Pharmacokinetic and Pharmacodynamic Sciences in Oncology Drug Development: Enabling Rational Dose Selection from Translational to Global Drug Development

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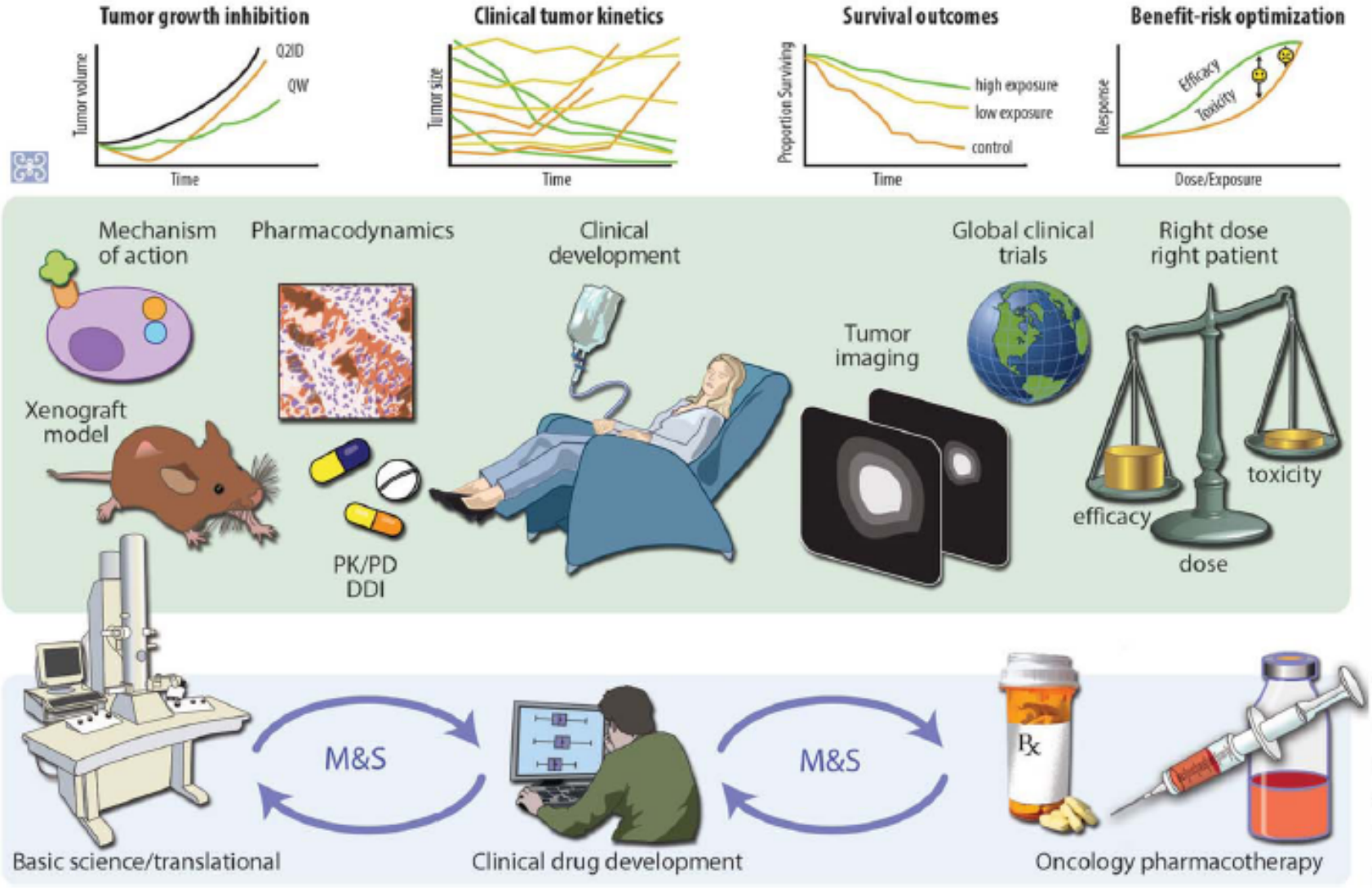
Outline of Presentation

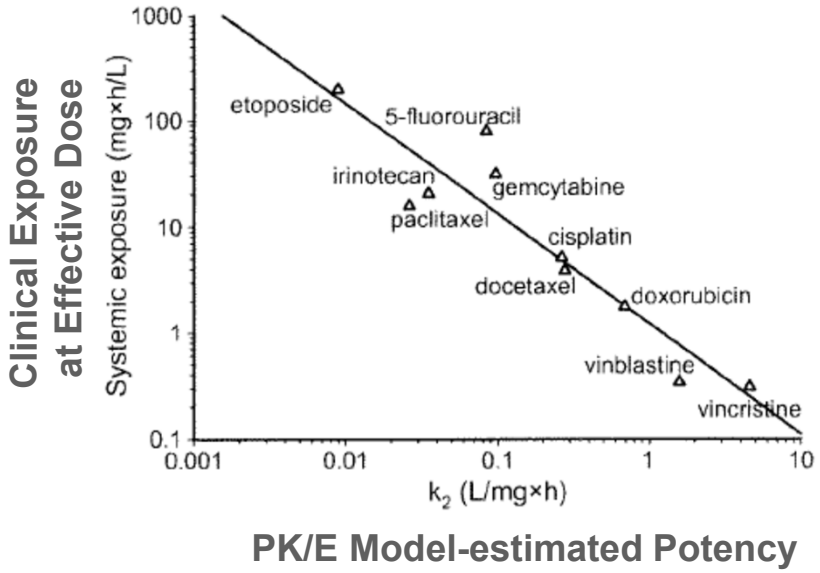
- Translational PK/PD Considerations
- Dose Selection in Early Drug Development
  - Case Study: Alisertib Single Agent and Combination with Paclitaxel
- Population Pharmacokinetics and Exposure-Response
  - Case Study: Ixazomib in Relapsed/ Refractory Multiple Myeloma
- Enabling Global Drug Development
  - Case Study: Alisertib in East Asian Patient Populations
- Concluding Remarks

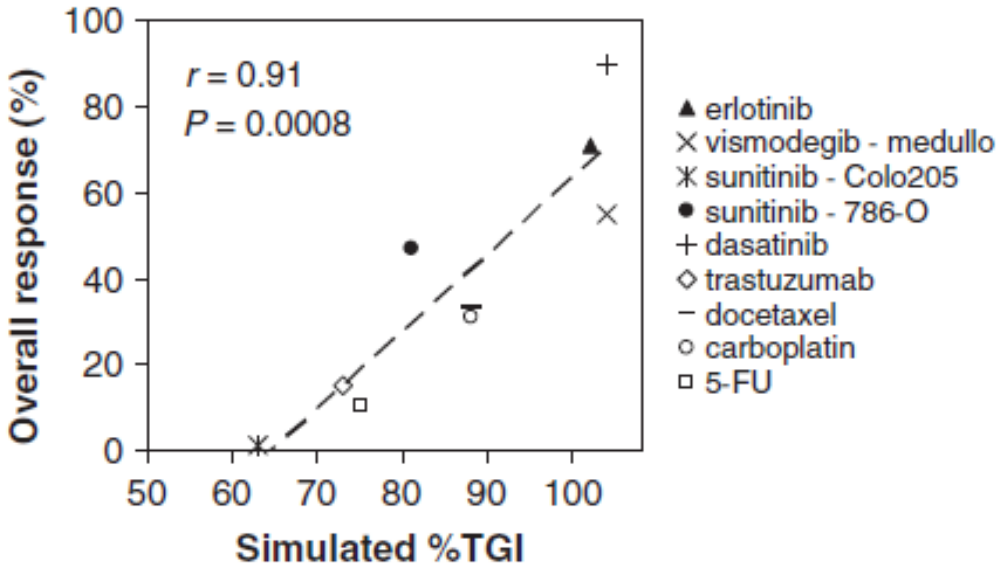
Quantitative Pharmacology Across the Continuum of Oncology Drug Development: Challenges and Opportunities



