



Strategic Dose Optimization and Tumor Targeting in Early-Phase Oncology Trials

Key Considerations for Biotech Innovators

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Agenda



Overview of
Oncology
Drug
Development



Principles of
Dose
Optimization



Model
Informed Drug
Development



Design
Considerations
for Early Trials



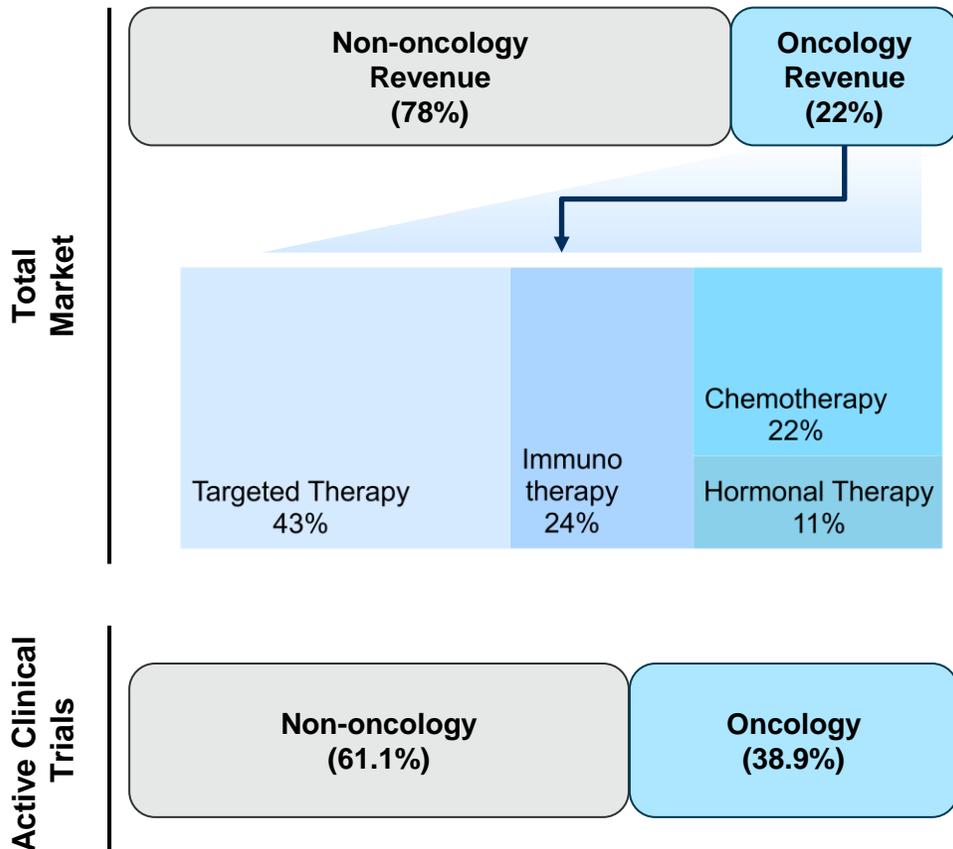
Future
Directions in
Trial
Optimization



Q & A

Oncology Will Continue to Hold Largest Share of Pharmaceutical Market With a Robust Pipeline Heavily Focused on Targeted Therapies and Immuno-Oncology, and Driven by First-In-Class Assets

Oncology Trends | 2026



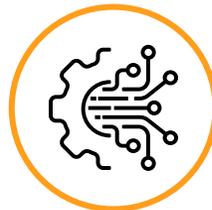
>100 oncology launches in period 2017-2021 doubling on corresponding numbers in 2012-2016



~2/3 oncology launches are focused on solid tumors; most assets are approved for lung, breast, skin and GI cancer



>80% of recent approvals are based on targeted therapy or immune-oncology approach
E.g, Enhertu (HER2 targeted), Anktiva (IL-5 superagonist)



~20% of drug approvals are first-in-class (e.g., new MoAs)
E.g., Exkivity (EGFRex20 inhibitor), Tivdak (TF directed ADC)

Note: Oncology Drugs Revenue (2026F): ~\$29B ;Oncology Drug Revenue 22% of total drug revenue; Immunotherapy Market Size (2026F): ~\$77B; Chemotherapy Market Size (2026F): ~\$70B; Targeted Therapy Market Size (2026F): ~138B; Hormonal Therapy Market Size (2026F): ~34B; Number of Oncology Trials 16,878 (Citeline)

