Oncology dose optimization – how to optimize the trade-offs

Chunze Li, Genentech, Inc

On Behalf of Roche/Genentech Dose optimization working group

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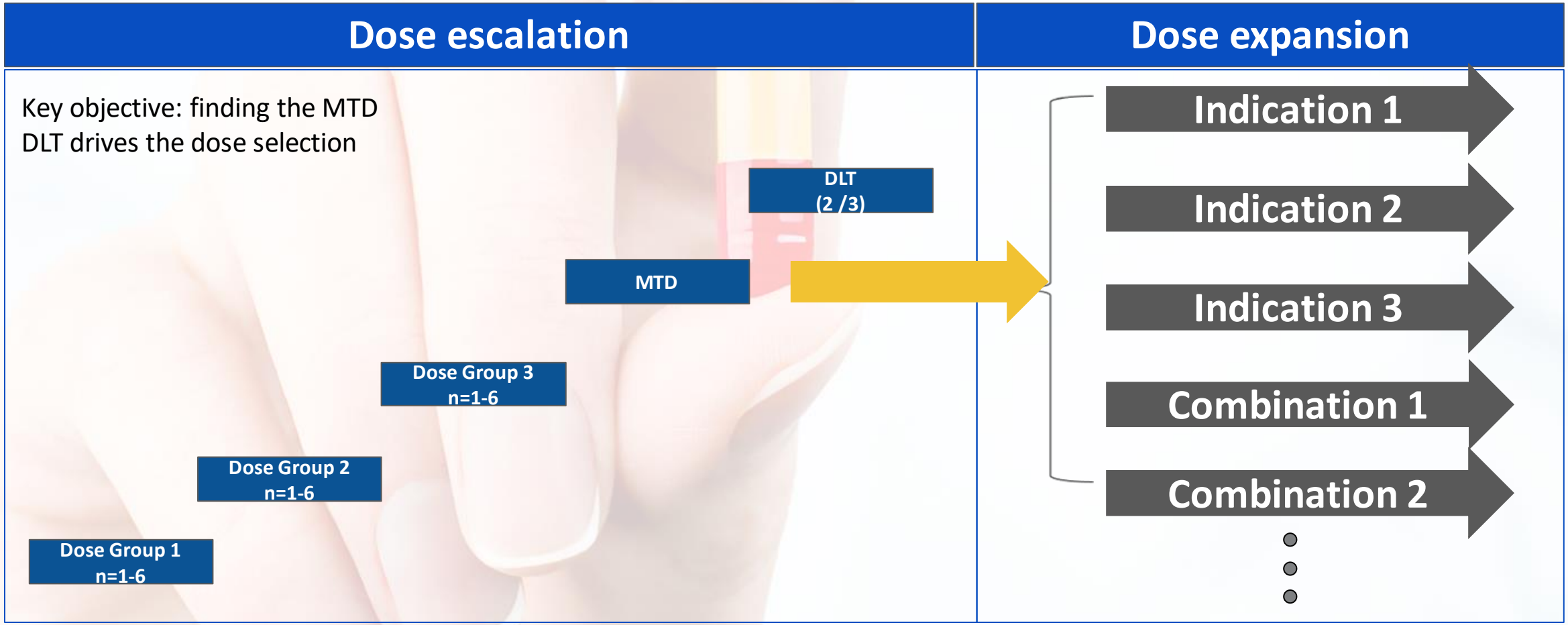
Traditional Oncology Dose Finding - MTD Paradigm

