# Project Optimus: Statistical and Regulatory Considerations in Dosage Optimization

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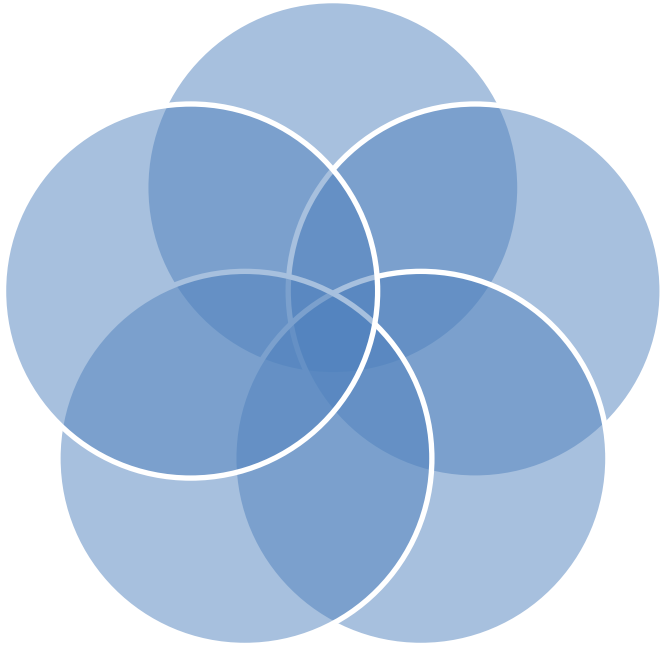
# Disclosures for Jonathon Vallejo, PhD

- I have no financial interests to disclose
- I will not discuss off-label use of unapproved agents
- These slides represent current thinking in a rapidly evolving field of regulatory science

