

Beyond MTD: Integrating non-safety endpoints into Oncology dose-finding

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Disclosures

- I am a shareholder in Novartis Pharmaceuticals Corporation
- This presentation represents the views of the authors and may not represent the views of Novartis or its subsidiaries.

Key messages

- First-in-human studies need to continue to minimize risk to patient safety
- but....these studies should be designed based on principles of dose-finding with greater real-time use of PK and PD endpoints as primary endpoints
- Historical/contextual data from across populations should be incorporated in design and decisions
 - Age (adult, adolescent, pediatric) or region (Western, Japanese)
 - Healthy volunteers
 - Tumor types (solid, hematology)
- Increased interactions between Statisticians and Pharmacometricians are essential for better dose-finding

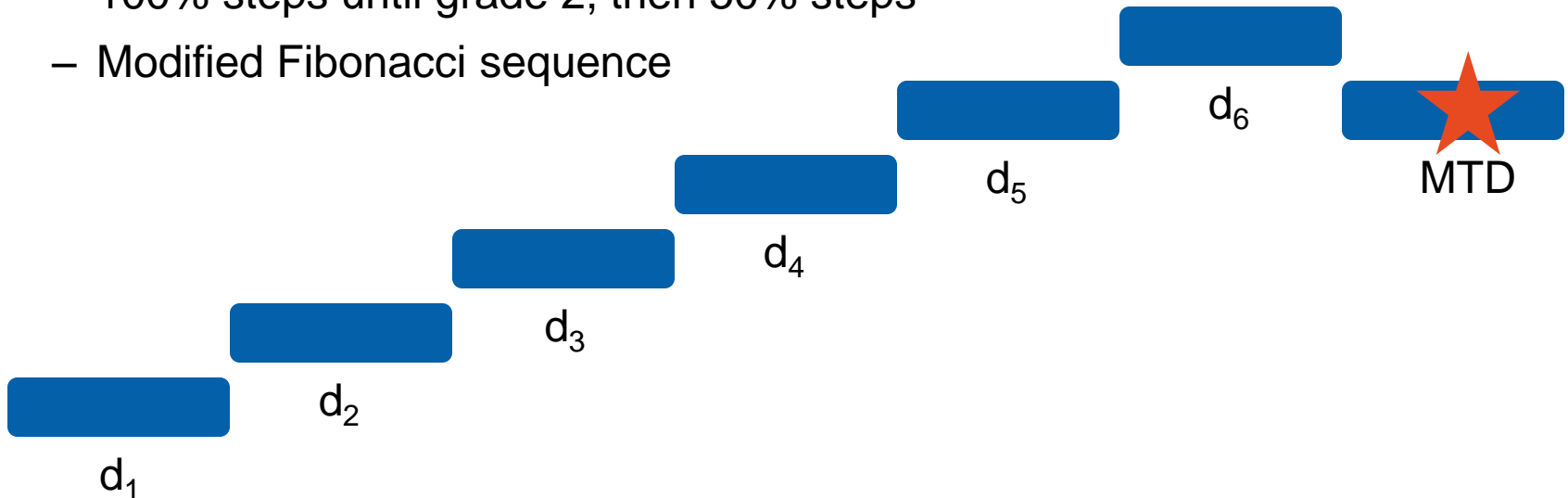
Traditional dose-escalation considerations

Phase I Trial Challenges	Design Requirements
Untested drug/combination in treatment-resistant patients	Escalating dose cohorts (3-6 patients)
Primary objective: determine MTD	Accurately estimate dose-limiting toxicity (DLT) rate
High toxicity potential: safety first	Robustly avoid toxic doses (“overdosing”)
Most responses occur 80%-120% of MTD (Joffe and Miller 2006 JCO)	Avoid subtherapeutic doses while controlling overdosing
Complete trial in timely fashion	Use available information efficiently

Find best dose(s) for next stage of development	Enroll additional patients at relevant doses (flexible cohort sizes)
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Dose escalation

