Challenges and Opportunities of Oncology Dose Optimization - Industry Perspective

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Outlines

- Introduction
- Challenges and opportunities of oncology dose finding and selection
  - Tailored dose optimization framework by molecular class
  - Novel study design
  - Modeling and simulation tools
  - Case example - POLIVY™ polatuzumab vedotin-piiq
- Summary

Concept of oncology dose finding has evolved with new therapies

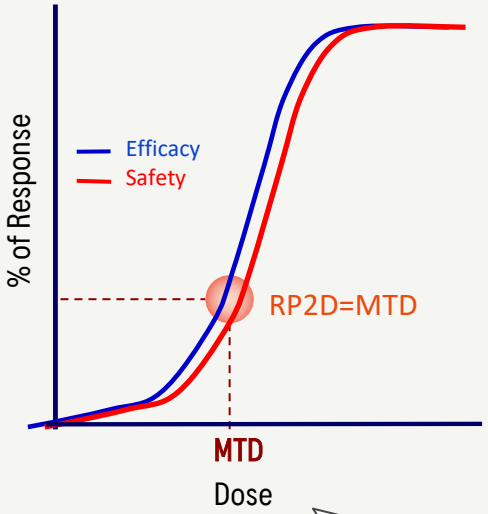
Roche

Narrow therapeutic window

Older

Traditional Chemotherapy

(e.g., Paclitaxel, Carboplatin, Doxorubicin)



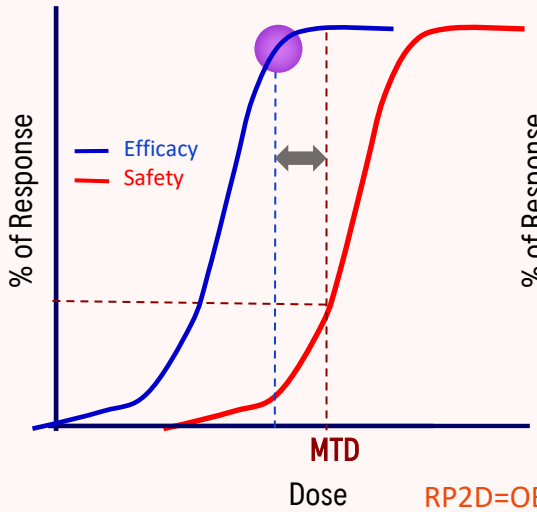
MTD Paradigm: driven by DLT with simple dose decision rule

Wider therapeutic window (TW)

NEW

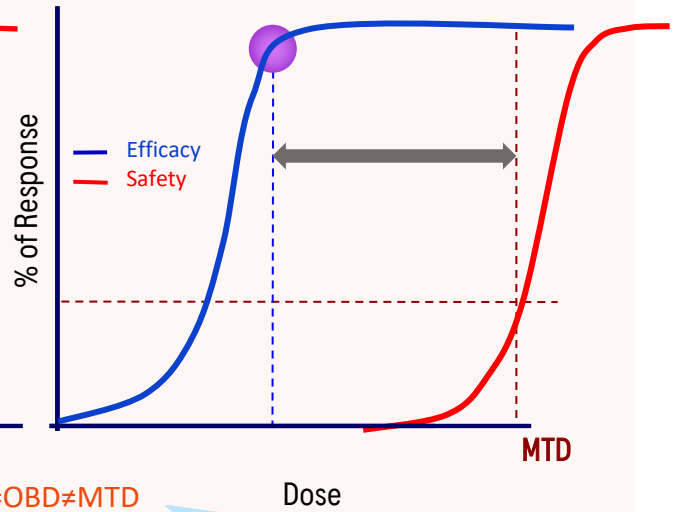
Targeted Therapies (SM/ADCs)

(e.g., Erdafitinib, Osimertinib, Polatuzumab)



mAbs

(e.g., Pembrolizumab, Trastuzumab, Bevacizumab)



RP2D=OBD≠MTD

DLT alone is not sufficient to inform RP2D, dose decision requires consider both safety and efficacy

MTD: Maximal Tolerated Dose; RP2D: Recommended Phase 2 Dose; OBD: Optimal Biological Dose; SM: Small Molecules, ADCs: antibody-drug conjugates