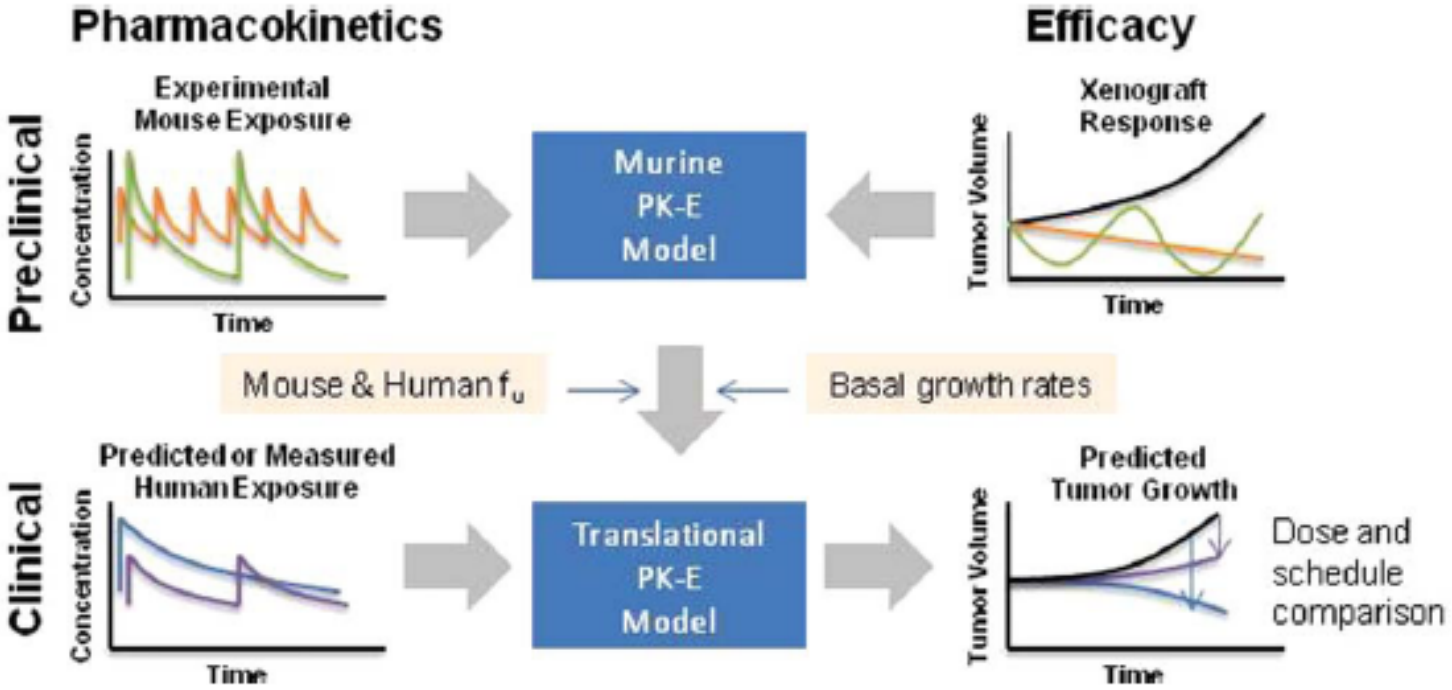
Venkatakrishnan K et al., Clinical Pharmacology and Therapeutics 97(1): 37-54, 2015

PK/PD Scientific Considerations are Crucial to Enhance Translational Utility of Mouse Xenograft Models





Translational PK/Efficacy Modeling and Simulation to Guide Clinical Dosing Schedules



Clinical Tumor Pharmacodynamic Studies –
Are they Adding Value as Designed and Analyzed?

VOLUME 34 · NUMBER 4 · FEBRUARY 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Analysis of Impact of Post-Treatment Biopsies in Phase I Clinical Trials

Randy F. Sweis, Michael W. Drazer, and Mark J. Ratain

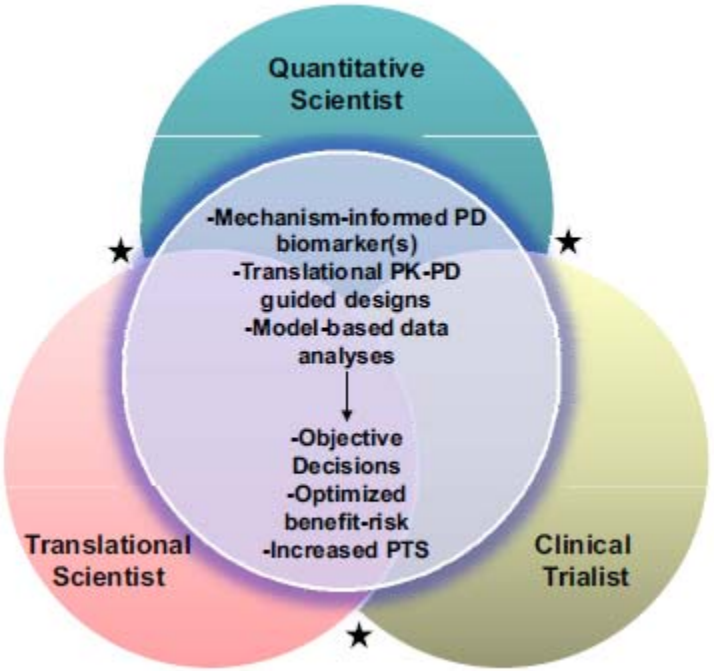
Only 17% of Ph 1's with Tumor PD assessments demonstrated positive PD effects!

Enhancing Value of Clinical Pharmacodynamics – *An Opportunity for Quantitative Clinical Pharmacology*

REVIEWS

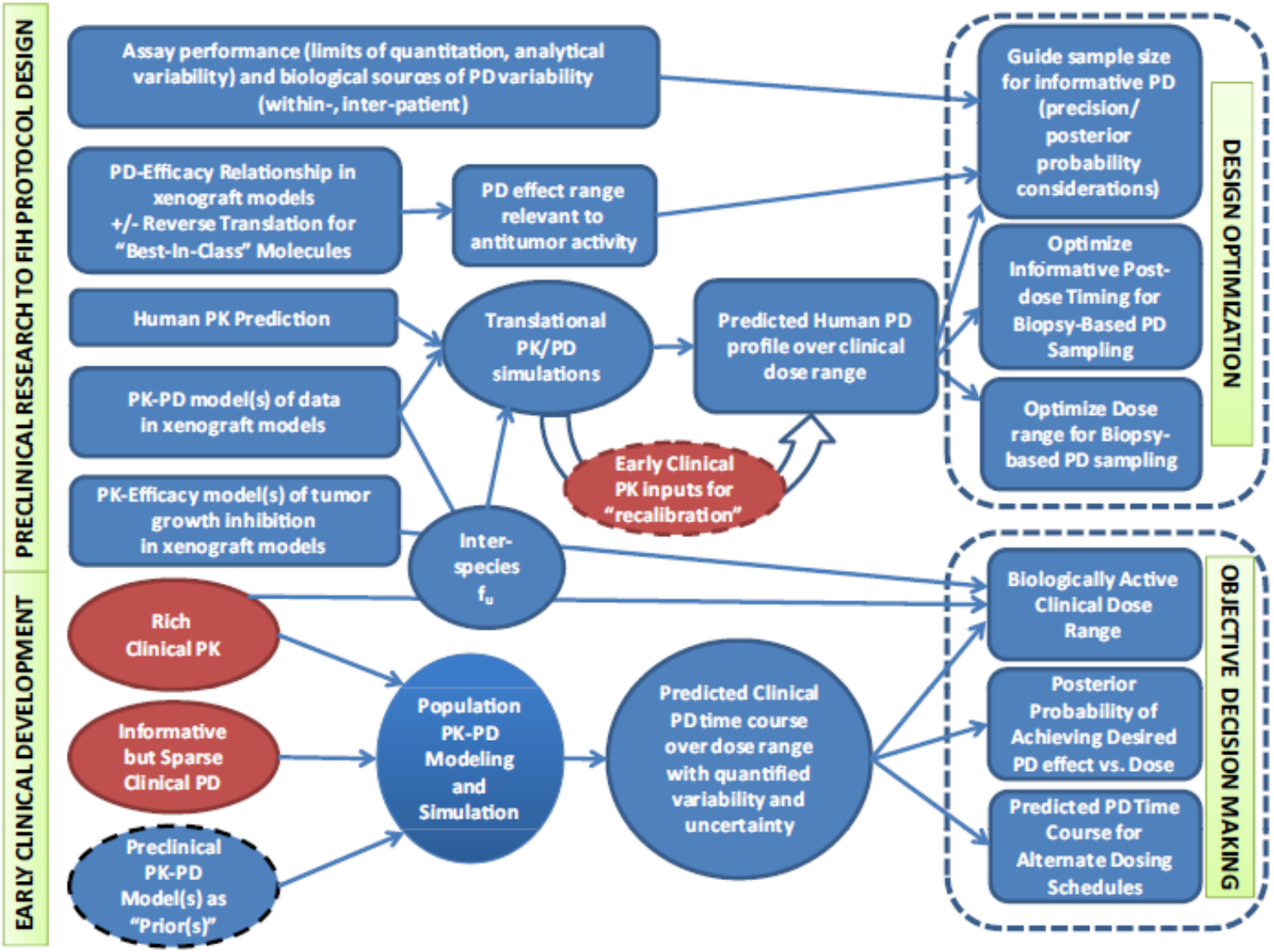
Enhancing Value of Clinical Pharmacodynamics in Oncology Drug Development: An Alliance Between Quantitative Pharmacology and Translational Science

K Venkatakrishnan[1] and JA Ecsedy[2]



Enhancing Value of Pharmacodynamics

An Analytical Framework Enabled by a *Totality of Evidence* Mindset



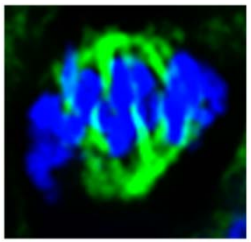
Venkatakrishnan K and Ecsedy JA, Clinical Pharmacology and Therapeutics 101(1): 99-113, 2017