# Caveats for Jonathon Vallejo, PhD

I am not a toxicologist

I do not run or fund clinical trials

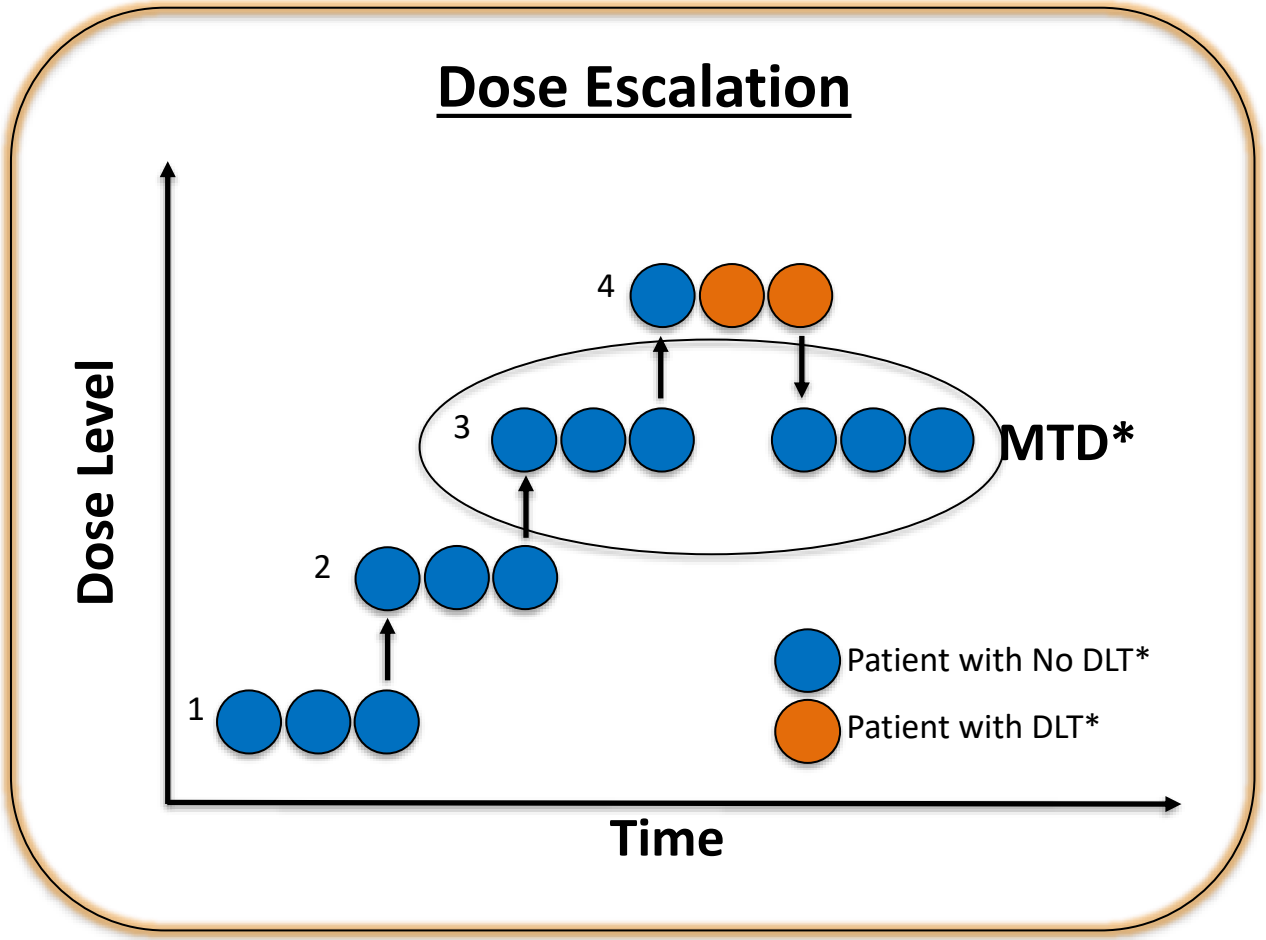


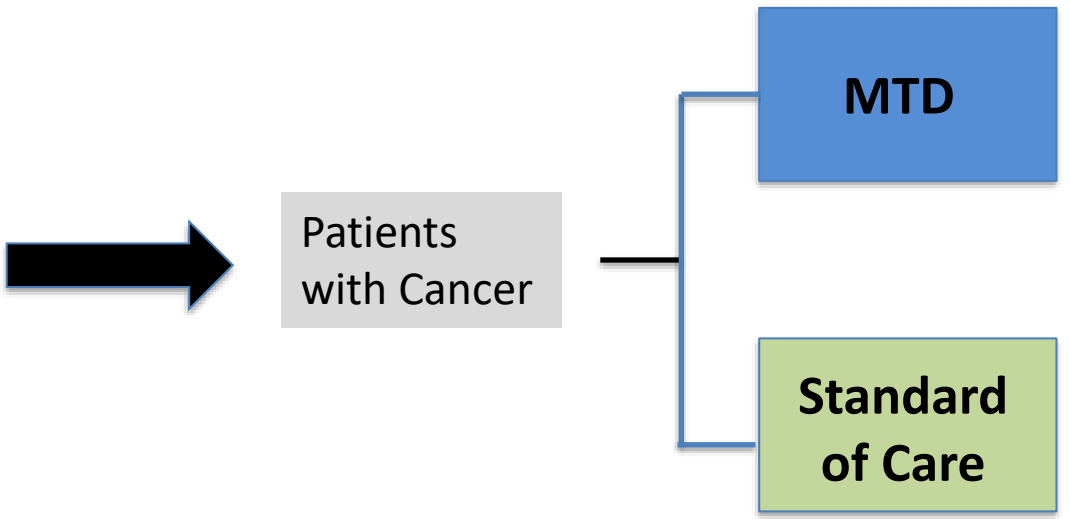
I am not a clinical pharmacologist

I am not an academic statistician

I am not an oncologist or patient

# Traditional Dosage Selection



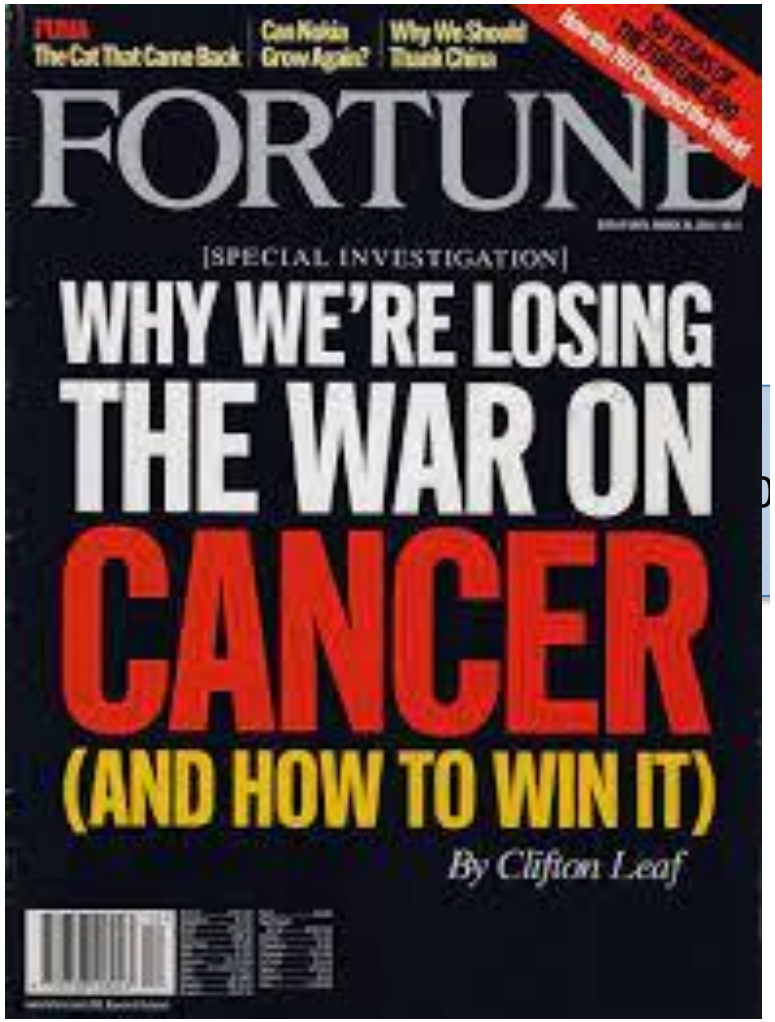




*DLT Dose-limiting toxicity,
*MTD Maximum tolerated dose

**Hallmarks:**

- Few patients at each dose level
- Short observation period for DLTs
- Emphasis on DLTs, but not other safety