New Framework for dose finding for new anti-cancer therapies

Multi-dimensional optimization - safety, efficacy, PK, PD biomarker, PRO

Dose → **PK** → **PD** → **Response**

Efficacy

Safety

Efficacy: ORR, CR, tumor dynamics
Biomarker: clinically relevant, e.g., ct-DNA

Safety: Acute & chronic
Tolerability: PRO, dose modification

Dose decision requires benefit-risk assessment of different doses

Challenges for Oncology Dose optimization

Complex and multidimensional

- **Multiple, Interconnected objectives** for a FIH study - MTD/MAD, patient population, POM, POA, POC, combination planning
- Ethical Constraints - **avoid exposing large numbers of patients to a poorly tolerated or suboptimal dose**
- **Biological & Patient Heterogeneity** - challenging to establish robust dose/exposure-response with early trials
- Short Observation Windows - **Long-term tolerability** often limited in early-phase studies
- **Lack of reliable biomarkers** that are clinically relevant to efficacy
- **Early efficacy endpoints** does not always reflect long-term efficacy benefit (e.g., PFS, OS)
- **Complex, Context-Driven** Decision-Making - trade off/balance multiple factors
  - No simple one-size-fits-all solution
  - Dose decision based on benefit-risk assessment could be subjective

Opportunities to Optimize Oncology Dose Finding for the 1st indication

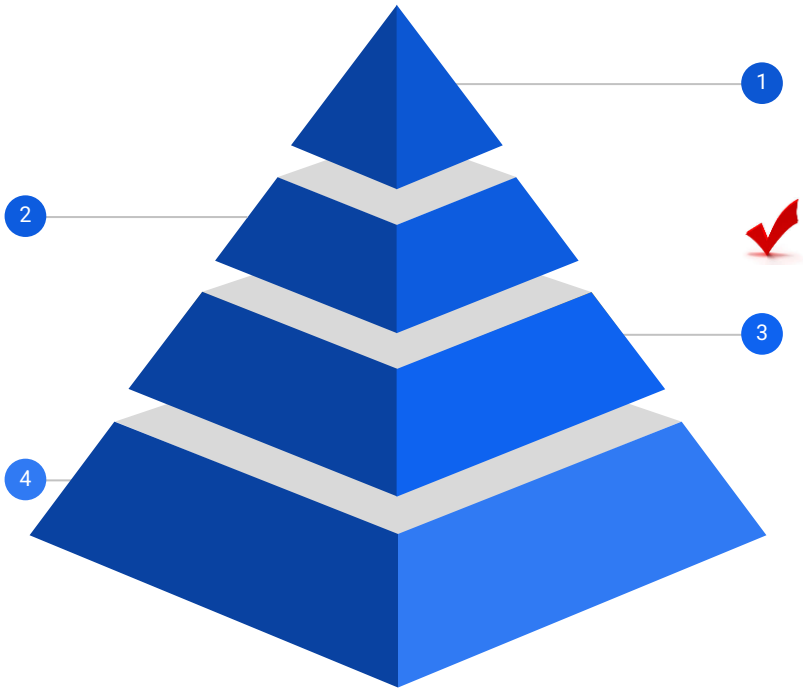
Call for innovation and collaboration

Novel Study Design

- Rule-based vs model-based vs model-assisted
- Toxicity only vs efficacy/Toxicity-driven,
- BOIN, EffTox, BOIN12, utility

Collaboration

Enhance collaboration and communication across Pharma industry, health authority, HTA, and academia



Tailored Dose optimization

by molecular class based on expected single agent activity, and mode of action

Modeling and simulation

Integrate totality of the evidence (preclinical, clinical PK, PD, safety/tolerability and efficacy), to guide study design and dose decision