Immunotherapy approaches are highly present in solid tumors, while CAR-T technology holds promise for the liquid tumors; ADCs and bi-specific antibody are likely to become SoC across most tumors



Tumor Type		Solid Tumors												Liquid Tumors										
		SCLC	Pancreatic	CCA	CRPC	Ovarian	CRC	Gastric	Esophageal	NSCLC	Urothelial	BC	cSCC	Cervical	MDS	AML	ALL	CML	NHL	MM	CLL	HCL	HL	
Technology	Targeted Therapy	ADCs																						
	Bispecific Antibody																							
Immunotherapy	PD-1/PD-L1																							
	CAR T therapy																							
	RNA Therapy																							
	Non-GMO Cell Therapy																							

Note: Small Molecules, Monoclonal Antibodies, Cancer Vaccines have been excluded from the above analysis

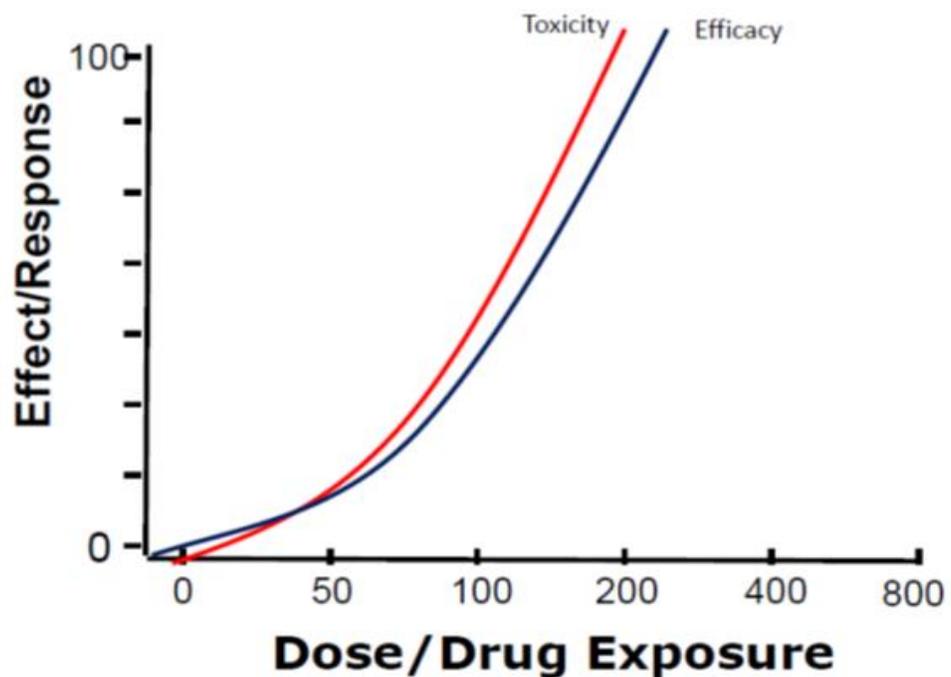
Pipeline Density		
Heavy Pipeline (>30 assets)	Moderate Pipeline (11 – 30 assets)	Light Pipeline (<10 assets)