Case Study:
Investigational Aurora A Kinase Inhibitor Alisertib

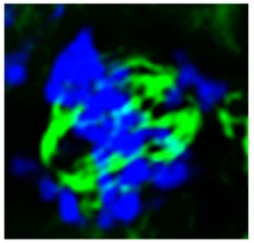
Selecting RP2D Leveraging Clinical Exposure-Tumor PD and Exposure-Safety Relationships

Exposure- Tumor PD Relationships for the Investigational Aurora A Kinase Inhibitor Alisertib to Guide RP2D/ Schedule Selection

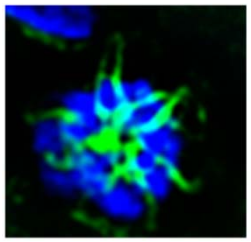
Aligned chromosomes
Bipolar spindle

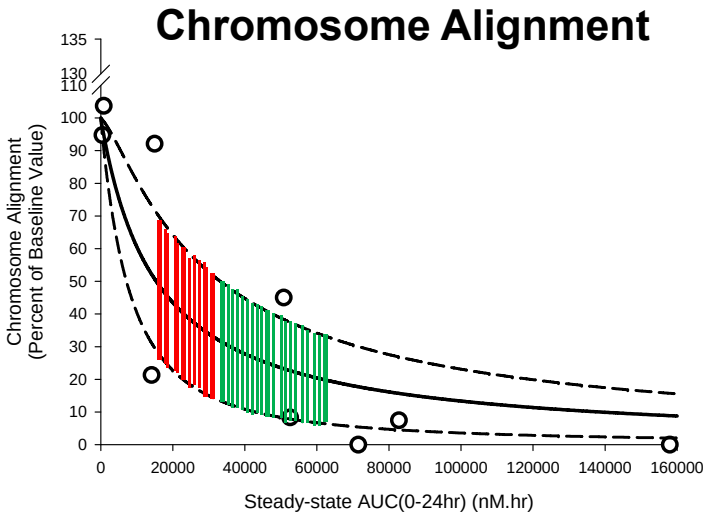


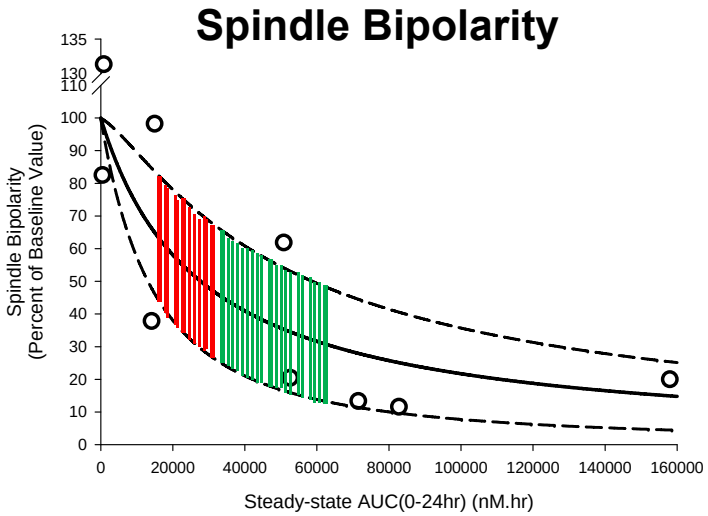
Unaligned chromosomes
Bipolar spindle



Unaligned chromosomes
Non-bipolar spindle



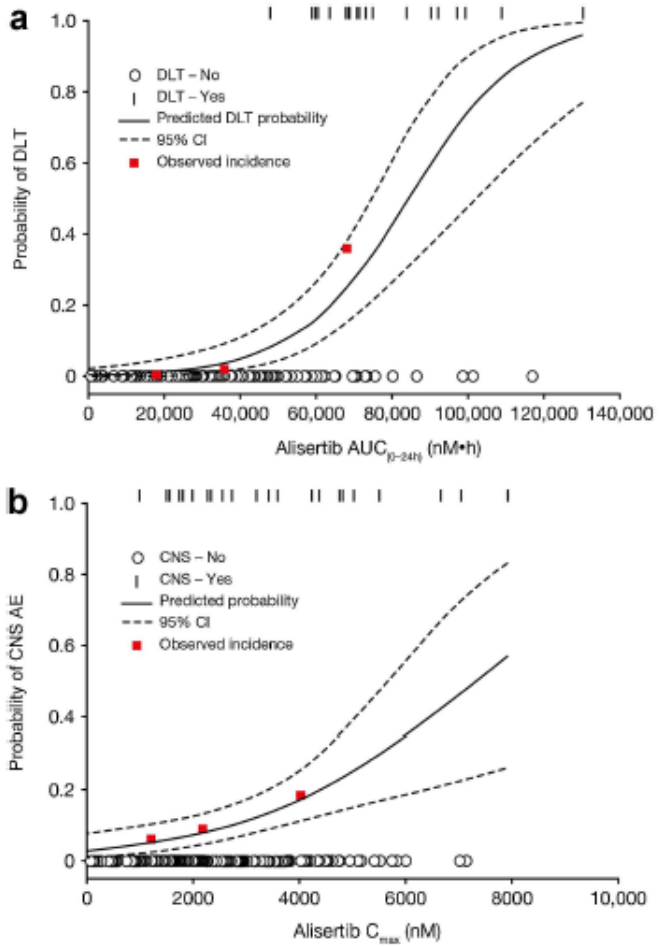


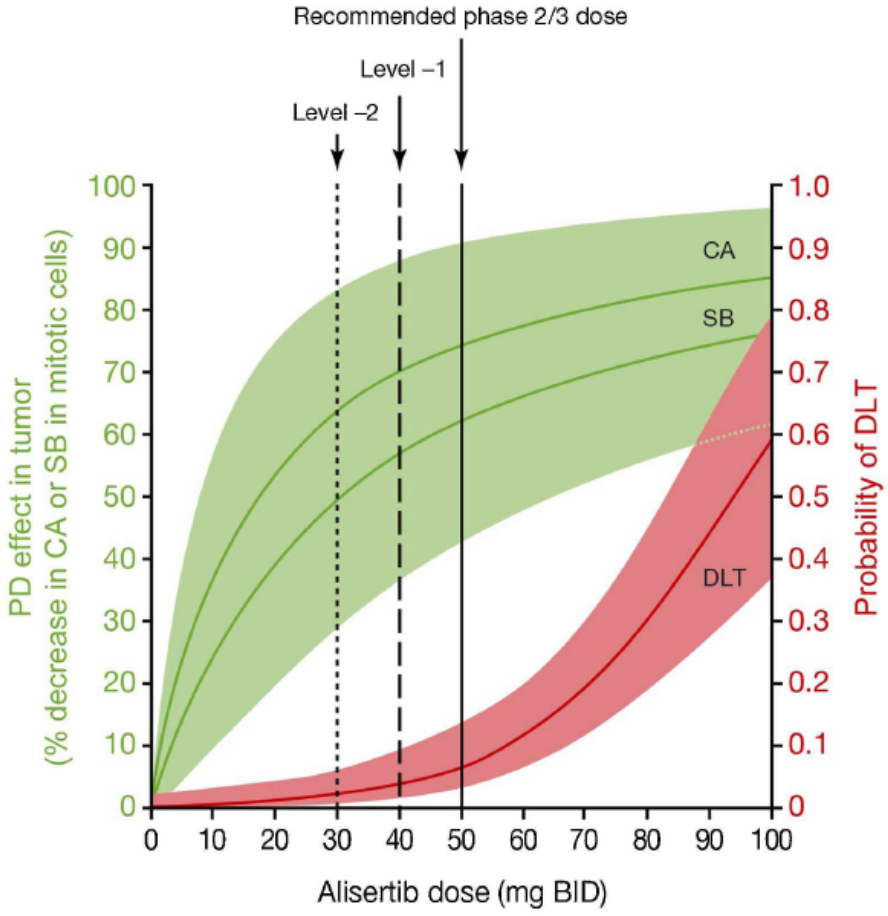


Schedule	MTD	Dose density (mg/day)	$AUC_{0\text{-}24h,ss}$ (μM.hr) IQR	Tumor PD (%↓ in CA/SB) IQR
7on/ 14off	50 mg BID	33.3	33-63	**68-80 / 55-70**
21on/ 14off	50 mg QD	30.0	17-31	**52-67 / 38-53**