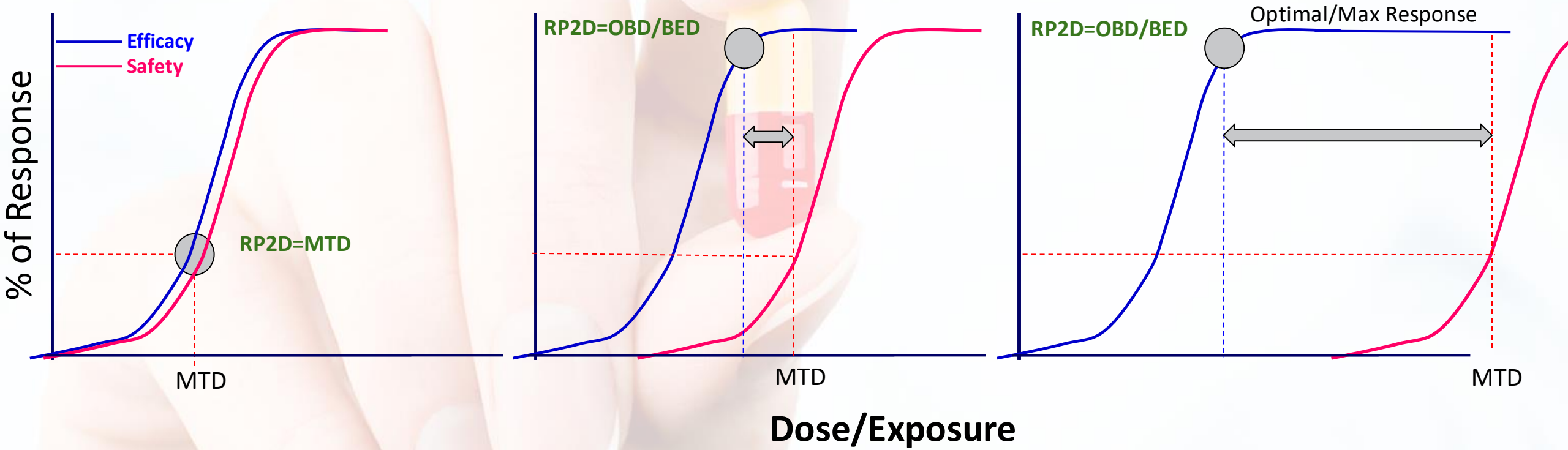


Concept of Oncology Dose Finding

Chemotherapy
(e.g., paclitaxel, carboplatin, doxorubicin)

Targeted Therapy (SM/ADCs)
(e.g., Erdafitinib, Osimertinib, pola)

mAbs
(e.g., Pembrolizumab, trastuzumab, bevacizumab)



MTD Paradigm: Designed for chemotherapy as efficacy & toxicity often correlated (more is better)

MTD Paradigm is not applicable for modern target or Immuno-therapeutics as higher dose does not necessarily results in greater anti-tumor effect: BED/OBD might be more relevant

In reality, the true dose response curve is unknown

MTD: maximal tolerant dose;
OBD: optimal biological dose,
BED: biological effective dose

Dose Optimization in Oncology: Path Forward

Holistic but not "one-size-fits-all" approach

Strategic Context

disease specific need for efficacy and patient tolerance/experience, CMC feasibility, unmet medical need, speed &competition

Innovative/adaptive Study Design

- Backfill cohorts
- Multiple dose expansion cohorts
- Randomized dose finding
- adaptive study with registration potential
- WoO Biomarker study
- Collect robust clinical data across multiple doses, especially when benefit-risk is not clear across doses

Full Spectrum of Data & knowledge

- Preclinical & translational evidence
- PK (linearity, t1/2)
- PD biomarkers (MOA markers, IL-6, ct-DNA, MRD, tumor size)
- Pharmacology (RO)
- Safety (Cumulative Tox)
- Efficacy
- PRO (QoL, patient experiences)
- Competitor's data
- Platform data
- Disease biology

Predictive modeling (MiDD)

- Dose/exposure response analysis & PKPD (e.g., PK-biomarker, PK-TGI, translational PKPD, QSP) to provide quantitative evidence of dose selection
- Statistical & AI/ML modeling (e.g.,multivariate) to understand patient heterogeneity across doses