Dose Selection for Oncology

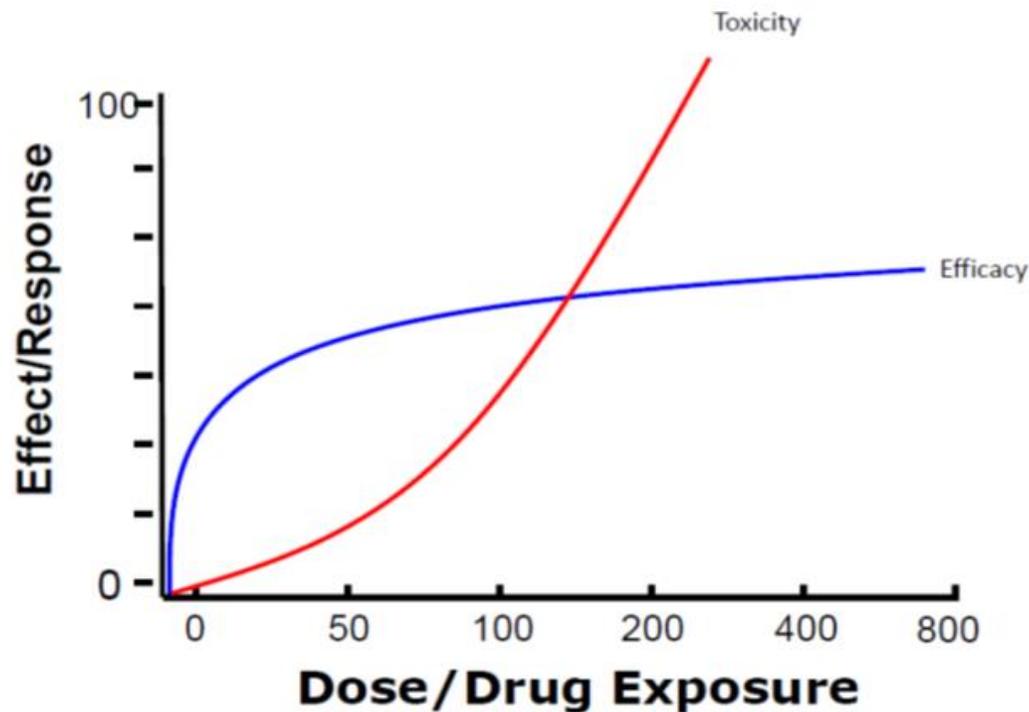
Dose Optimization Rather Than MTD



Cytotoxic Chemotherapy



Targeted Therapies



Historical perspectives



Lack of Dose Optimization Oncology Drugs with PMRs/PMCs Related to Dose

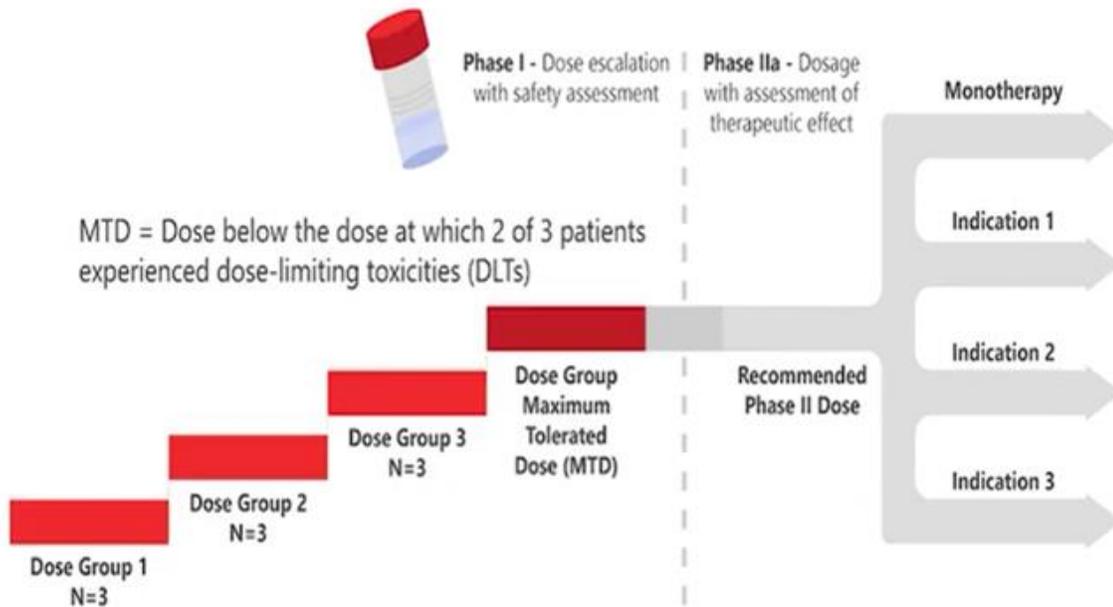
2011	2012	2013	2014	2015	2016	2017
ipilimumab vandetanib abiraterone rivaroxaban vemurafenib brentuximab vedotin crizotinib deferiprone ruxolitinib asparaginase <i>Erwinia</i> <i>chrysanthemi</i>	glucarpidase axitinib vismodegib peginesatide pertuzumab carfilzomib ziv-aflibercept tbo-filgrastim enzalutamide bosutinib regorafenib omacetaxine cabozantinib ponatinib	pomalidomide T-DM1 radium RA-223 trametinib dabrafenib afatinib obinutuzumab ibrutinib	ofatumumab ramucirumab siltuximab ceritinib belinostat idelalisib pembrolizumab blinatumomab olaparib nivolumab	panobinostat palbociclib lenvatinib dinutuximab sonidegib trifluridine trabectedin cobimetinib osimertinib daratumumab ixazomib necitumumab elotuzumab alectinib	venetoclax atezolizumab olaratumab rucaparib	ribociclib niraparib midostaurin brigatinib durvalumab avelumab rituximab SC neratinib enasidenib inotuzumab tisagenlecleucel gemtuzumab copanlisib abemaciclib