Venkatakrishnan K et al., Journal of Clinical Pharmacology 55(3): 336-347, 2015

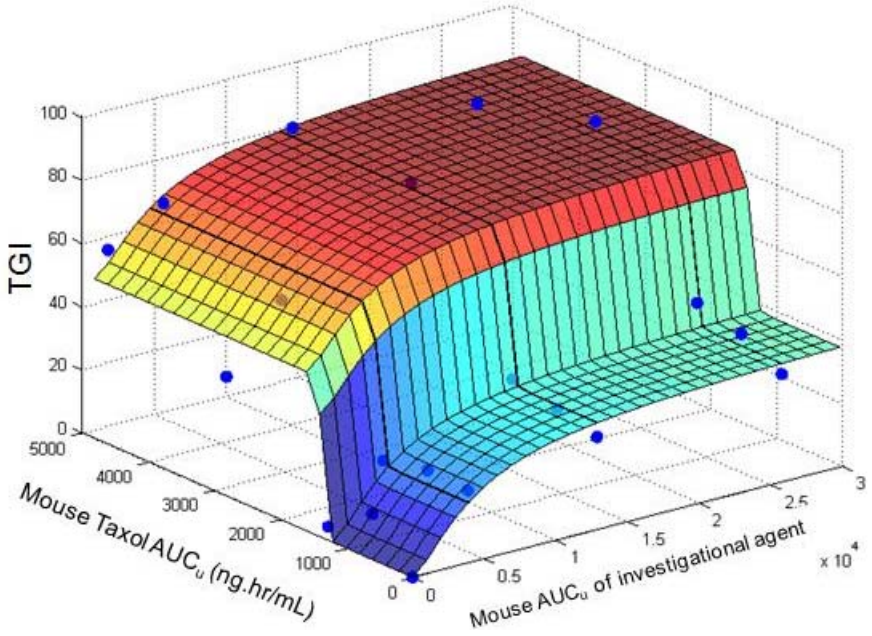
Therapeutic Index Understanding for the Investigational Agent Alisertib Informed by Population PK, Exposure-PD and Exposure-Safety Analyses



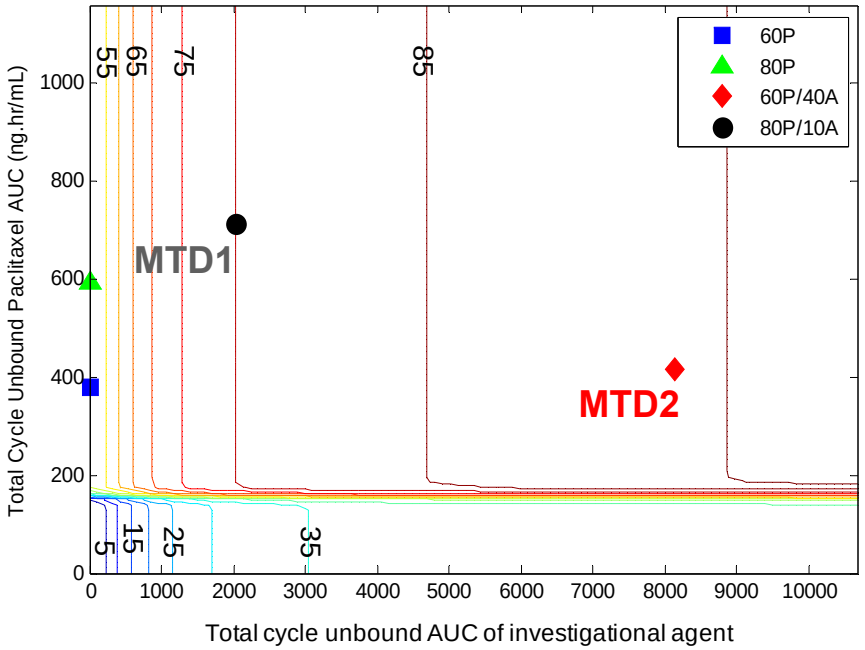


Translational Exposure-Efficacy Modeling for Drug Combinations: RP2D Selection for Alisertib-Paclitaxel

TGI Response Surface



Isobologram



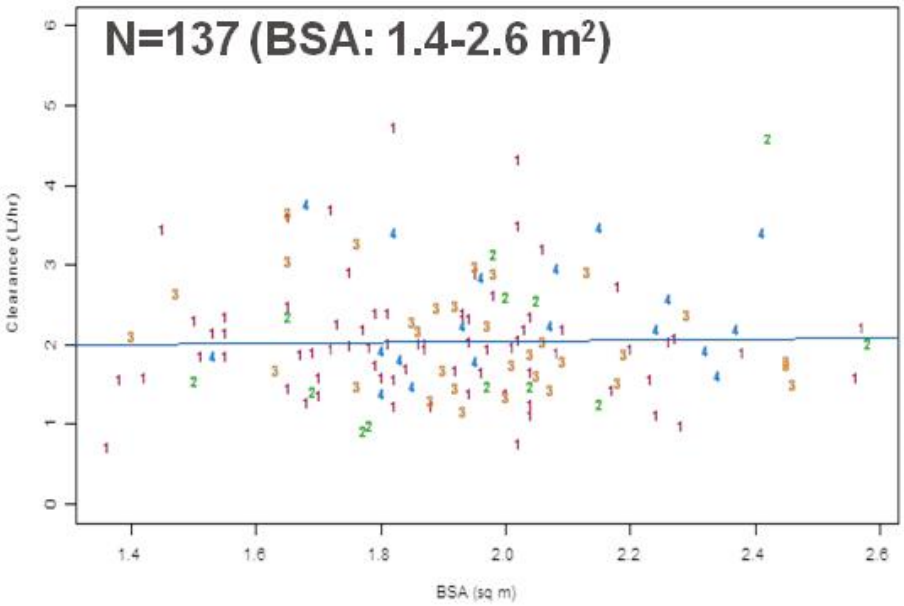
- Two MTDs determined in Phase 1b
  - MTD1: Full weekly paclitaxel dose (80 mg/m^2) plus 10 mg BID alisertib
  - MTD2: Level -1 weekly paclitaxel dose (60 mg/m^2) plus 40 mg BID alisertib
- MTD2 selected as RP2D based on translational PK/PD considerations

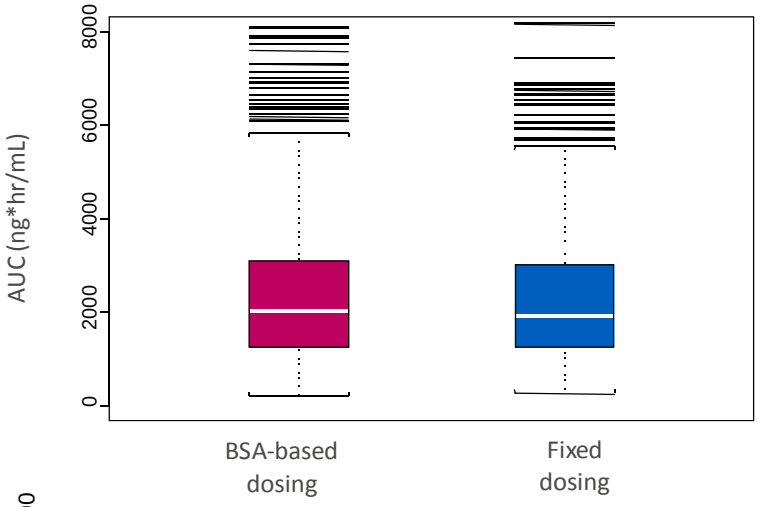
Huck JJ et al., Molecular Cancer Therapeutics 13(9):2170-83, 2014

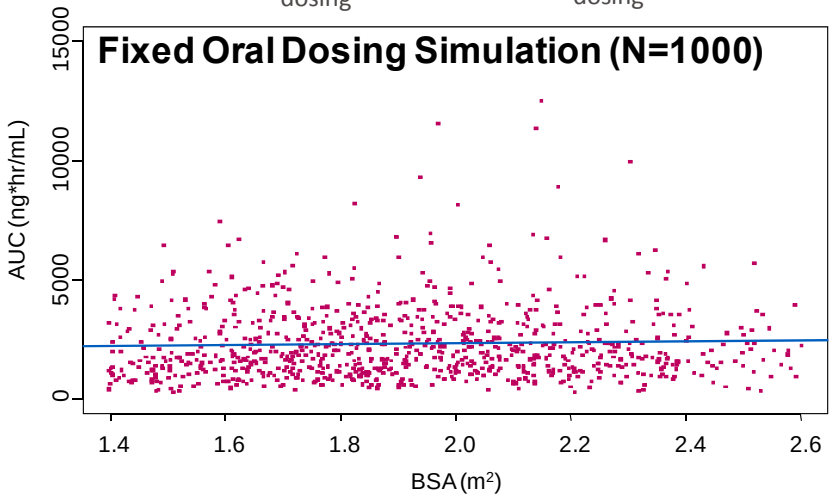
Case Study:
Ixazomib for Relapsed/ Refractory Multiple Myeloma

Population PK and Exposure-Response Applications in Support of the Approved Dose in Combination with Lenalidomide and Dexamethasone (Len-Dex)

Population PK Analysis at End of Phase 1: Model-Informed Switch from BSA-Based to Fixed Dosing