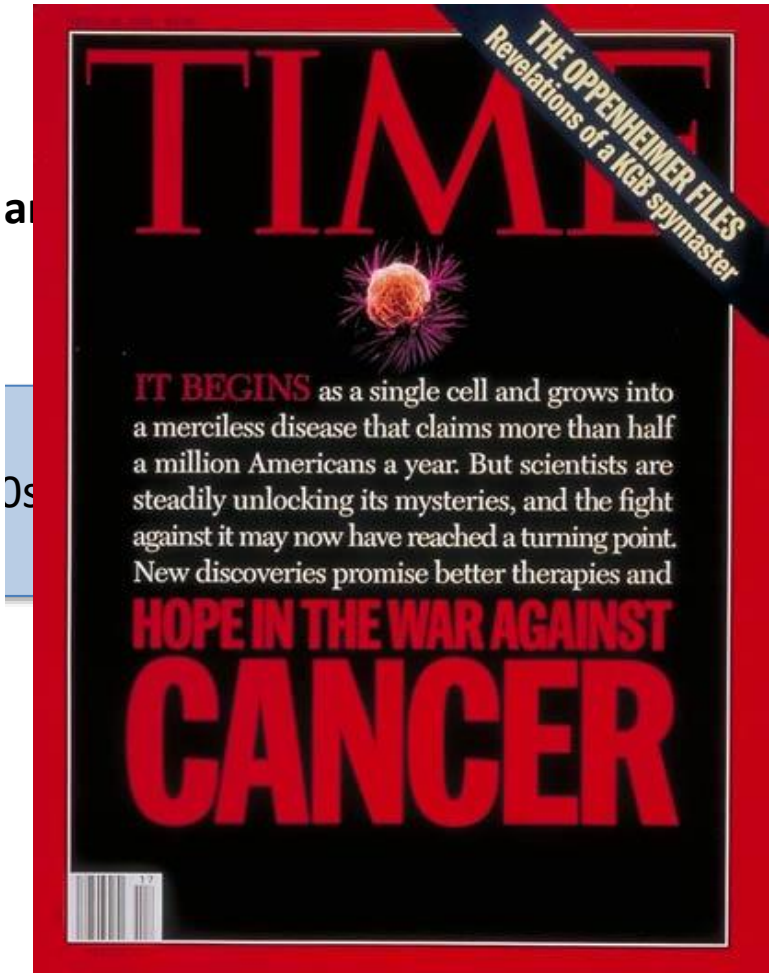
# History of Cytotoxic Chemotherapy
# "More is Better"