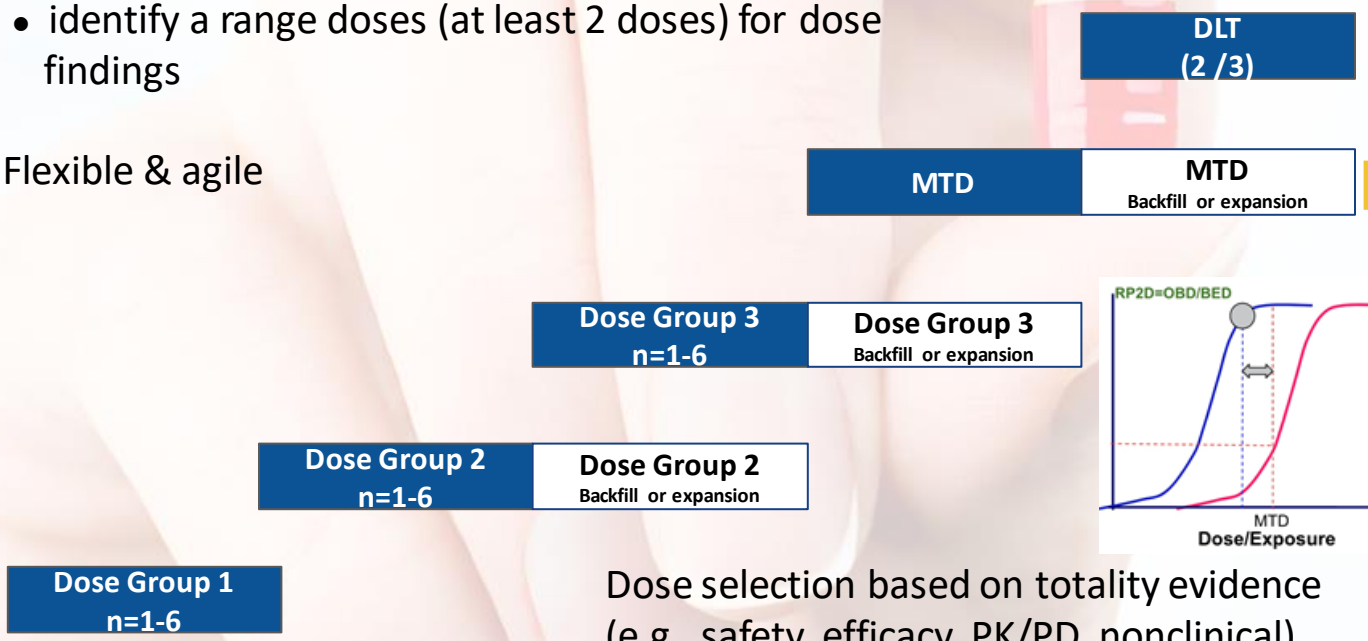
Integrated totality of data/evidence/practicality to support dose selection

Oncology dose finding - New Concept Framework

Dose Ranging

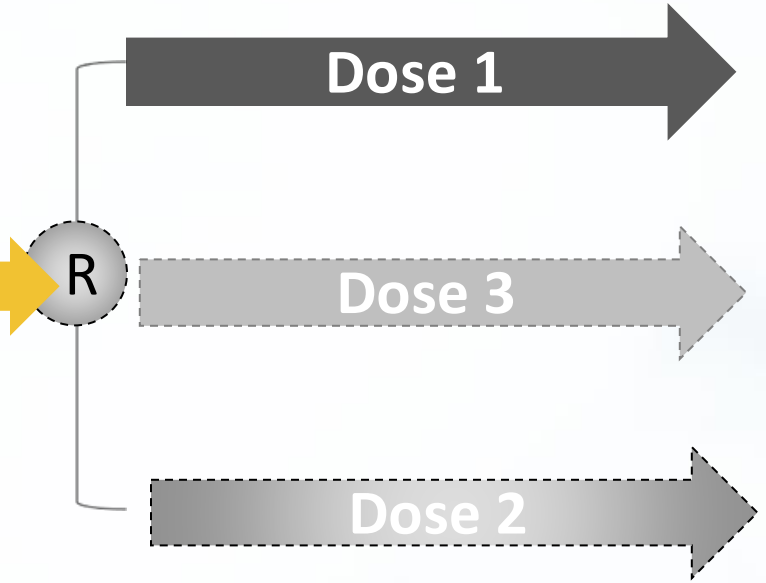
Key objectives
- Characterize the dose response curve
- identify a range doses (at least 2 doses) for dose findings