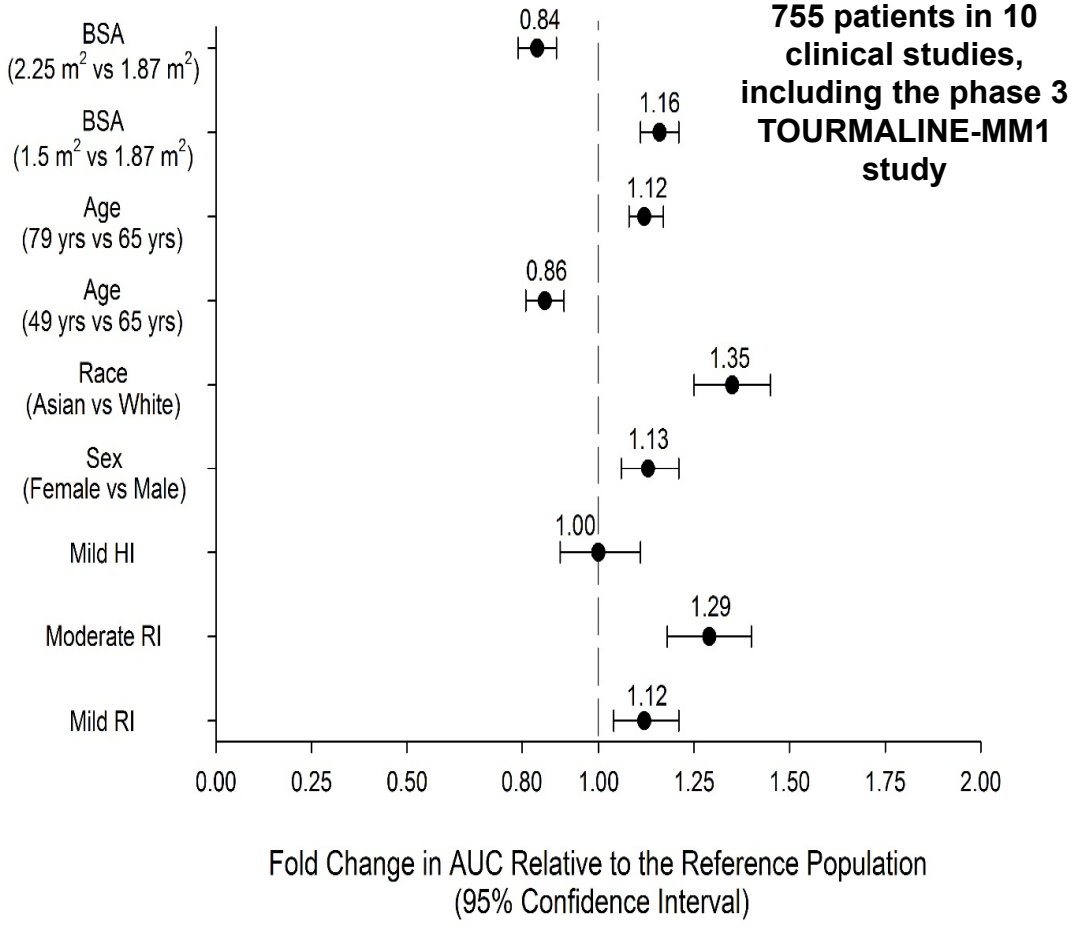




Gupta N et al., British Journal of Clinical Pharmacology 79(5):789-800, 2015

Population PK analysis at End of Phase 3: Model-Informed Labeling/ Dosing Recommendations

- No dose adjustments for
  - BSA
  - Age
  - Race
  - Sex
  - Mild hepatic impairment
  - Mild/moderate renal impairment



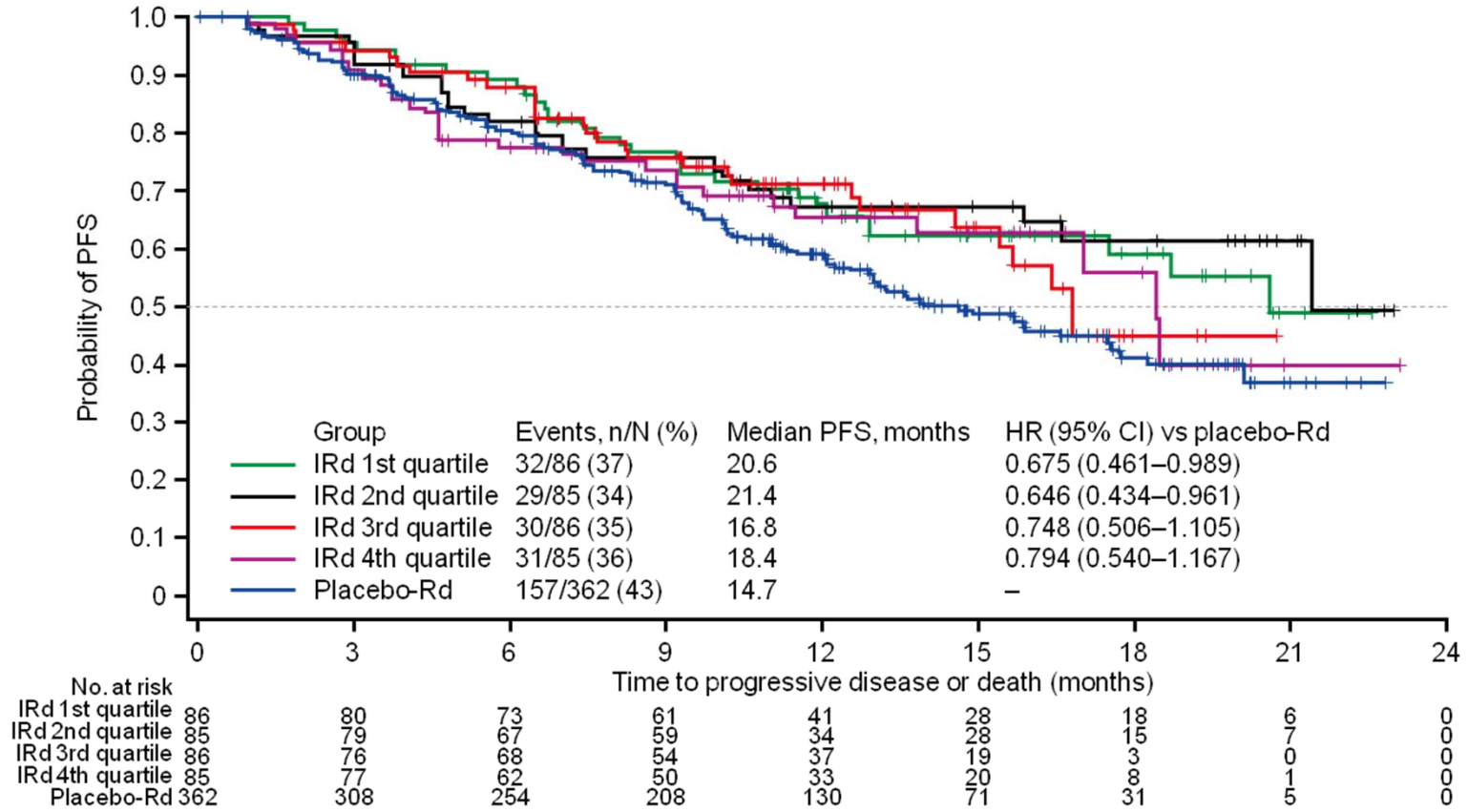
755 patients in 10 clinical studies, including the phase 3 TOURMALINE-MM1 study

For BSA and Age, median values are compared 5th and 95th pct

Gupta N et al., Clinical Pharmacokinetics 56(11):1355-1368, 2017

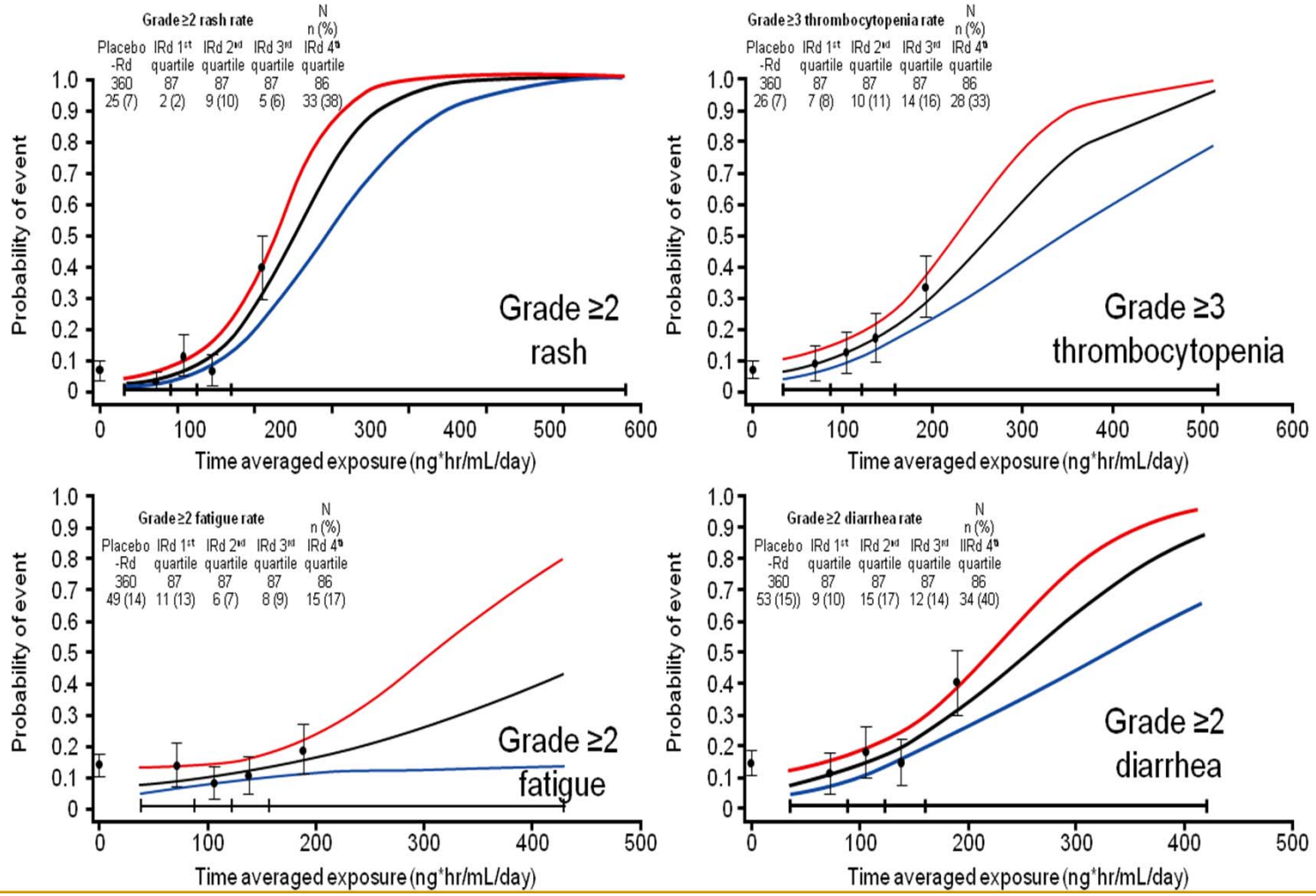
Ixazomib-Len-Dex in Relapsed/ Refractory Multiple Myeloma in TOURMALINE-MM1 Phase 3 Trial –