PMR: post marketing requirements; PMC Post marketing commitments

Historical perspectives

Historically Standard Oncology Phase 1 Study Design

3x3 Dose Escalation to Maximum Tolerated Dose



- The choice of dose and schedule is often in the upper range of the therapeutic window, driven by the maximum tolerated dose (MTD) model of previous cytotoxic agents.
- There is increasing recognition that this needs to change, by taking a more holistic approach to determine the optimal dose for desired biological effects and tolerability early in clinical development.
- In the US, the FDA's Oncology Centre of Excellence is addressing this *via* the Project Optimus initiative: aiming to reform dose optimization studies so that they can demonstrate the most appropriate dose selection.

Project Optimus

What?

- Initiative to reform the dosage optimization and dose selection paradigm in oncology drug development

Who?

- A multidisciplinary team of medical oncologists, clinical pharmacologists, biostatisticians, toxicologists, and other scientists with expertise in key facets of dosage optimization

More Information:

- [OptimusProject Optimus | FDA](#)

Project Optimus Supports Evaluating All Data to Inform Dosage Selection for Clinical Trials



Consider all data: pharmacokinetic (PK), pharmacodynamic (PD), activity/efficacy, safety, and tolerability data at each step



Evaluate safety information beyond DLTs, e.g., low-grade symptomatic toxicities, dosage modification frequencies, patient-generated data for treatment-related symptoms



Identify a target dosage range early and then further evaluate several dosages (ideally in a randomized trial)



Characterize dosage- and exposure-response relationships for efficacy and toxicity



Focusing on Dosage Before Approval

Administering
'optimized' dosages in
registration trial

- Improves tolerability and adherence
- Reduces dosage modifications (i.e., discontinuations)
- Potentially increases likelihood of treatment response

Earlier understanding
of dose- and exposure-
response relationships
may allow for more
rapid development of
new therapies, such as

- Combination regimens, new dosing regimens & new formulations
- More efficient to evaluate multiple dosages early in development
- Challenging to conduct dosage optimization trials post-approval

Consequences of Not Optimizing Dosage Before Approval

Drug is poorly-tolerated at the approved recommended dosage

- Patients may stop taking a potentially effective drug
- Patients choose to try a different drug

Drug does not make it to market or must be withdrawn from the market

- Takes long time to evaluate alternative dosages following approval
- Patients may not want to participate in trial if commercially available

MAIN GOAL: Educate, innovate, and collaborate with companies, academia, professional societies, international regulatory authorities, and patients to move forward with a dose-finding and dose optimization paradigm across oncology that emphasizes selection of a dose or doses that maximizes not only the efficacy of a drug but the safety and tolerability as well.



Specific Goals include:



DOSE-FINDING AND DOSE OPTIMIZATION:
Communicate expectations through Guidance, workshops, other public meetings