POLIVY™
polatuzumab vedotin-piiq
INJECTION FOR INTRAVENOUS USE 140MG

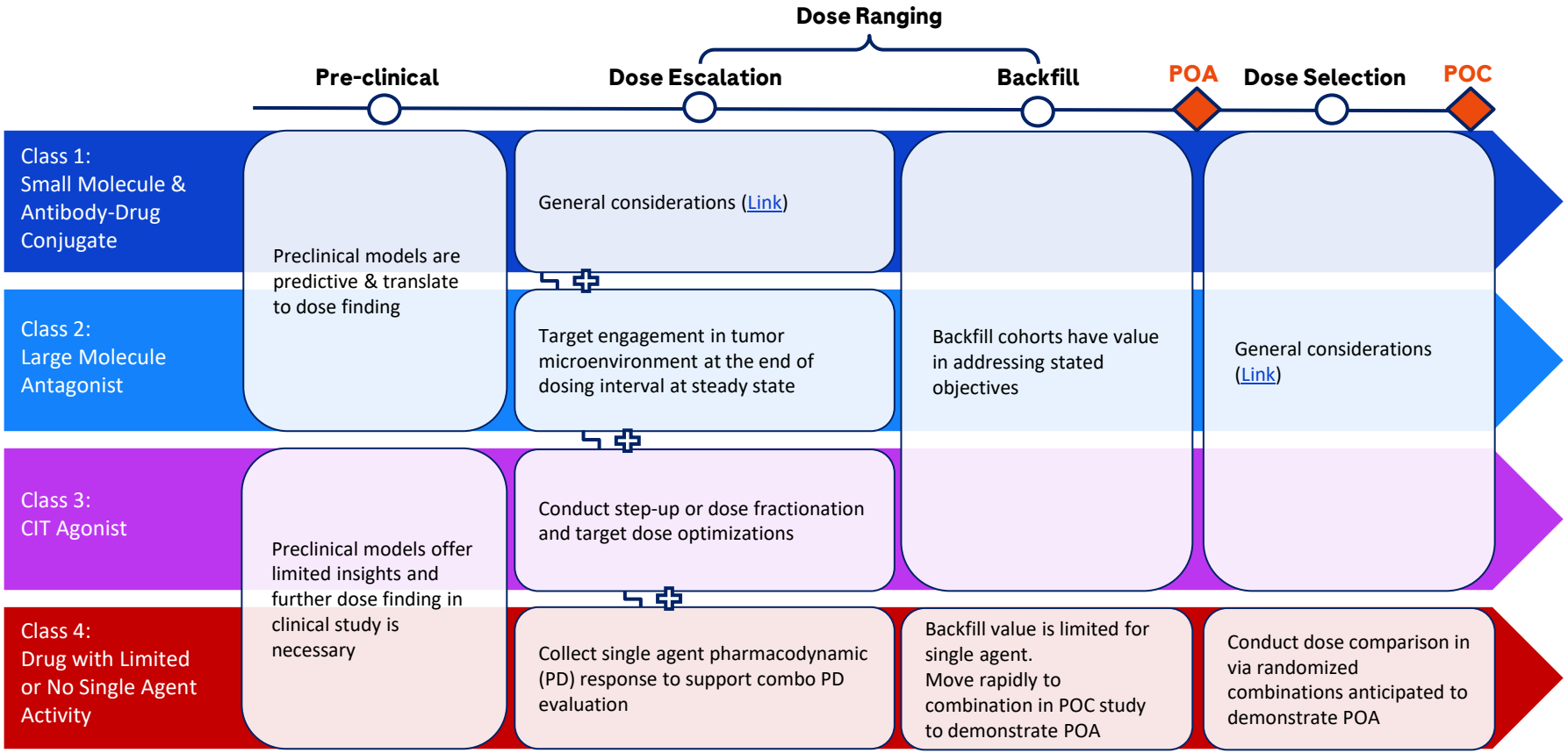
Molecule class is defined by expected single agent activity and mode of action

Molecules with Single Agent Activities

Class 1: Small Molecule & Antibody-Drug Conjugate	Class 2: Large Molecule Antagonist	Class 3: Cancer Immunotherapy Agonist	Class 4: Drug with Limited or No Single Agent Activity
Small Molecules e.g. asciminib, sotorasib, **ADCs** e.g. polatuzumab vedotin, trastuzumab deruxtecan	e.g. atezolizumab, pembrolizumab, isatuximab, trastuzumab	**T-cell engagers** e.g. mosunetuzumab, epcoritamab, teclistamab **Cytokines** e.g. Interleukin-2	**Agonists or Antagonists** e.g. relatlimab (LAG-3)