Consistent Efficacy Across Ixazomib Exposure Quartiles Supports 4 mg Weekly Starting Dose



Gupta N et al., Targeted Oncology 12(5):643-654, 2017

Exposure-Related increase in Probability of TEAEs of Clinical Interest Supports Ixazomib Dose Reduction Guidelines (4 mg → 3 mg → 2.3 mg)

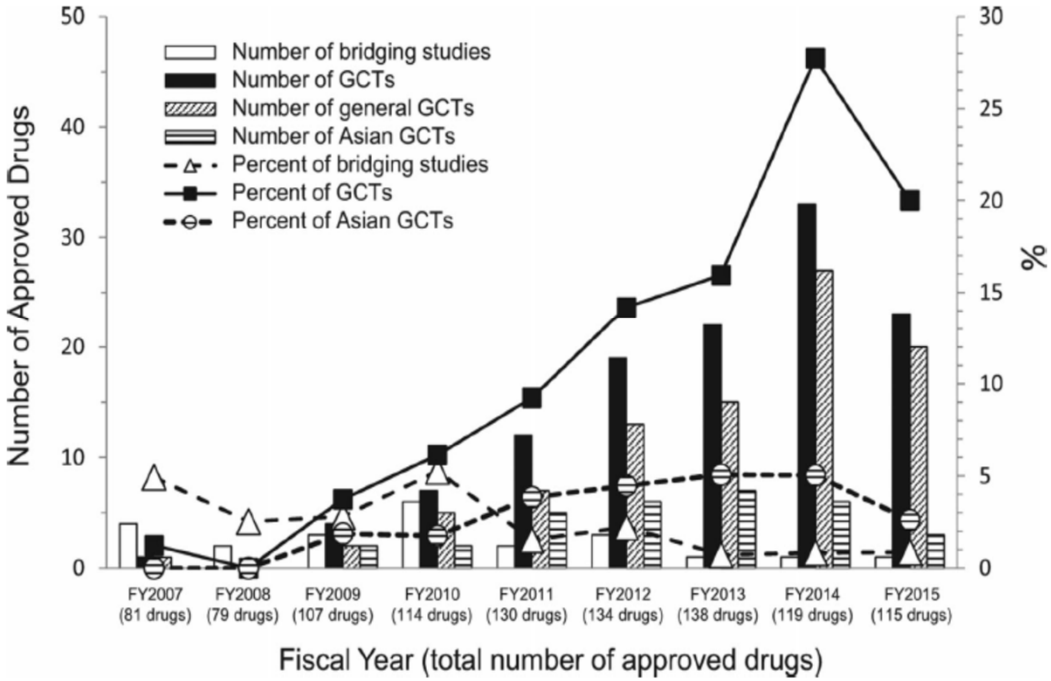


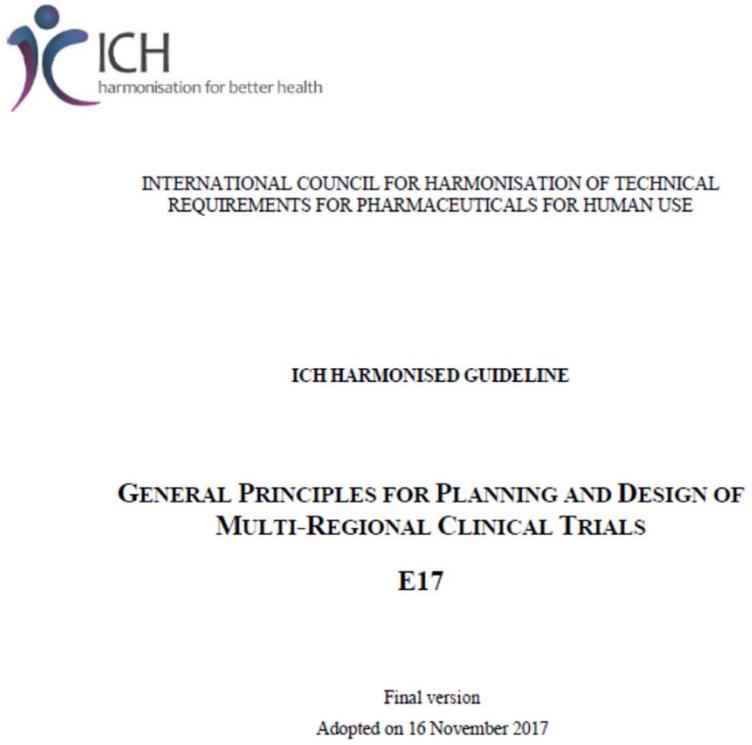
Gupta N et al., Targeted Oncology 12(5):643-654, 2017

Case Study:
Alisertib in East Asian Patient Populations

Value of Population Pharmacology in Defining Dosage for Global Clinical Development

Multi-Regional Clinical Trials and ICH E17 – Opportunities for East Asia-Inclusive Global Clinical Development





ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GENERAL PRINCIPLES FOR PLANNING AND DESIGN OF MULTI-REGIONAL CLINICAL TRIALS