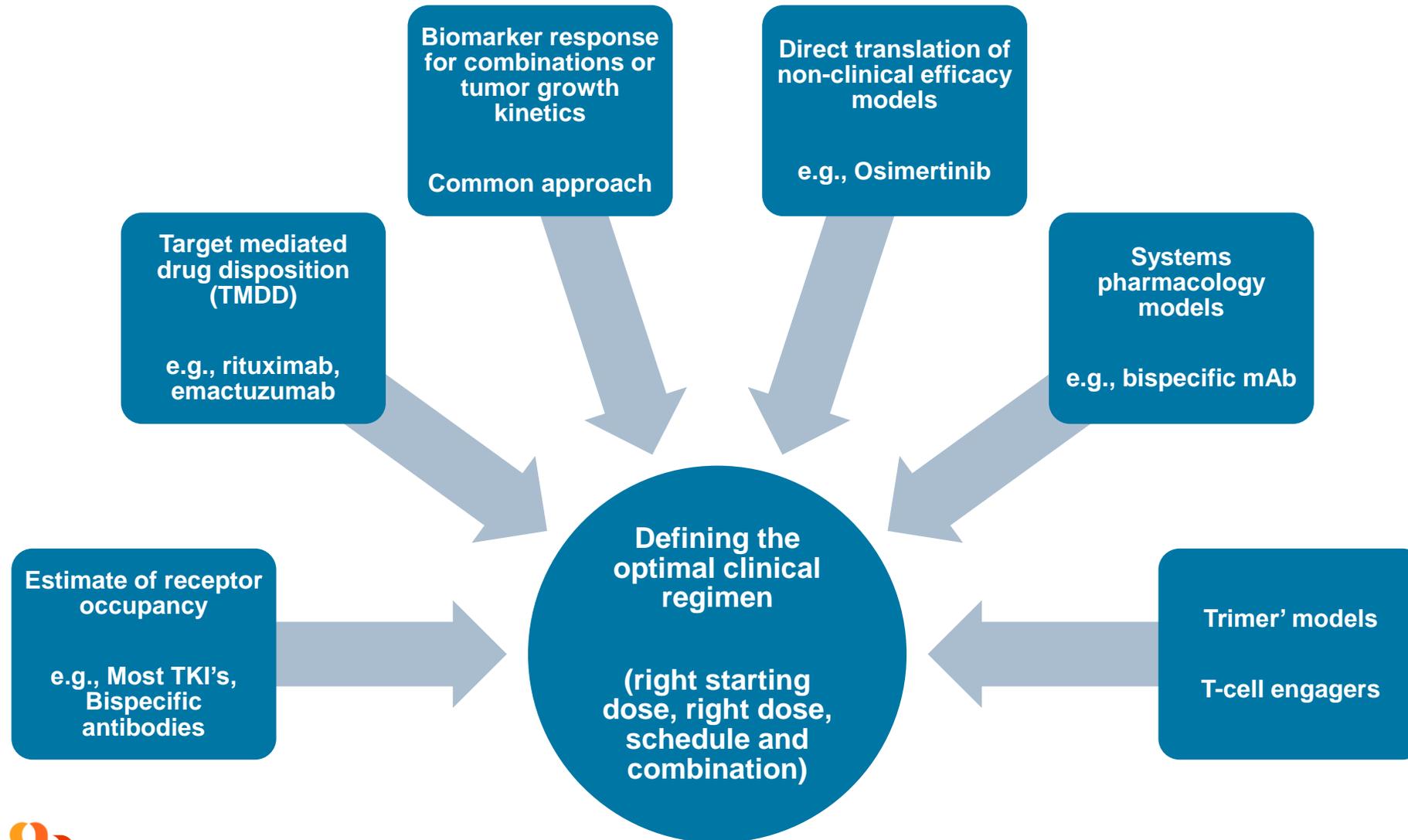


EARLY ENGAGEMENT OF DRUG DEVELOPERS WITH FDA ONCOLOGY REVIEW DIVISIONS TO DISCUSS DOSE-FINDING AND DOSE OPTIMIZATION:
well **before** conducting trials intended for registration.



DEVELOP STRATEGIES for DOSE FINDING and DOSE OPTIMIZATION that leverages NONCLINICAL and CLINICAL DATA
in dose selection, including randomized evaluations of a **range of doses** in trials with emphasis on performing these studies **as early & as efficiently** as possible in the development program