Clinical development considerations could be unique for different molecule class

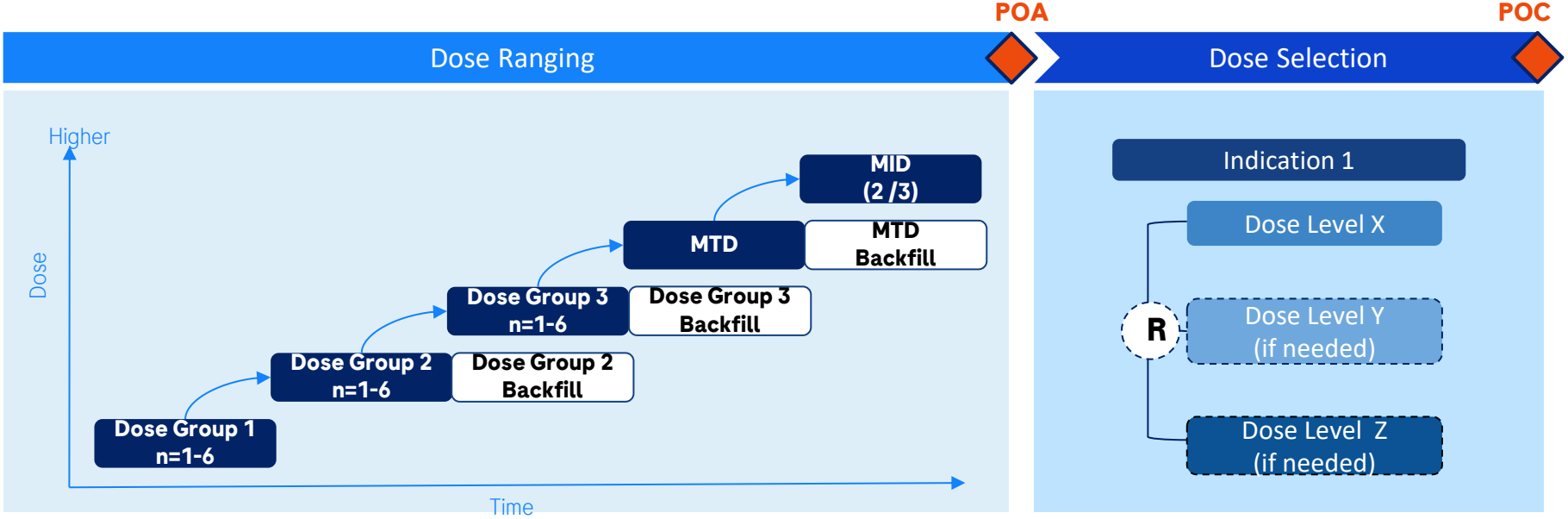
Unique considerations for each molecule class



POA: Proof of Anti-Tumor Activities; POC: Proof of Concept; CDP: Clinical Development Plan

Zhu et al, *CPT*, 2025

Novel study design to enable efficient yet robust dose finding



Novel methods

Model-assisted dose escalation - BOIN, BOIN12, U-BOIN, DROID

Yuan et al, *Clinical trials*, 2024

→ Identify acceptable dose(s)*

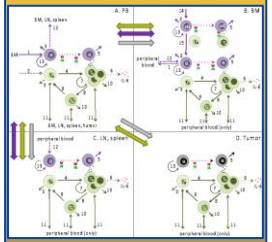
→ Dose decision rule, e.g., decision tree, utility, MERIT

* Dose are safe with promising antitumor activities based on totality of evidence. Factors considered may include e.g. safety, efficacy, PK/PD, nonclinical, patient reported outcome, biomarker. Data integration enabled through In Silico and Quantitative Analysis Plan.

MTD: Maximum Tolerated Dose; DLT: Dose Limiting Toxicity; MID: Minimal Intolerable Dose; R: patient randomization (may not always be needed), BION: Bayesian optimal interval , U-BOIN: utility-based BOIN, DROID: dose-ranging approach to optimizing dose, Guo et al, 2023, MERIT: Multiple-dosE RandomIzed Trial design for dose optimization based on toxicity and efficacy, Yang et al, 2023, POA: Proof of activity, POC: Proof of concept

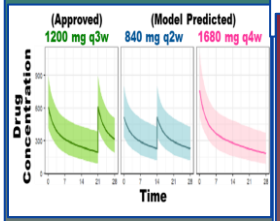
Modeling and Simulation Tools to Support Dose Finding and Selection

QSP Modeling



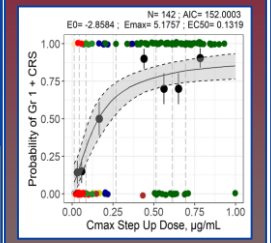
Connects biology, systems & pharmacology