Flexible & agile



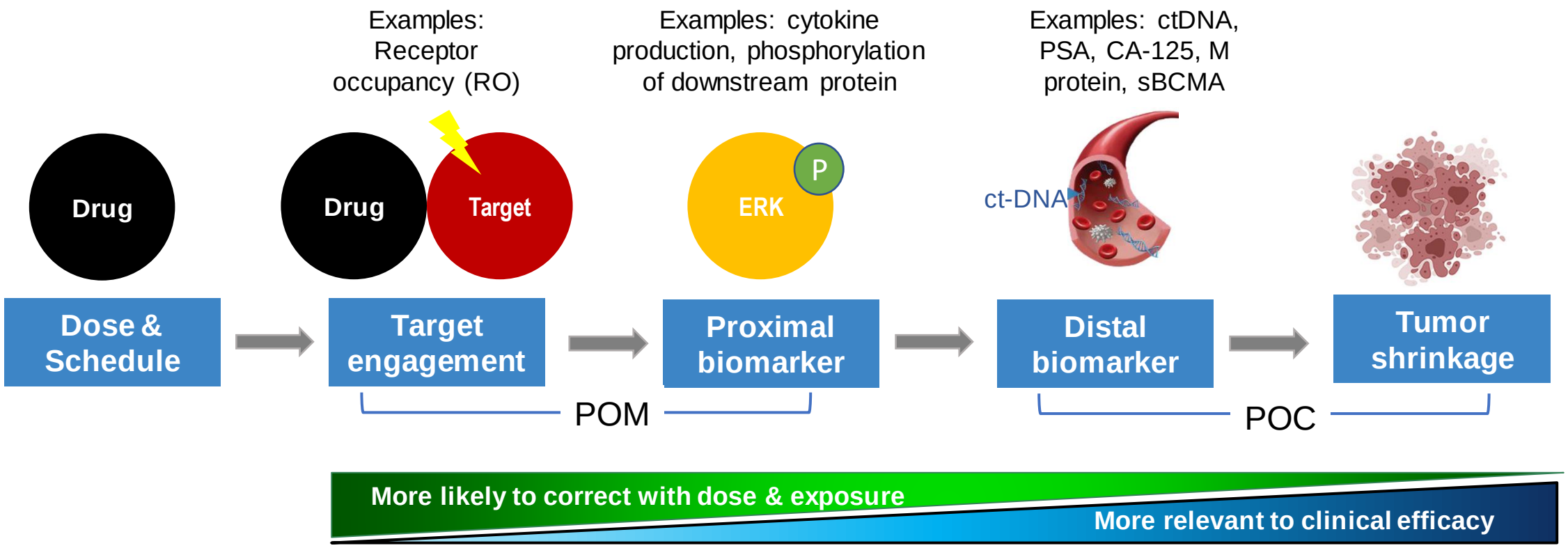
Dose selection based on totality evidence (e.g., safety, efficacy, PK/PD, nonclinical)

Dose Finding



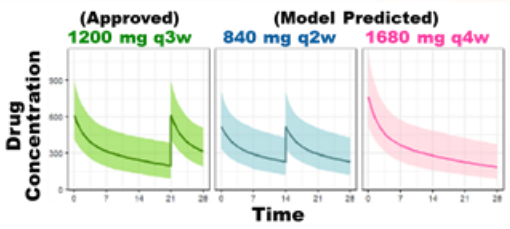
Could be part of adaptive pivotal study design