Model-based approaches to starting dose and dose optimization based on efficacy

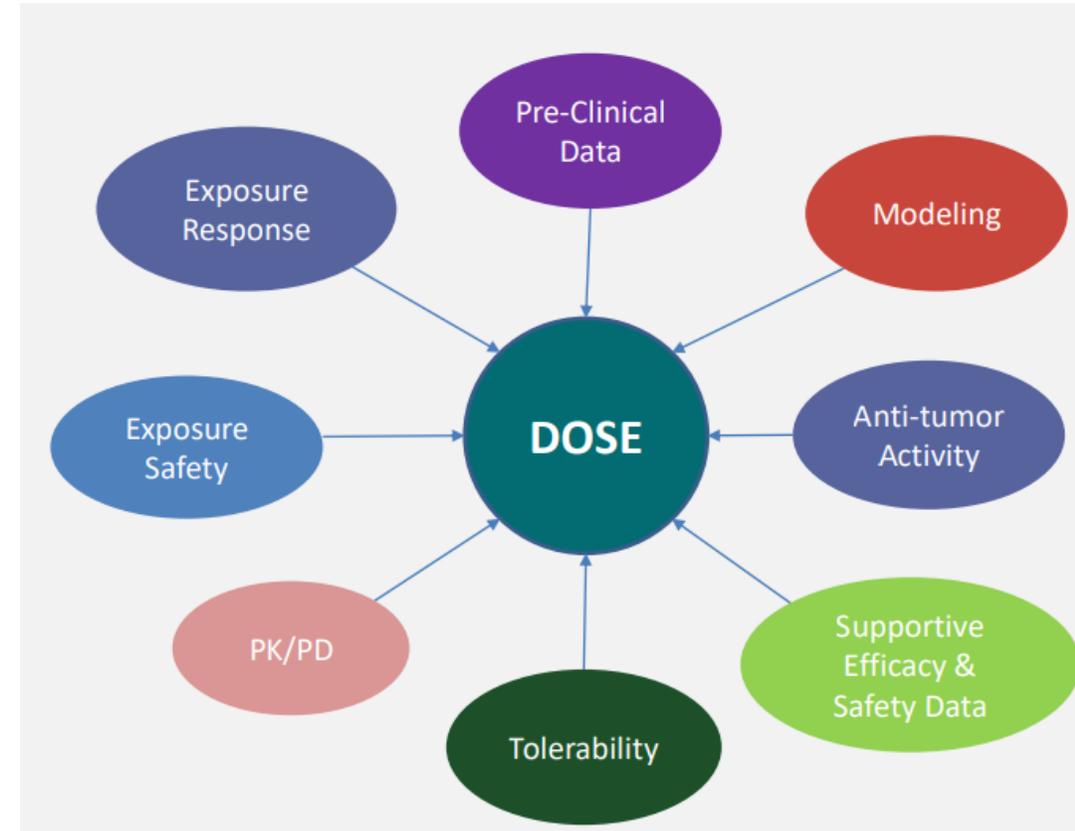


Model-based approaches to dose optimization In monotherapy: Balancing efficacy against safety

Identify a safe starting dose with some predicted efficacy

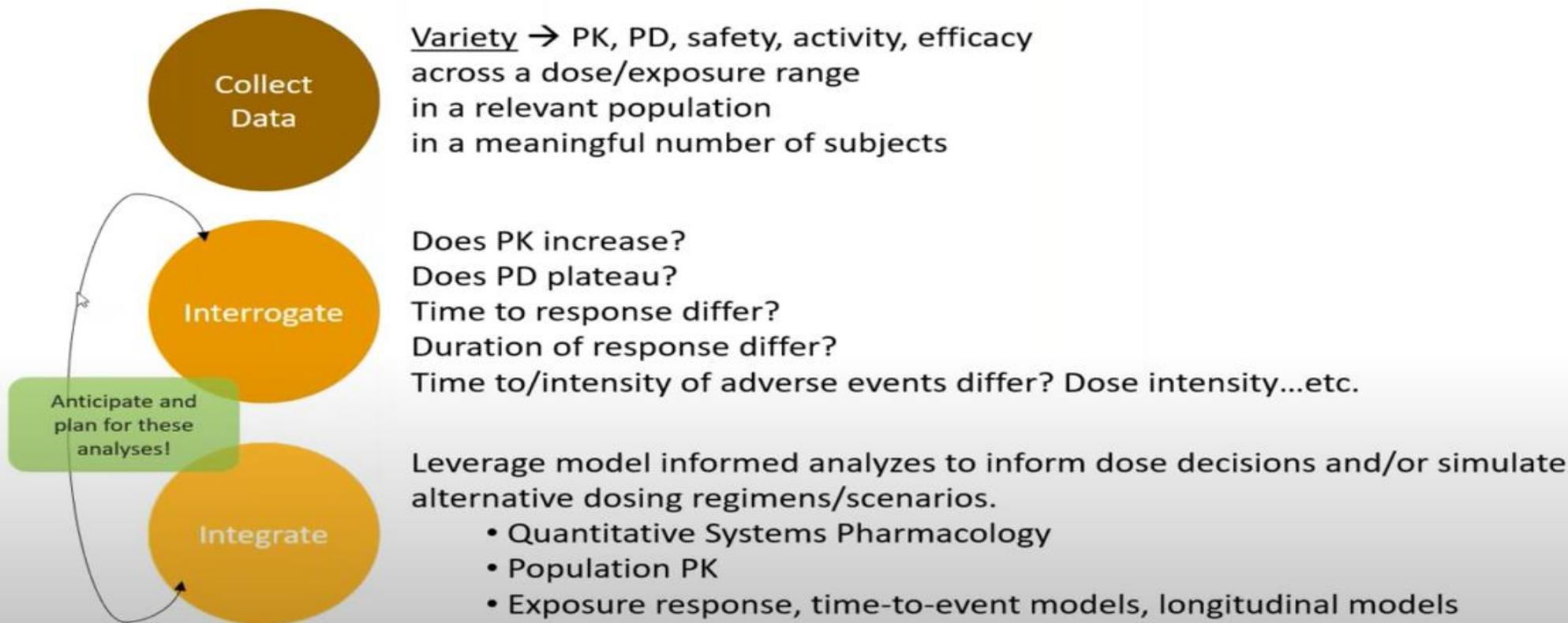
Identify an active dose range to explore