E17

Final version

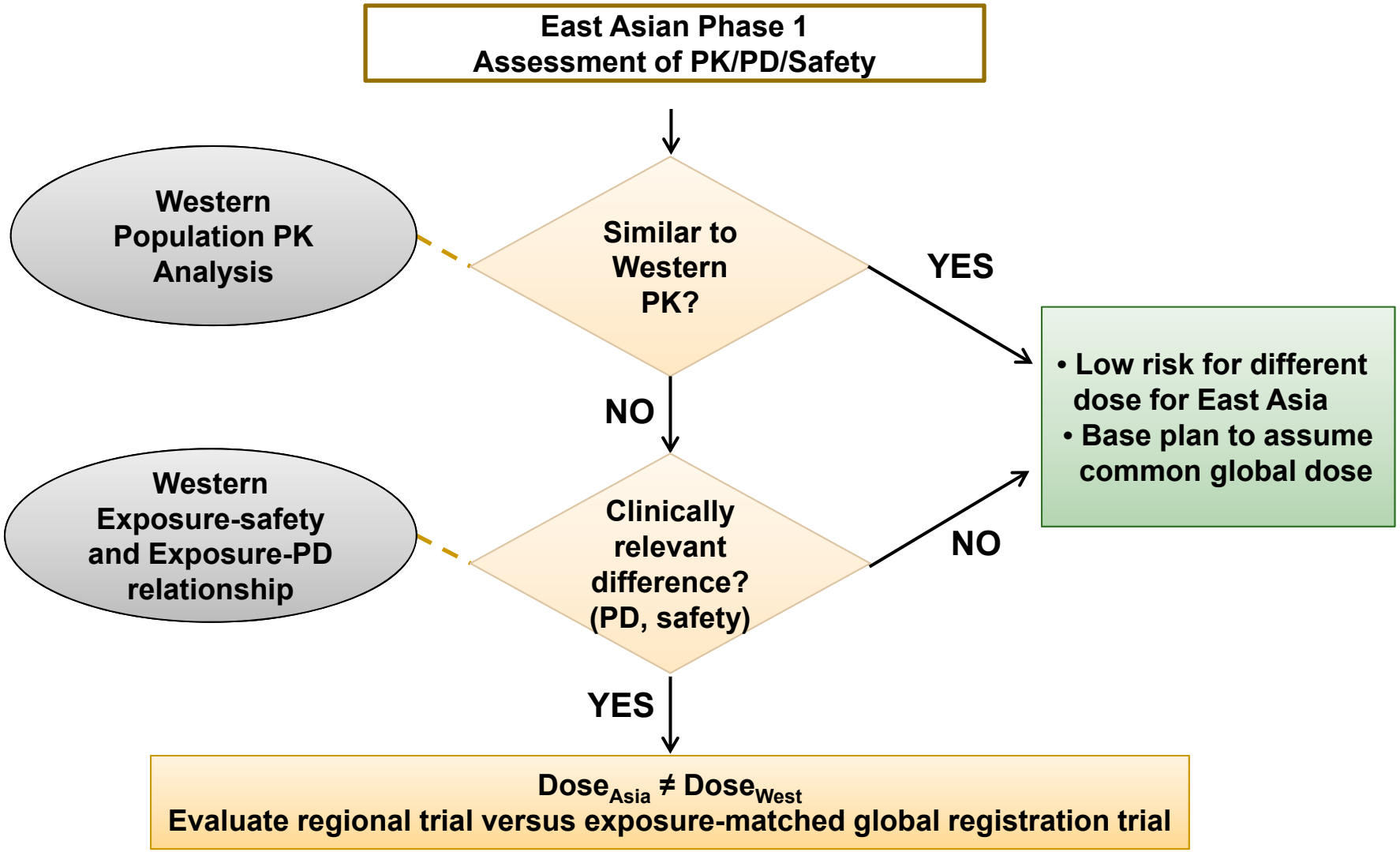
Adopted on 16 November 2017

- Global MRCTs on the rise, notably in oncology and in rare diseases
- ICH E17 offers opportunities for efficient global drug development

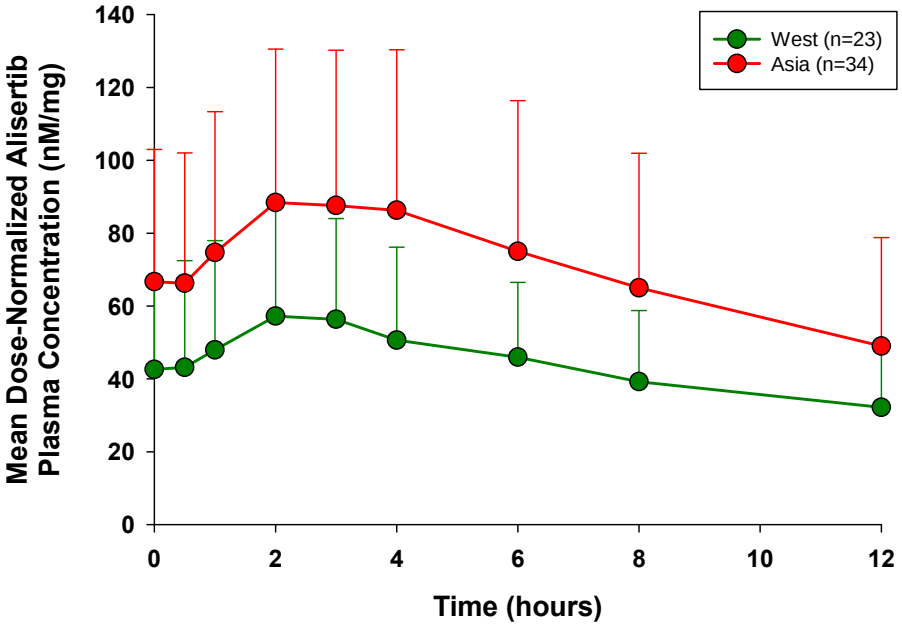
Asano K et al., Clinical and Translational Science 11: 182–188, 2018

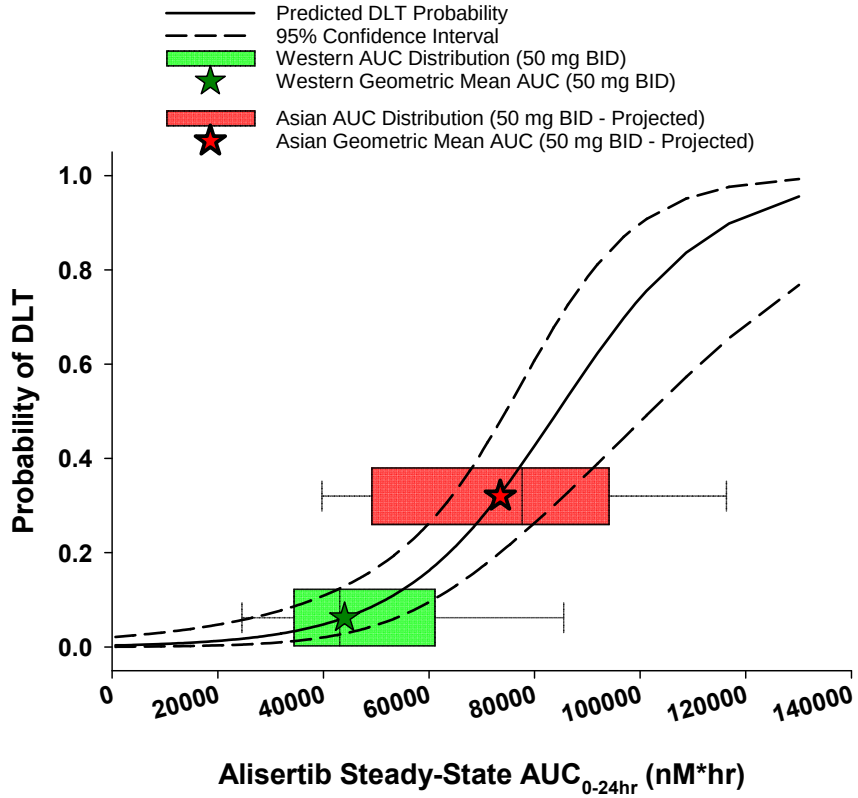
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E17/E17EWG_Step4_2017_1116.pdf

Roadmap for PK/PD/Safety Guided Dose Decisions in East Asia-Inclusive Global Oncology Drug Development