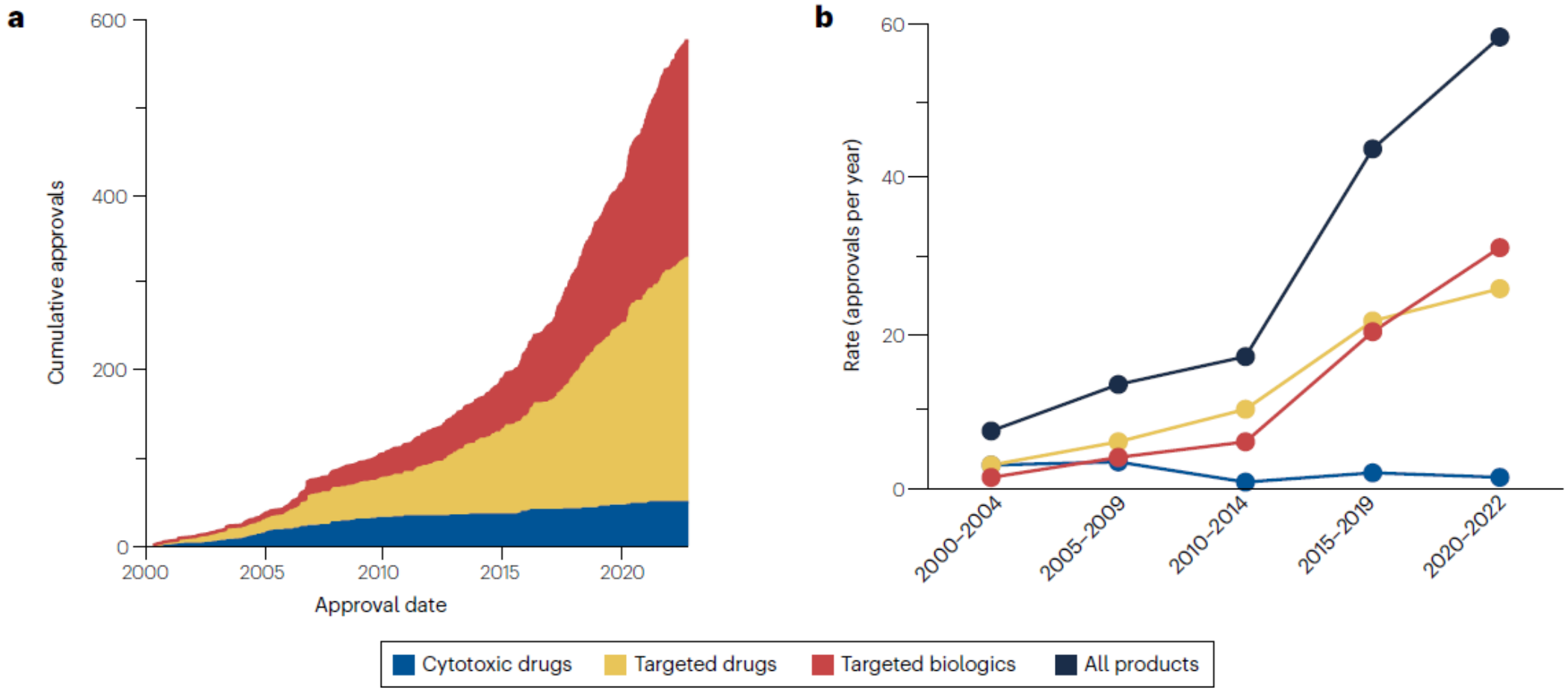

## The 'war on cancer' isn't yet won

The US National Cancer Act of 1971 has fostered tremendous progress in our understanding of the biology that underlies cancer. However, scientific and social challenges remain.

Richard Nixon signed the National Cancer Act at the White House on 23 December 1971. Since then, the idea of an 'all-out assault' on cancer has been moderated, with progress understood to be more likely to occur in small steps. Credit: Linda Bartlett/NIH/National Cancer Institute



# Cancer Drugs Are Changing




Scott EC, Baines AC, Gong Y, Moore R Jr, Pamuk GE, Saber H, Subedee A, Thompson MD, Xiao W, Pazdur R, Rao VA, Schneider J, Beaver JA. Trends in the approval of cancer therapies by the FDA in the twenty-first century. *Nat Rev Drug Discov*. 2023 Aug;22(8):625-640.

# Key Differences

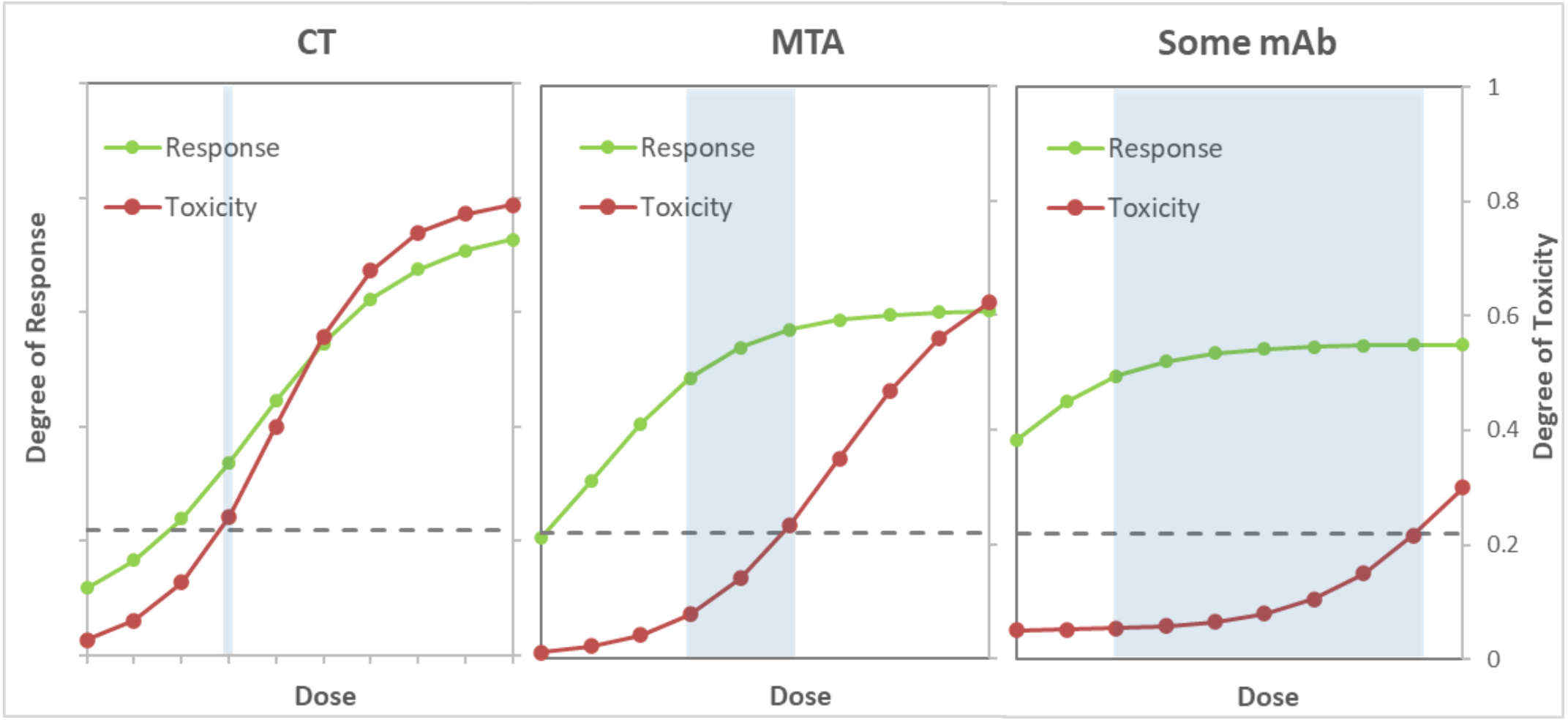
## Cytotoxic Chemotherapies

- Steep dose-response, narrow therapeutic index
- MTD reached
- Fixed number of cycles or short duration of treatment
- Serious toxicities predictable, occur early
- Patients recover with time off of treatment