- 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

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

1. Model-based dose-DLT relationships

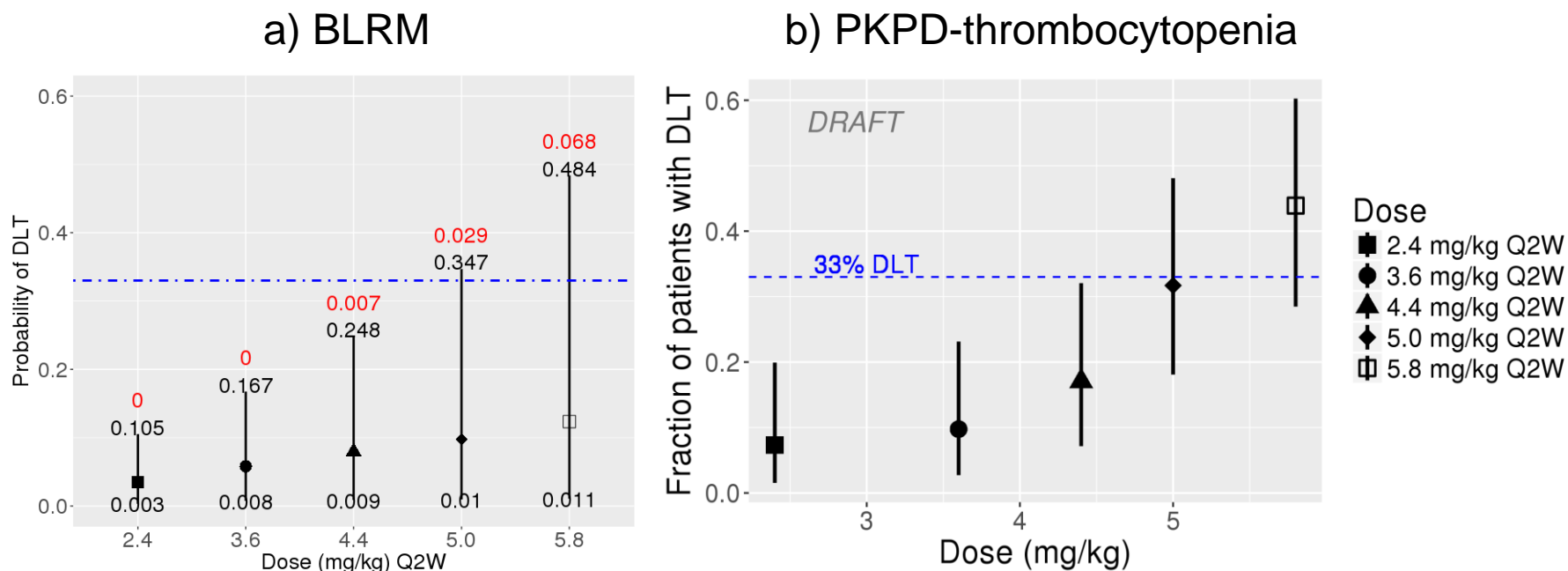
- Bayesian logistic regression model (BLRM) (Neuenschwander 2008)
 - Incorporate mixture priors accounting for species variability
 - Allow for a variety of shape parameters reflecting uncertainty
 - Adaptive dose-levels and cohort sizes
 - Exchangeability extensions to share information across populations (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)

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

Business or Operating Unit/Franchise or Department



Dose-escalation

- What if we do not expect to see DLT?
- Novel treatments have potential for reduced risk of acute toxicity
 - Immunotherapy (e.g., PD-1/PD-L1 checkpoint inhibitors)
 - Cook et al. (2015) provide a nice review
- May see longer-term side effects from chronic dosing
 - Incorporate longitudinal safety review
 - Model-based approaches (e.g., TITE-CRM, By-Cycle BLRM)
 - Assessing by grade and type of toxicity (Meille et al. 2008)
 - Study designs should allow the study of alternate schedules without need for amendment to mitigate longer-term safety concerns
 - Modeling should assess impact of PK on safety, PD and tumor growth

Moving from dose-escalation to dose-finding paradigm

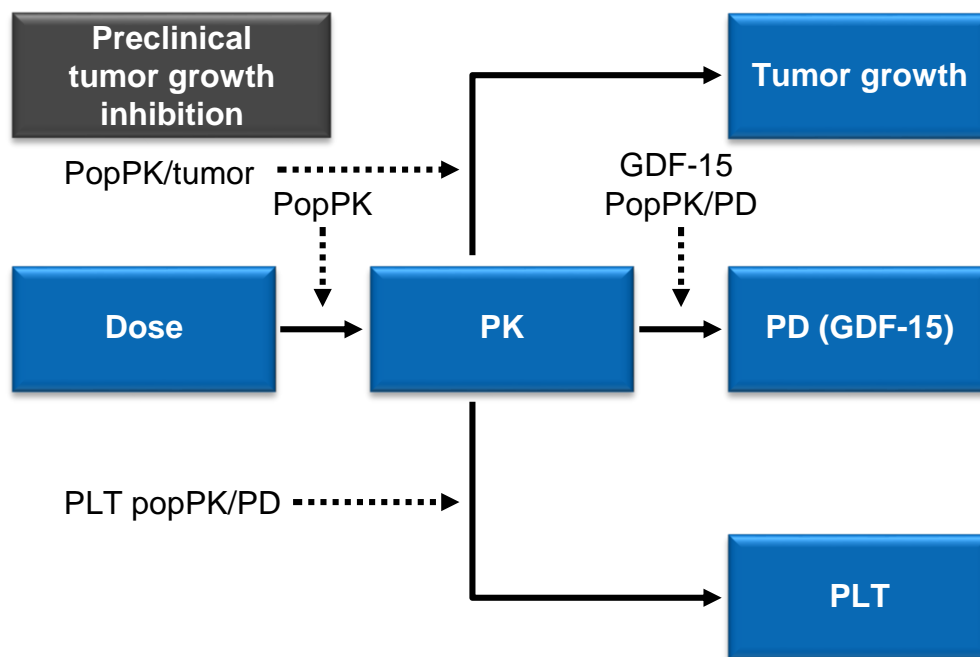
- From preclinical studies we have data on
 - Exposures related to tumor stasis and regression
 - PK/PD modeling of target engagement
 - Physiological models for PD or lab changes related to potential adverse events
- Non-safety primary endpoints
 - Need to increase data across multiple “relevant” doses
 - 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

