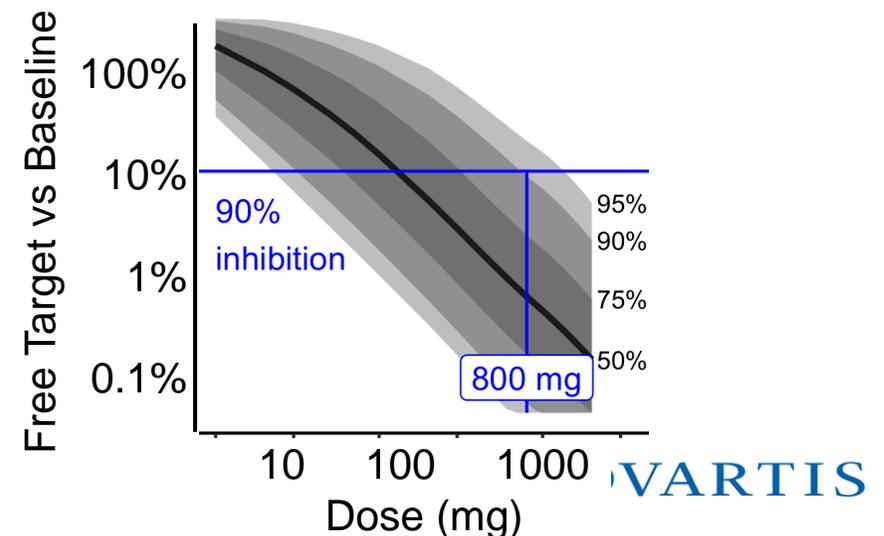


When safety, efficacy, and biomarker data is insufficient for dose selection, we can use target engagement prediction

- Identify dose predicted to reduce free target to 10% of baseline levels in 90% of patients (Extension of Stein and Ramakrishna, 2017)

$$\text{Free target \%} \approx \frac{K_{ss} \cdot T_{acc}}{B \cdot C_{min,ss}}$$

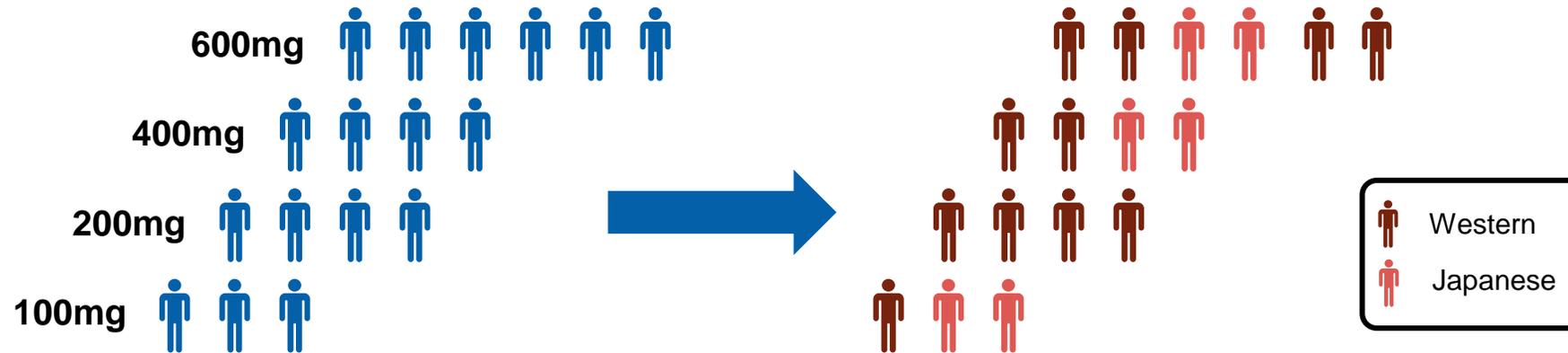
| | |
|--------------|---|
| K_{ss} | steady state binding constant from preclinical or clinical data |
| T_{acc} | fold target accumulation (or downregulation) when bound to drug |
| B | biodistribution coefficient (~30% for tumor interstitial fluid) |
| $C_{min,ss}$ | steady state trough from PopPK |