Population Pharmacokinetics popPK



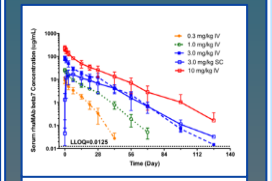
Characterizes PK properties

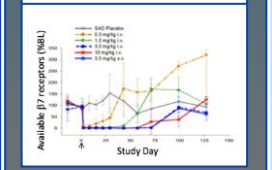
Dose/ Exposure Response



Characterizes the causal chain between dose & response

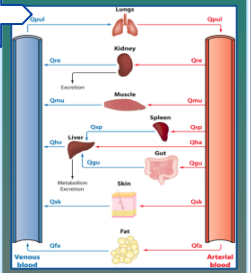
PK / PD





Links PK & PD to evaluate exposure - response

PBPK

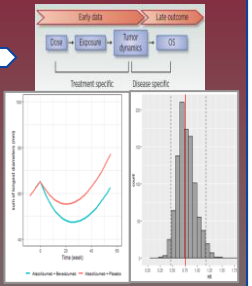


Predicts drug performance using mechanistic modeling

Model Based Meta Analysis

Leverages published data along with internal data to inform dose optimization

Predictive Disease Modeling



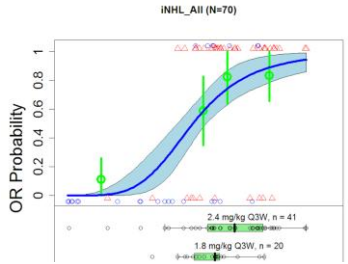
Uses Mathematical models to forecast future outcomes

Exposure-Response Analyses and Time-To-Event Modeling to Guide Dose selection of Polatuzumab vedotin

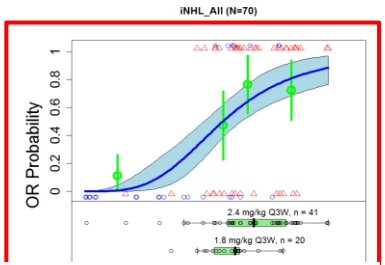
Exposure-Efficacy

Objective Response

Treatment Till Progression



Treatment Duration Capping to 8 Cycles

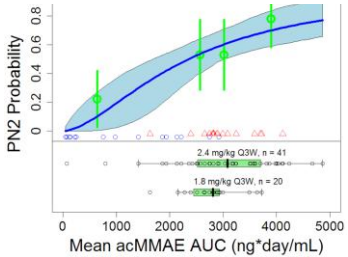


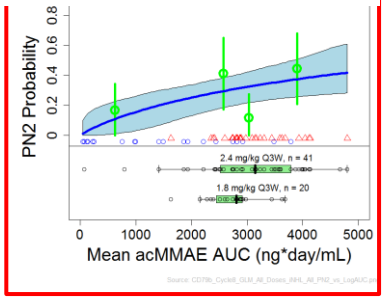
Capping to 8 cycles:

- Safety: Shallower trend for exposure-peripheral neuropathy
- Efficacy: No apparent impact on exposure-efficacy

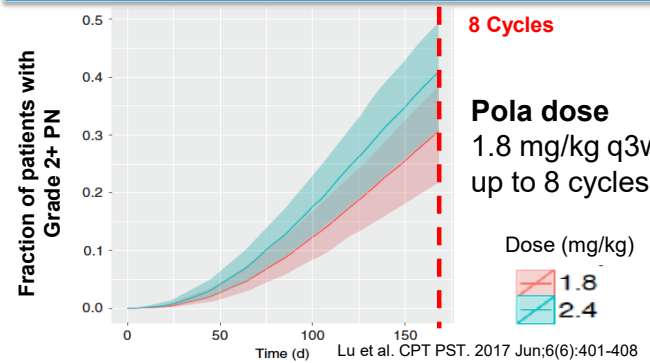
Exposure-Safety

Peripheral Neuropathy (Gr 2+)