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

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)

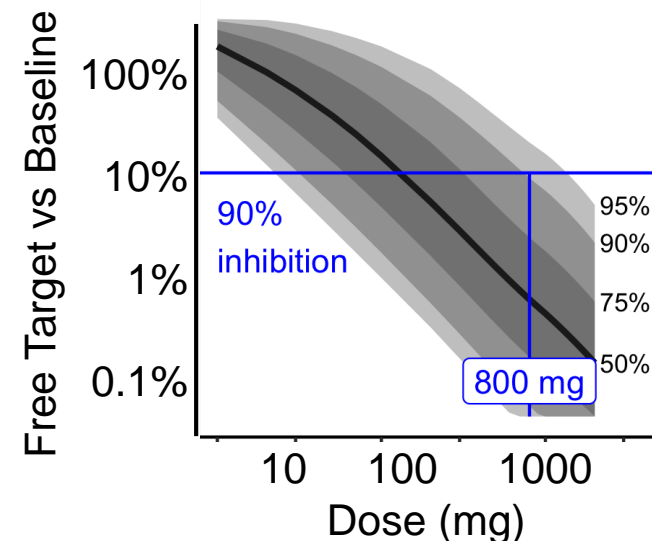


When safety, efficacy, and biomarker data is insufficient for dose selection, we can use target engagement prediction

- 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



Conclusions

- Can't forget safety but..
- We need to move beyond the “more-is-better” mindset and be smarter in dose-finding and design
- Complementary modeling approaches should support decision making while safety is controlled
- May need to study more than one dose level or regimen within phase II or pivotal studies

References

- Braun T (2006). Generalizing the TITE-CRM to adapt for early- and late-onset toxicities. *Statist. Med.*, 25(12); 2071-2083
- Cook, N. et al. (2015). Early phase clinical trials to identify optimal dosing and safety. *Molecular Oncology*, 9: 997-1007
- Cotterill, A. et al. (2015). A practical design for a dual-agent dose-escalation trial that incorporates pharmacokinetic data. *Statist. Med.*, 34, 2138–2164
- Joffe, Miller (2006). Rethinking risk-benefit assessment for Phase I cancer trials. *Journal of Clinical Oncology*, 24: 2987-2990
- Meille, C. et al. (2008). New Adaptive Method for Phase I Trials in Oncology. *Clinical Pharmacology and Therapeutics*, 83(6); 873-881
- Meille C et al. (2017) Optimization of the dose and schedule of an HDM2 inhibitor NVP-HDM201 in a first-in-human Phase I study using a mechanism-based PK/PD model [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2017; 2017 Apr 1-5; Washington, DC. Philadelphia (PA): AACR; Cancer Res 2017;77(13 Suppl):Abstract nr CT154. doi:10.1158/1538-7445.AM2017-CT154

References

- Neuenschwander, B. et al. (2010) Summarizing historical information on controls in clinical trials. *Clinical Trials*, 7: 5–18.
- Neuenschwander, B. et al. (2016). Robust exchangeability designs for early phase clinical trials with multiple strata. *Pharm. Stat.*, Mar-Apr;15(2):123-34.
- Piantadosi, S. and Liu, G. (1996). Improved designs for dose escalation studies using pharmacokinetic measurements. *Statist. Med.*, 15, 1605–1618.
- Stein, A and Ramakrishna R. (2017). AFIR: A Dimensionless Potency Metric for Characterizing the Activity of Monoclonal Antibodies. *CPT Pharmacometrics Syst. Pharmacol.* 00, 00
- Ursino et al. (2017). Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations. *Biom. J.*, Jul;59(4):804-825
- Wandel S, Wan K, Bailey S. (2018). A phase I dose-escalation model for anti-cancer immunotherapy combinations. *Submitted to JRSS-C*

Thank you