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

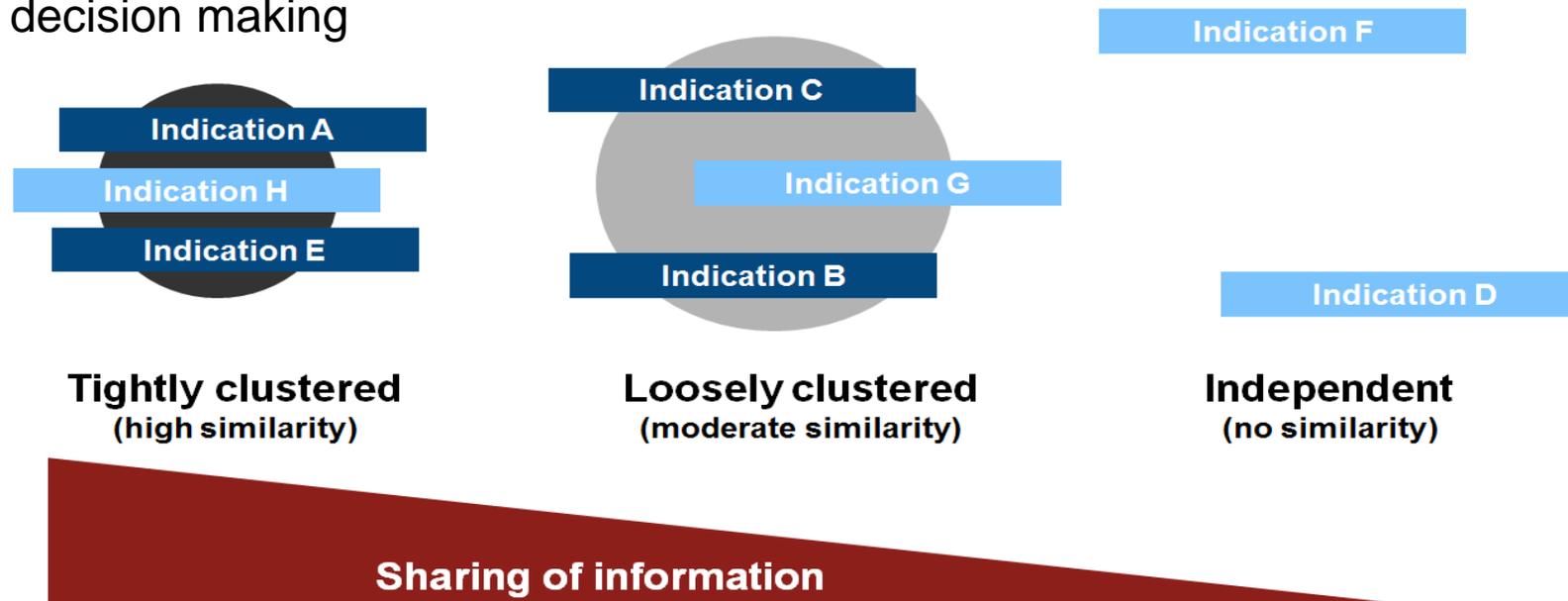
Regional exchangeability in dose-escalation