Clinically Relevant PD Biomarkers Important to support the Dose Optimization, but Unlikely to be useful in Isolation

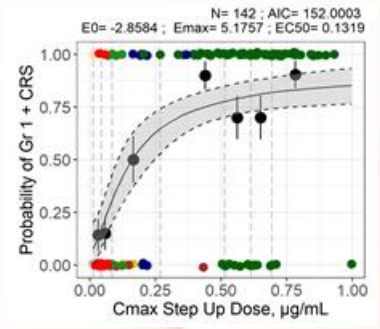


The selection of the relevant marker(s) for exposure-response (E-R) characterization is driven by the available **preclinical data**, drug MoA, and the biomarker(s) characterization, variability, dynamics, covariates etc.

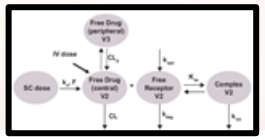
Quantitative Pharmacology Tools to Support Dose Finding and Selection

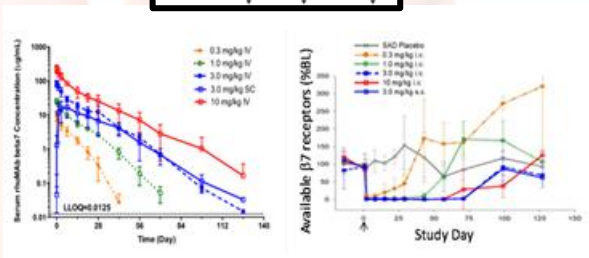


popPK

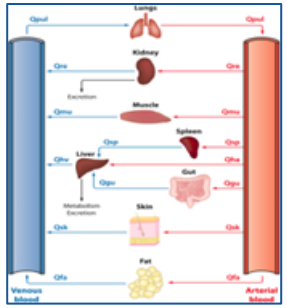


D/E-R



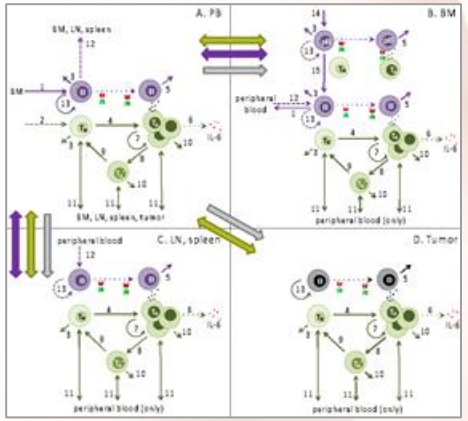


PKPD

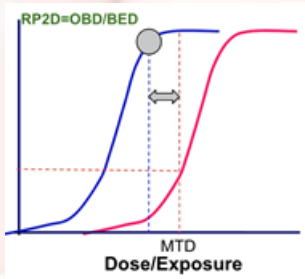


PBPK: DDI/specific populations/site of action

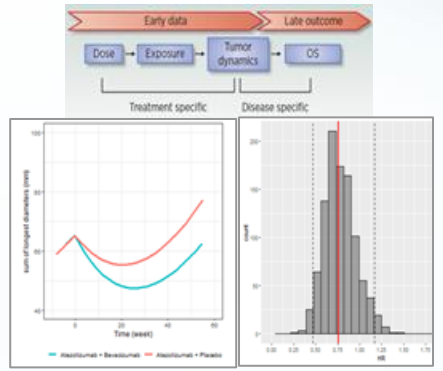
Model-based Meta Analysis



QSP



Dose Finding & Selection



Predictive Disease modeling (TGI-OS)

Path forward: Introduction to the Dose Snapshot:

Summary of key information critical for the rationale for dose selection

Key Areas included in the Dose Snapshot:

- **Supporting Evidence**
  - Mechanism of action (MOA) and format
  - Recommended dose, schedule, and route of administration
  - **Translational evidence**
- **Clinical Evidence**
  - Clinical studies
  - **PK characteristics**
  - **Safety summary**
  - **Efficacy summary**
  - Other considerations
- **Additional Clinical Evidence**
  - Planned clinical studies
  - Other evidence

Reference: Friends of Cancer Research White Paper

TEMPLATE: Clinical Pharmacology (Dose & Administration) Snapshot

Please note: The table below describes the supportive evidence for the proposed dose and schedule. The target length of the completed snapshot is 2-5 pages.

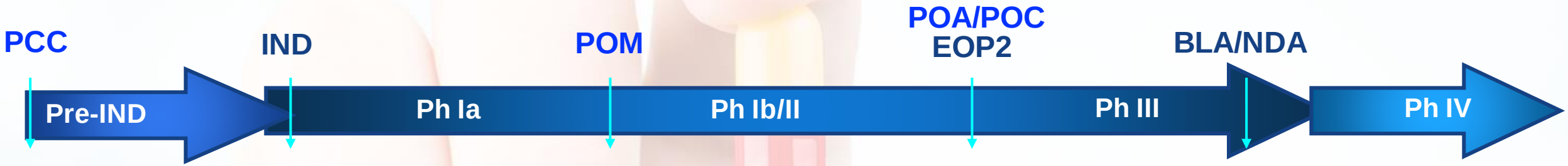
Key area of consideration	Supporting Evidence
Recommended dose, schedule and route of administration	• *What is the current dose, schedule and route of administration? Has the RP2D been selected? If the RP2D has not been selected, what key questions are outstanding?* • *When do you anticipate that a R2PD will be selected?* • *Are other routes of administration being investigated?*
Mechanism of Action (MOA) and Format	• *Is the therapeutic a small or large molecule? Another platform? What is the MOA?*
Translational evidence	• *Is there established pharmacological evidence (e.g. target engagement, MOA, outcome-based biomarkers, tumor volume) in the relevant preclinical species?* • *Is the dose-PK relationship established in the non-clinical species?* • *Are the pharmacological/efficacious target concentrations for patients defined?* • *Is the dose/exposure-response relationship identified from the in vitro cellular systems or the in vivo animal models?*
Clinical Evidence	

Clinical studies	• *List of ongoing and completed studies (i.e. single agent and/or combination studies, indication)*
	• *Brief description of study design including doses and schedules evaluated, e.g.:*
	  ○ *Phase 1 (expansion cohorts with or without randomization)*
	  ○ *Phase 2 (single arm or with dose randomization)*
	  ○ *Phase 3 (dose, design, randomization)*

PK characteristics	• *Is the dose-PK relationship established (i.e. is the PK dose proportional)?* • *Do the PK characteristics (accumulation, half-life) justify the dosing interval?* • *Are there any intrinsic or extrinsic factors (e.g. food, body weight, immunogenicity) that would majorly influence PK? (i.e. if these warrants dose adjustments in a subset of patients)* • *Was the PK variability considered when selecting a dose that would achieve target exposure for the majority of patients?*
Safety summary	• *Summary of key AEs of interest by dose?* • *Is there a dose/exposure-safety or PK-PD relationship upon the adjustment of potential confounders relationship for safety?*

- US FDA's Oncology Center of Excellence has piloted a version of the 'Dose Snapshot' as a tool to optimize communication on dose optimization for drugs granted Breakthrough Therapy Designation
- Used as a "living document" to engage both internal and external stakeholders cross stages of development.