## Molecularly Targeted Agents

- Different dose-response, potentially wide therapeutic index
- MTD may not be reached (or needed)
- Treatment for many months to years
- Serious toxicities may occur later
- Long-term tolerability, including chronic symptomatic Grade 1-2 toxicities, very important
- No time off of treatment

# Dose-Response Relationships for Common Oncological Agents



# Oncology Center of Excellence

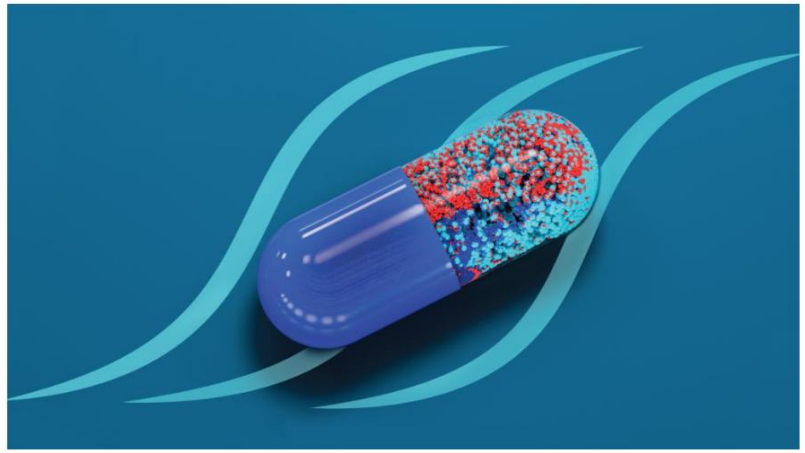
## Project Optimus

**Mission:** To reform the dosing paradigm in oncology drug development

**Main Message: Dosage optimization is essential to safe and effective cancer therapies**

**Who We Are:** A multidisciplinary team of medical oncologists, clinical pharmacologists, biostatisticians, toxicologists, and other scientists with expertise in key facets of dosage optimization

**More Info:** Project Optimus website



# Engaging with Stakeholders

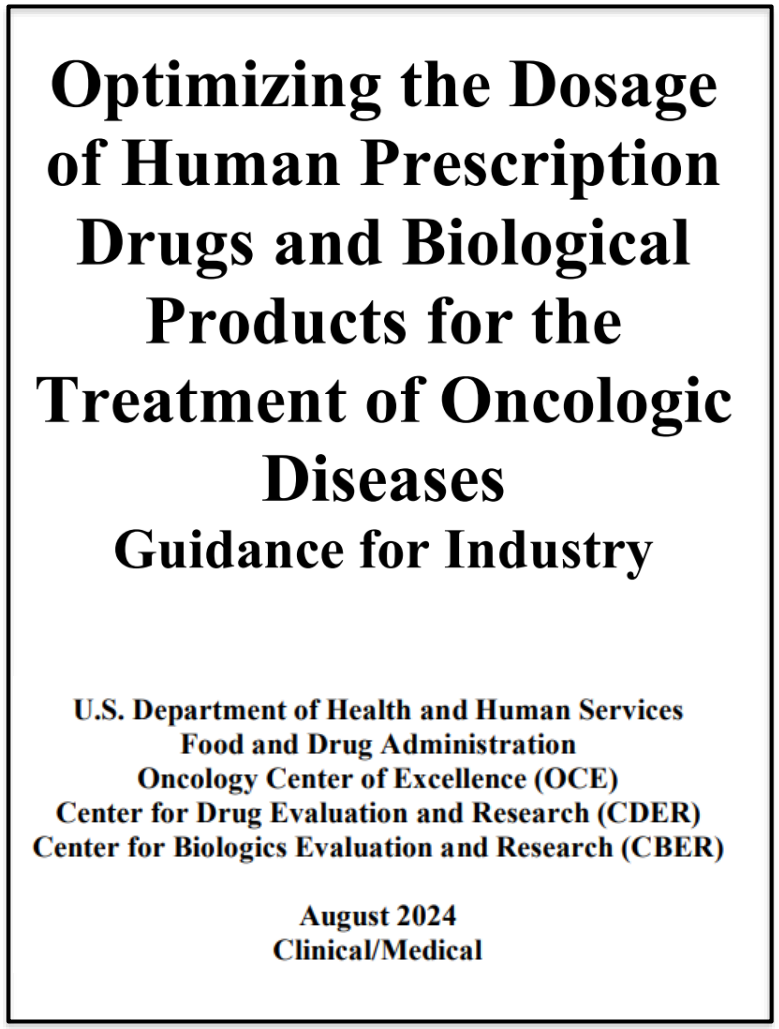
**Multi-Stakeholder Meetings**

- Friends of Cancer Research Annual Meeting 2021 and White Paper
- Conversations on Cancer: More Isn't Always Better
- AACR Annual Meeting 2022
  - Dose Optimization for Antibody Drug Conjugates
  - Using Patient-Generated Data to Optimize the Dose for Oncology Drugs
- FDA-ASCO Virtual Workshop 2022: Getting the Dose Right: Optimizing Dose Selection Strategies in Oncology
- ACCP Annual Meeting 2022
  - Revisiting Oncology Dose Finding: Striking the Optimum Balance Between Efficiency & Robustness
- American Conference on Pharmacometrics 13 (2022):
  - Oncology Drug Development - Getting Ready for Project Optimus
- Society for Immunotherapy of Cancer 2022
  - Assessment of Combination Therapies Regarding Safety, Dose, Contribution of Component
- 2023- FDA ASCO Combination Therapies Workshop
- 2024- FDA AACR Workshop