- 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

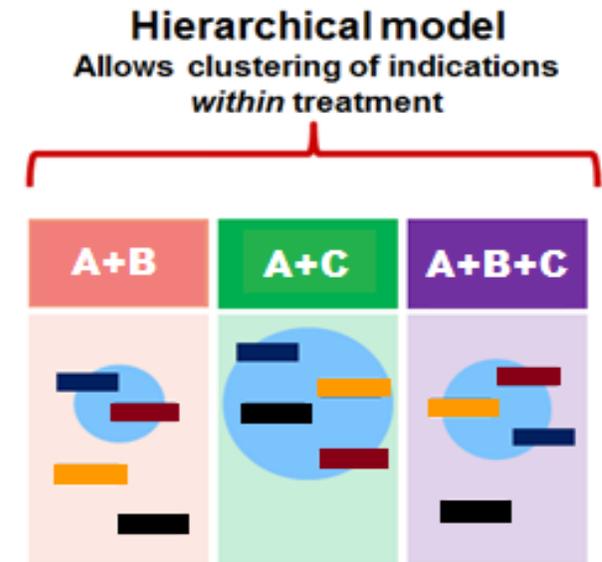
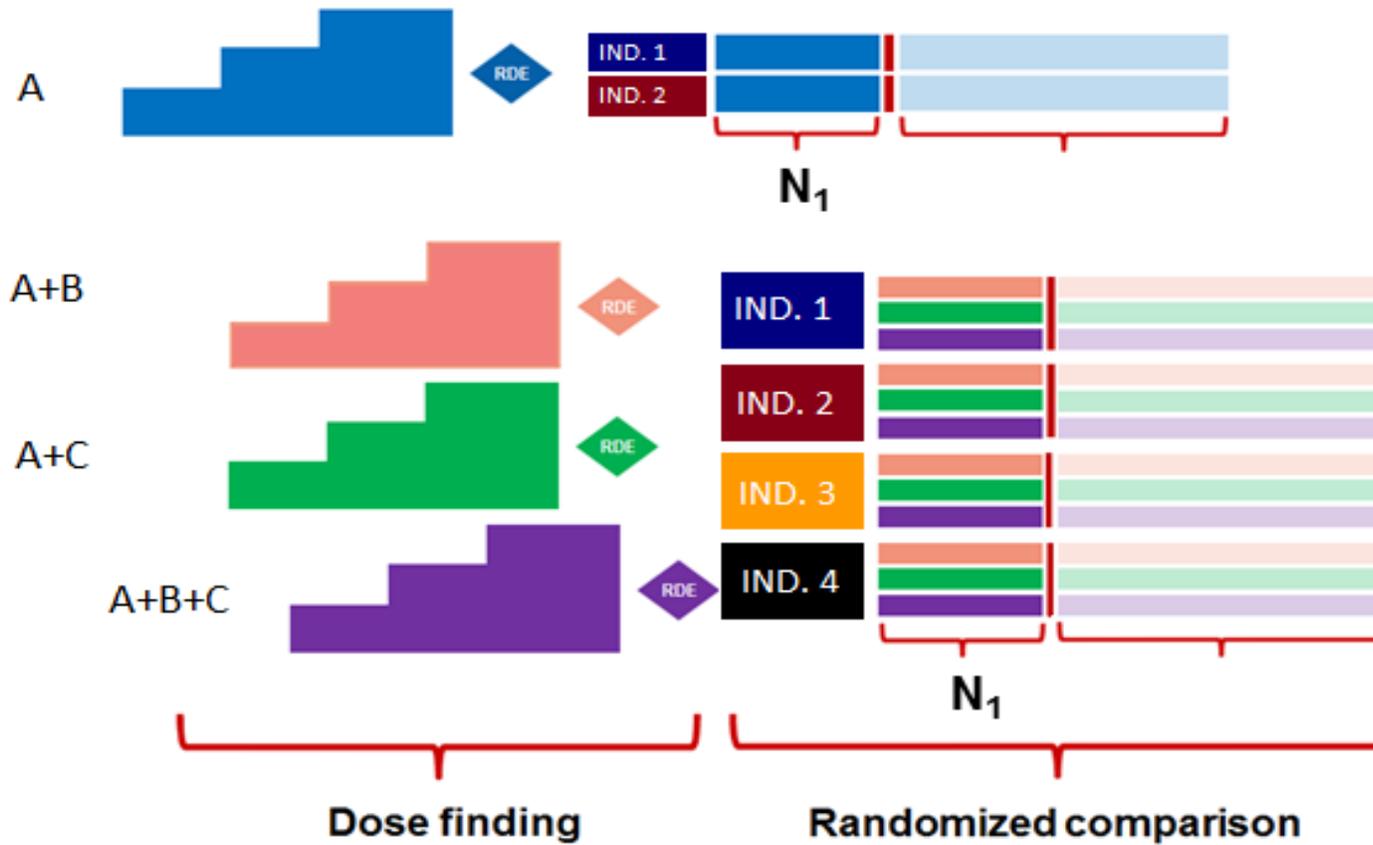
Exchangeability in dose-expansions

- 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

- Endpoints:
 - 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 to reflect this
- Methods:
 - 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
 - Adaptation should be built into protocols to respond to emerging data
- Accelerating vs improving knowledge:
 - Adaptive designs are not always about speed – can also be about generating more relevant data
 - May need to study more than one dose level or regimen within phase II or pivotal Oncology studies

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Thank you