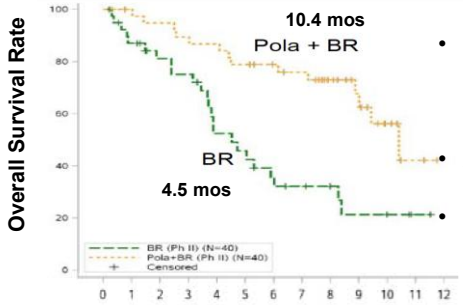


Predicted probability Grade≥2 PN



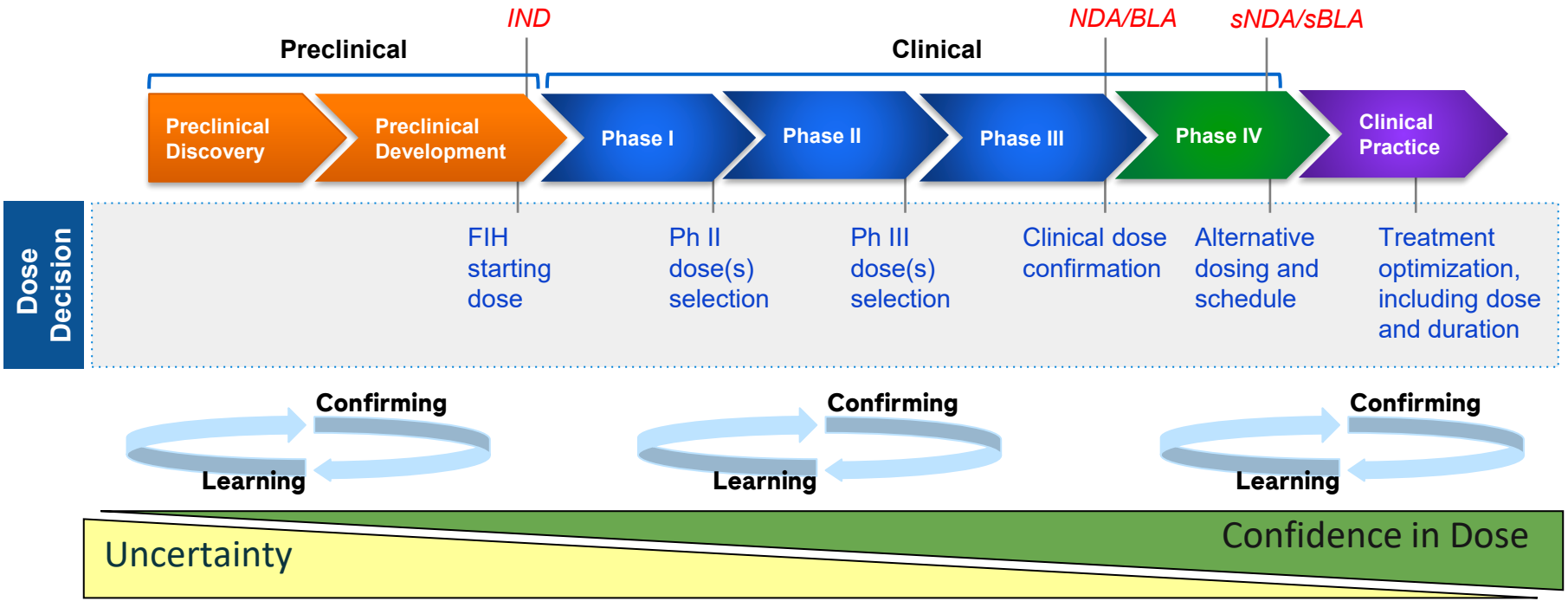
Lu et al. CPT PST. 2017 Jun;6(6):401-408

Strong efficacy in r/r DLBCL



- Phase 1/2 study with a new dose (1.8 mg/kg capped up to 8 cycles)
- Approx 18% G2+ PN
- Pola gained FDA and EMA approval

Oncology Dose Optimization — A Journey Beyond Clinical Development



Summary and future direction

- Dose optimization strategies should be seamless integrated into clinical development plan (CDP) across life-cycle (Dosing CDP)
- Tailored dosing CDP by molecule class set a foundation for developing tangible solutions
- Novel study designs enhance efficiency and robustness of dose finding
- Modeling and simulation play an integral role in drug development and dose selection
    - Effectively integrate totality of evidence (preclinical, clinical PK, PD, efficacy and safety/tolerability)
- Future direction - Novel biomarkers (e.g., ct-DNA), RWE post approval, AI/ML tools to optimize study design, and enable real-time dose adjustment and personalized dosing
- Topics to be discussed in the panelist - dose optimization for subsequent indication & combination and Regulatory path with EMA to determine dose

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