**Publications**

- The Drug-Dosing Conundrum in Oncology-When Less is More
- Improving Dose-Optimization Processes Used in Oncology Drug Development to Minimize Toxicity and Maximize Benefit to Patients
- How to Get the Dose Right

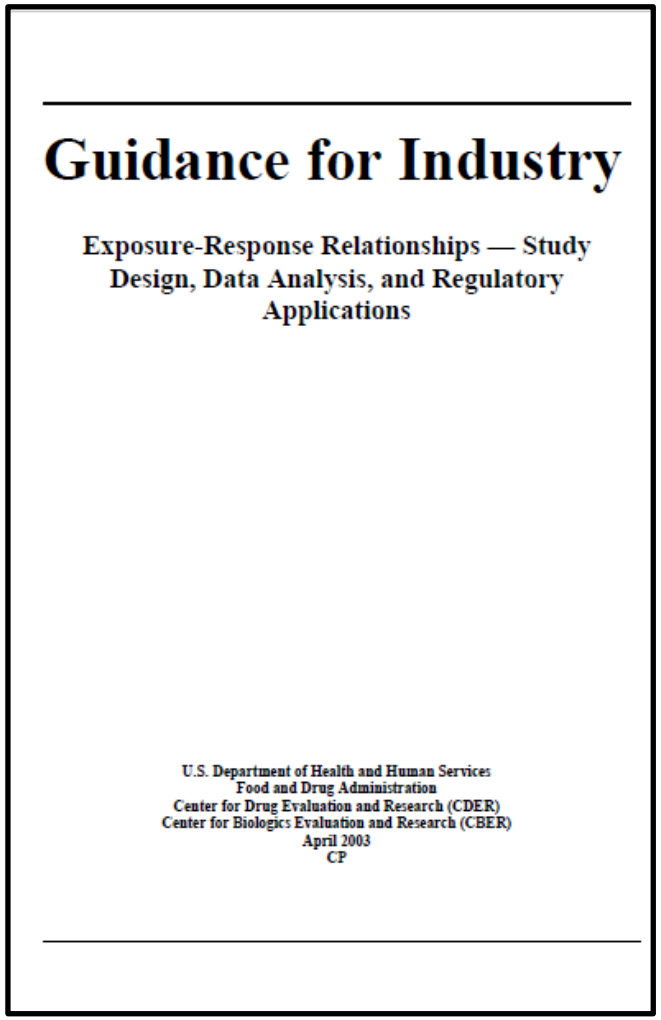
# Oncology Dosage Optimization Guidance

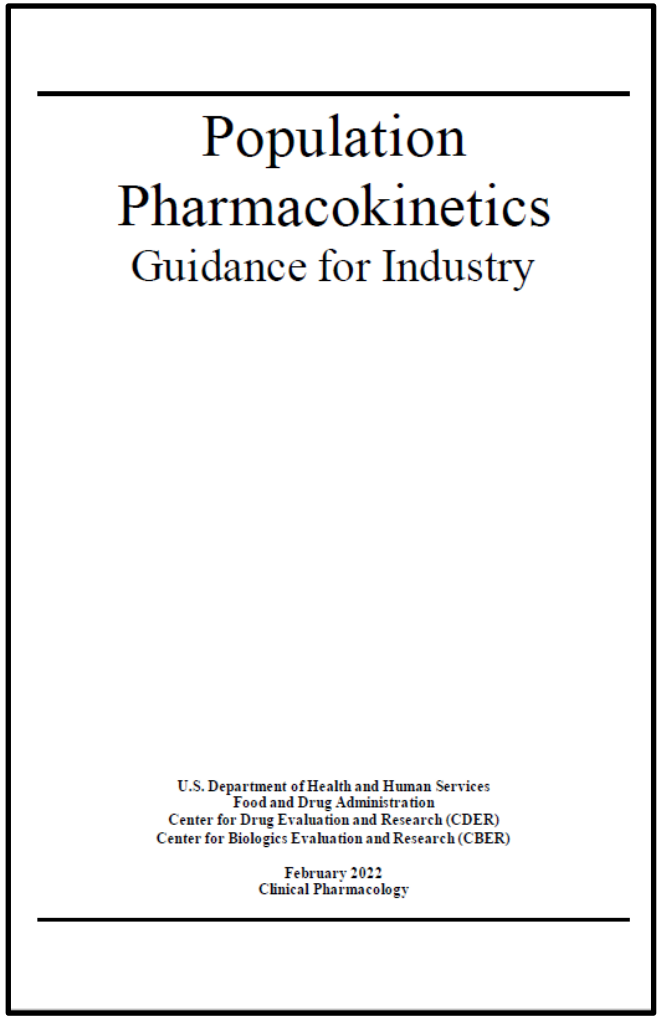



**2024**

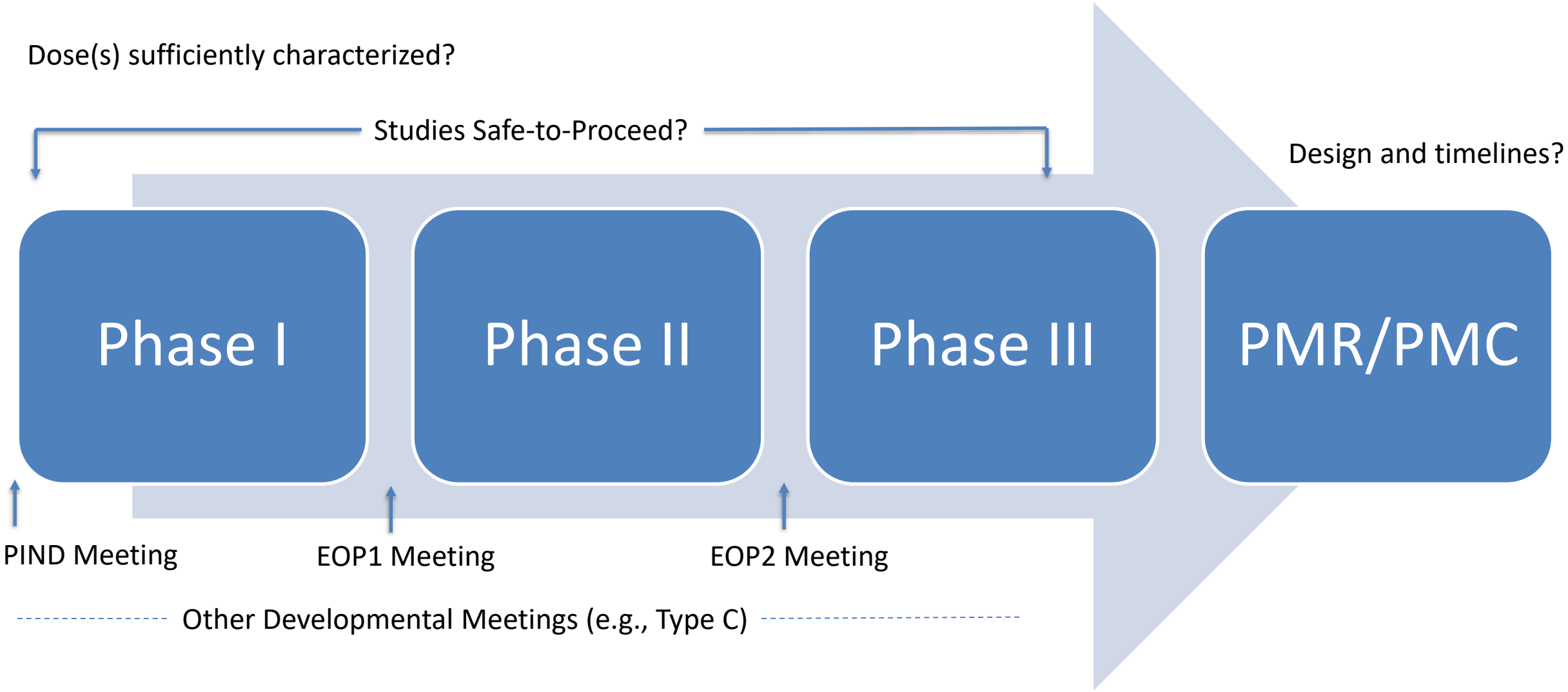
- Dosages must have justification appropriate to the stage of development
- Evaluate all data to select and support dosages
- Randomized comparisons support identification of optimized dosage(s)