Dose/Schedule Strategy should be integrated into early TPP/CDP and life-cycle planning



Pre IND

- Human FIH starting & target dose/regimen projection
- Translational PK/PD for efficacy and safety

Phase I/II/III

- Dose and regimen finding/identification for the first Indication
  - *Target engagement at site of action*
  - *Clinical PK/PD*
  - *Dose/Exposure-response analysis for efficacy & safety*
- Dose and regimen identification for additional indications
- Dose and regimen finding/identification in combination

- Alternative dose/schedule

Cross-Molecules Platform Clin Pharm Strategy (e.g., ADCs, TDBs and cell therapies)

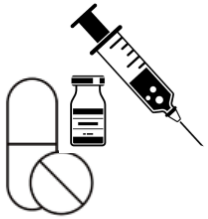
What & How to optimize is an Art

Strategic context

Data & Sciences

Perspectives

UNCERTAINTY



When

Before or after POA?

Efficacy: ORR, CR, tumor dynamics
Biomarker: clinically relevant

What

Toxicity: Acute & chronic
Tolerability: PRO, dose modification

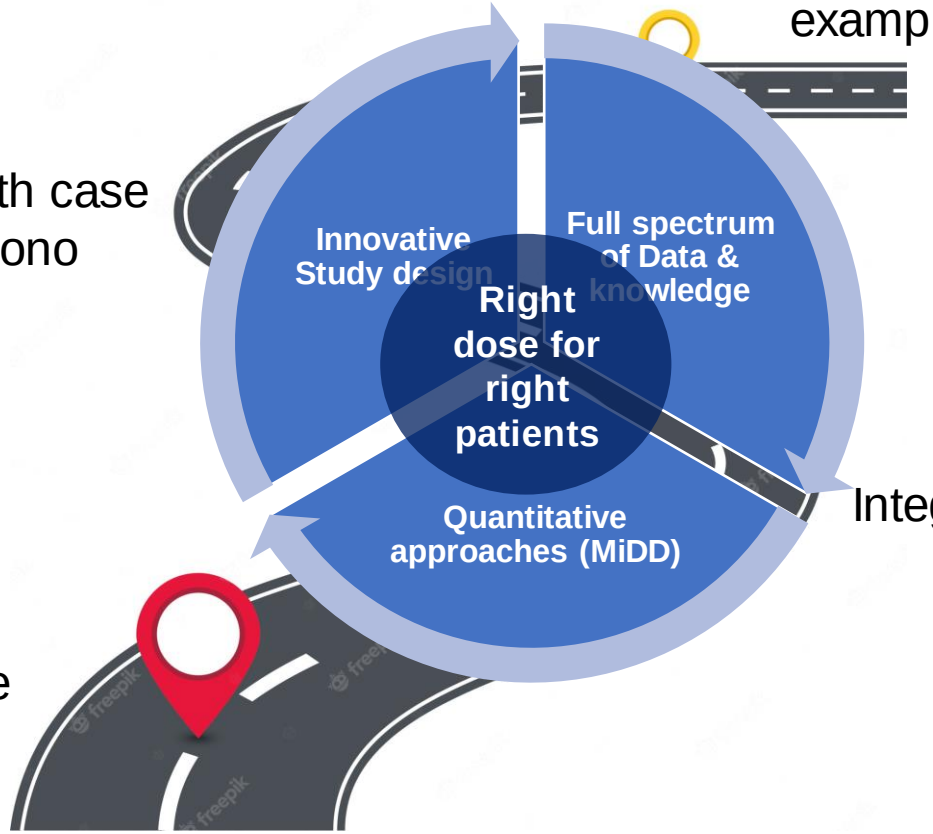
How

Collaboration & Communications

Dose Optimization – Options for the Path Forward

Industry Perspective with case examples – Divya Samineni

Academic Perspective with case examples – Johann De Bono



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Teams

Amy Schroeder

Christophe Boetsch

Chunze Li

David Dejardin

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Joanne Bergin

Nicola Treadwell

Patrick Willian

Peter Trask

Ting Liu

Bruno Gomes (past team member)

Daniel Waterkamp (past team member)

Antoinette Gooseff (past team member)