Alisertib in East Asia –
An example of clinically relevant PK differences

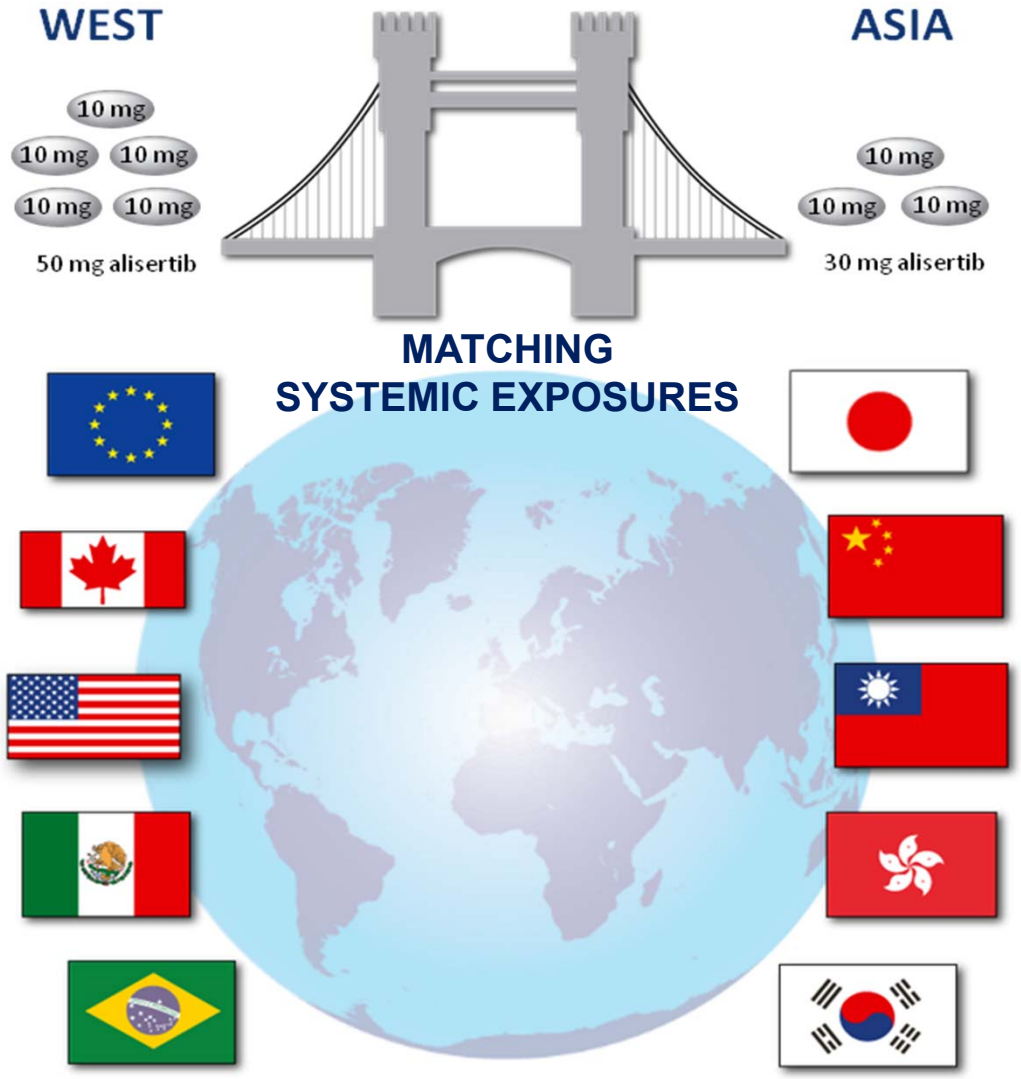




- **PK/PD considerations supported a lower (30 mg vs. 50 mg) dose in East Asia**

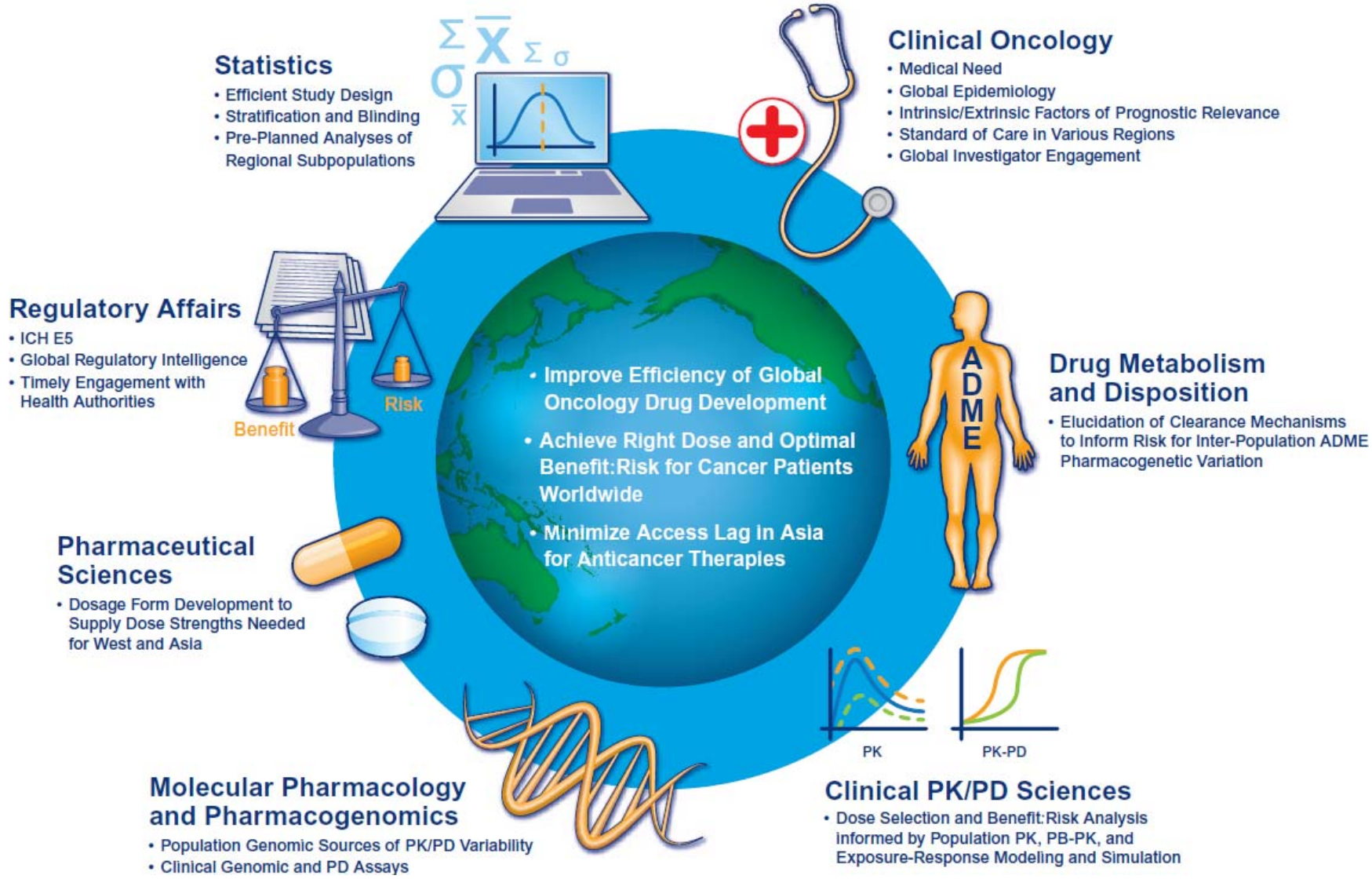
Venkatakrishnan K et al., Investigational New Drugs 33(4):942-53, 2015

Dosing Rationale for East Asia-Inclusive Global Development



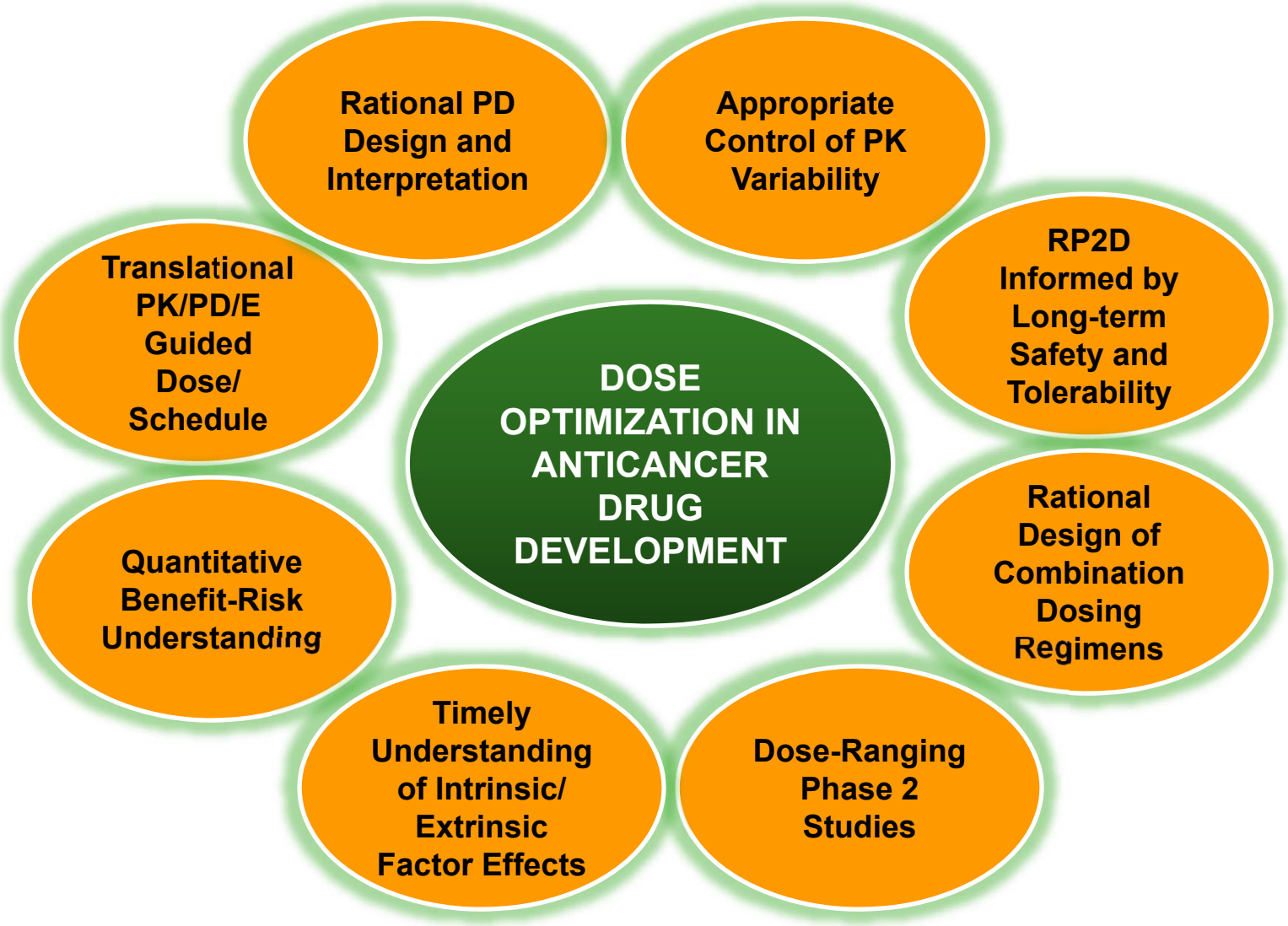
Global Oncology Drug development

A Multi-Disciplinary Approach



Venkatakrishnan K et al., Clinical and Translational Science 9: 9-22; 2016

To conclude…


Rational PD Design and Interpretation
Appropriate Control of PK Variability
RP2D Informed by Long-term Safety and Tolerability
Rational Design of Combination Dosing Regimens
Dose-Ranging Phase 2 Studies
Timely Understanding of Intrinsic/ Extrinsic Factor Effects
Quantitative Benefit-Risk Understanding
Translational PK/PD/E Guided Dose/ Schedule
DOSE OPTIMIZATION IN ANTICANCER DRUG DEVELOPMENT

Acknowledgments

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- Chirag Patel, Ph.D., Quantitative Clinical Pharmacology, Takeda
- Dean Bottino, Ph.D., Quantitative Clinical Pharmacology, Takeda

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- Takeda TREC/ OTAU Leadership

- Investigators
- Patients and their families

Thank you!

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