- Safety assessments should include low-grade symptomatic toxicities
- Important for all products, including those with anticipated rapid development timelines

# Other Guidance Documents Supporting Dosage Optimization

# FDA's Role in Dosage Optimization



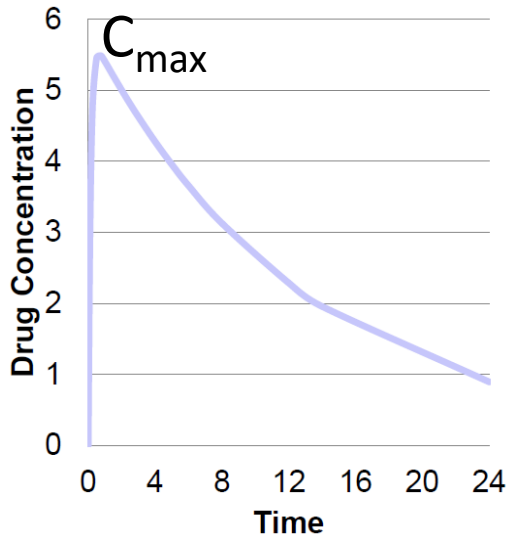

*Conduct research, issue guidance, engage stakeholders*

# Exposure-Response: Key to Translation

**Pharmacokinetics (PK)**
How body handles drug

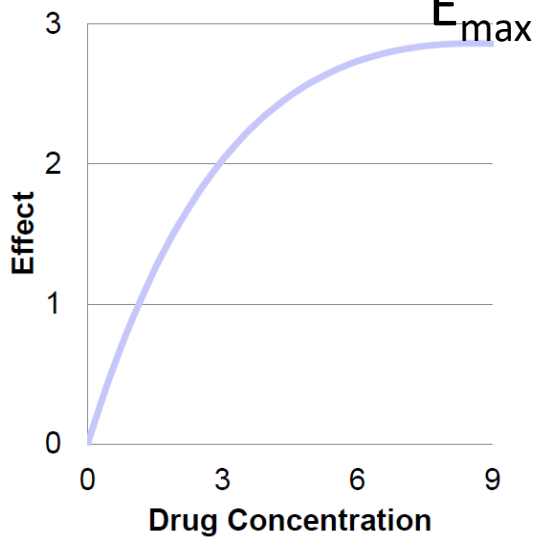
**Pharmacodynamics (PD)**
What drug does to body