Make an informed decision on dose to take forward to a Phase 3 trial



Multiple Endpoints Will Inform Dose Decision-making

Emphasis on establishing exposure/dose response



Why is MIDD so powerful?

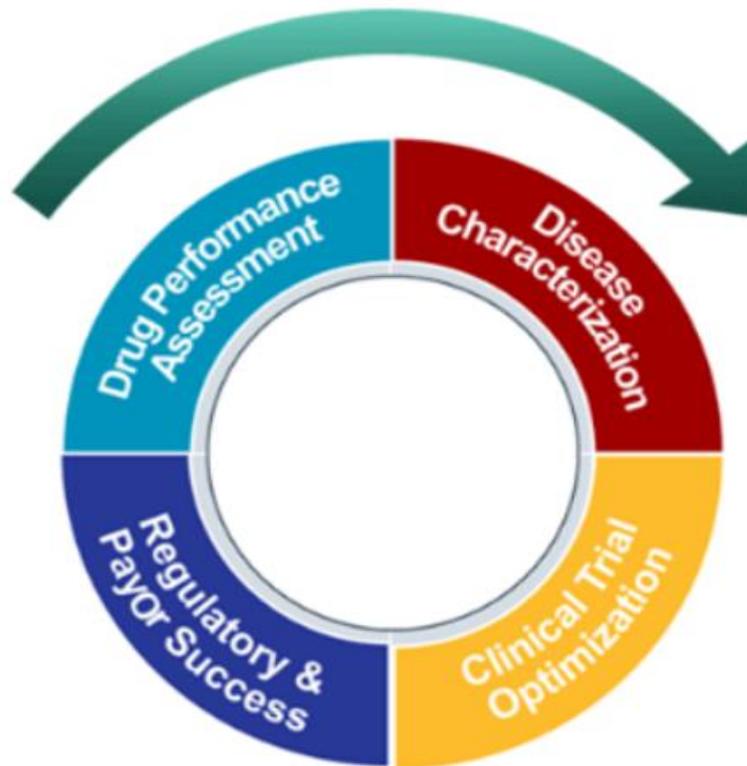
Maximizes the information from gathered data

Confidence in Drug

Confidence in Target

Confidence in Regulatory Decisions

Confidence in Endpoints

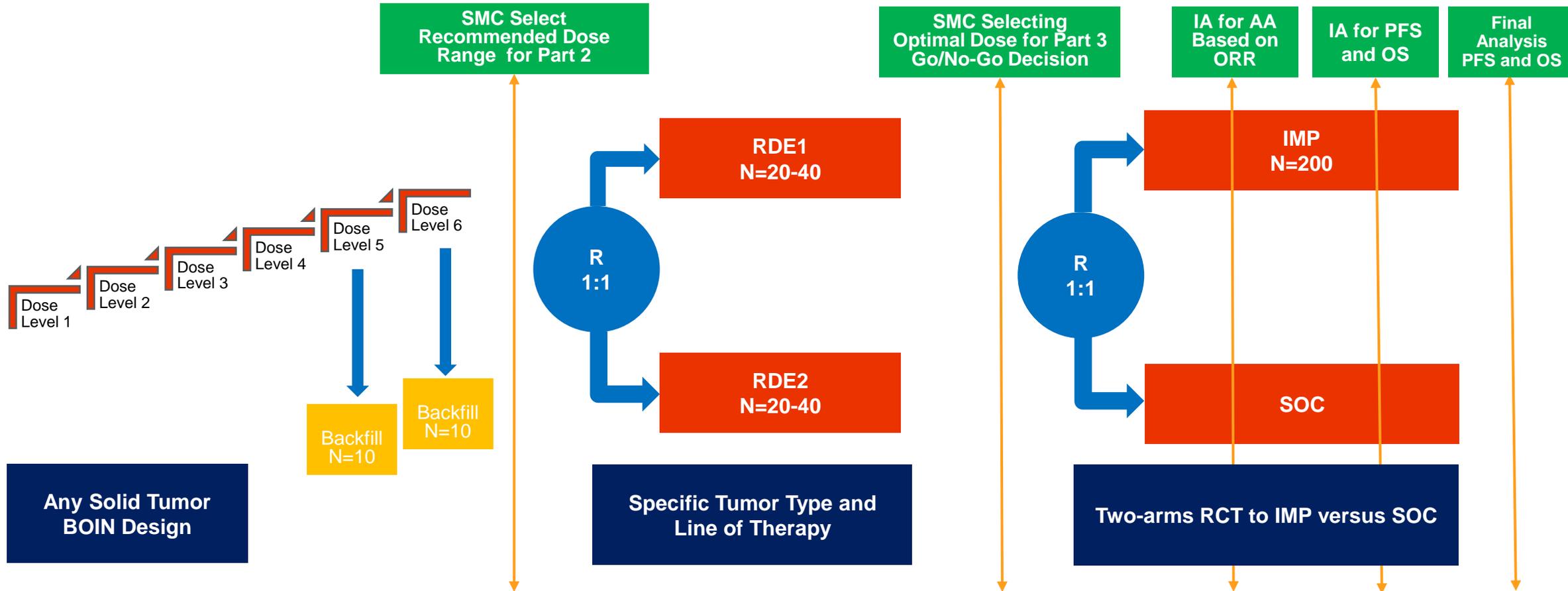


Allows Extrapolation to new situations

- Support for safety & efficacy of doses not studied
- Predictions of behavior in special populations
 - Elderly & children
 - Renal & hepatic impairment
- Avoid unnecessary studies
 - DDI Studies
 - BE Studies
- Combination selections

Proposed CDP for Expedited Market Access: Seamless Adoptive Phase 1/2 followed by Phase 3 Design for Specific Cancer

Part 1: Phase 1 Dose Escalation	Part 2: Dose Optimization Cohort 1 and Dose Expansion	Part 3: Phase 3 Registrational trial
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Project Optimus: FDA guidance documents- August 2024

Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases” released in August 2024.

1. **Collection and Interpretation** of Clinical Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Data
2. **Trial Designs** to compare multiple dosages to assess activity, safety, and tolerability to decrease uncertainty & identify an optimal dosage(s), in randomized parallel dose-response trial designs
3. **Safety and Tolerability to include:**
 - SAEs and lower grade AEs which may still significantly affect a patient’s ability to remain on the drug for extended periods (for example diarrhea and vomiting)
 - Patient-reported outcomes (PRO) can provide a systematic and quantitative assessment of expected symptomatic adverse events and their impact on function. Inclusion of PROs should be considered to enhance the assessment of tolerability in early phase dosage finding trials.
4. **Drug Formulation:** The appropriateness of the size and number of tablets or capsules required for an individual dose should be considered when selecting the final dosage form and strength(s). For parenteral- similar considerations
5. **Subsequent Indications and Usages:** Different dosages may be needed in oncologic diseases based on potential differences in tumor biology, patient population, treatment setting, and concurrent therapies (for combination regimens), among other factors. Strong rationale for choice of different dosages for specific indication should be provided.
6. **Expedited Programs:** Sponsors should note that development under an expedited program is not a sufficient justification to avoid identifying an optimized dosage before submitting a marketing application

Final Thoughts on Project Optimus

Project Optimus has really helped focus the Industry on the question of the right dose/exposure, particularly in avoiding too high doses

Model-based analysis, incorporating novel experimental systems, has the potential to decrease dose ranging studies across various indications to speed drug development and reach patients sooner