**Dosage & Administration** → **Exposure to Drug** → **Desired Effect and Toxicity**


**PK/PD**

**E-R**



# Exposure-Response: Common Metrics

Exposure:

- $C_{min}$, $C_{max}$, $C_{ss}$, AUC

Response:

- Objective Response Rate (ORR), Complete Remission (CR), Progression-Free Survival (PFS), Overall Survival (OS), Adverse Events of Special Interest (AESI), biomarkers

Choice of metric depends on:

- Goal of analysis
- Product type
- Data collected

**Recommendation: Consult your resident clinical pharmacologist on what metrics are relevant!**

$C_{min}$: trough plasma concentrations; $C_{max}$: peak plasma concentrations; $C_{ss}$: concentration at steady-state; AUC: area under the curve

# How Much Do We Know About E-R Relationships?

Previously, we considered theoretical dose-response relationships

- Since typically only one dose is evaluated in depth, there is limited data at the other doses
- Exposure may be highly correlated with baseline factors
- Exposure-response relationships based on a single dose may be misleading

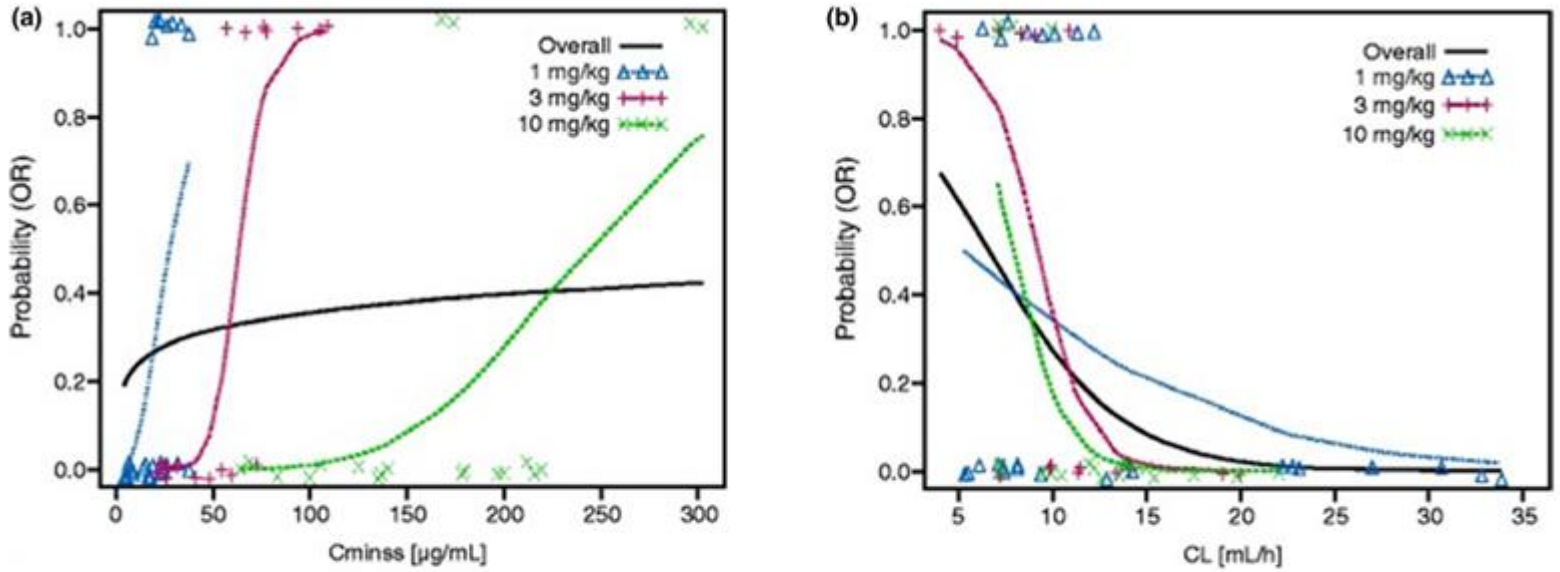



**Figure 2** Nivolumab data from multiple dose levels for (**a**) exposure–efficacy relationship and (**b**) clearance-efficacy relationship. Figures adapted from Agrawal *et al.*[7] and are distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Figure from Dai et al., Clinical Pharmacology & Therapeutics, 2020; adapted from Agrawal, Journal for immunotherapy of cancer, 2016.

# How Much Do We Know About E-R Relationships?

Yang (2013) explored case-control analyses for ER relationships for trastuzumab in HER2-overexpressing metastatic gastric cancer

- RCT of trastuzumab + FC vs. FC
- Exposure quartiles matched based on 5 identified risk factors
- Lowest trough concentration in Cycle 1 ($C_{min,1}$) quartile showed no difference in OS
- FDA issued PMR to evaluate impact of increasing exposure[1]

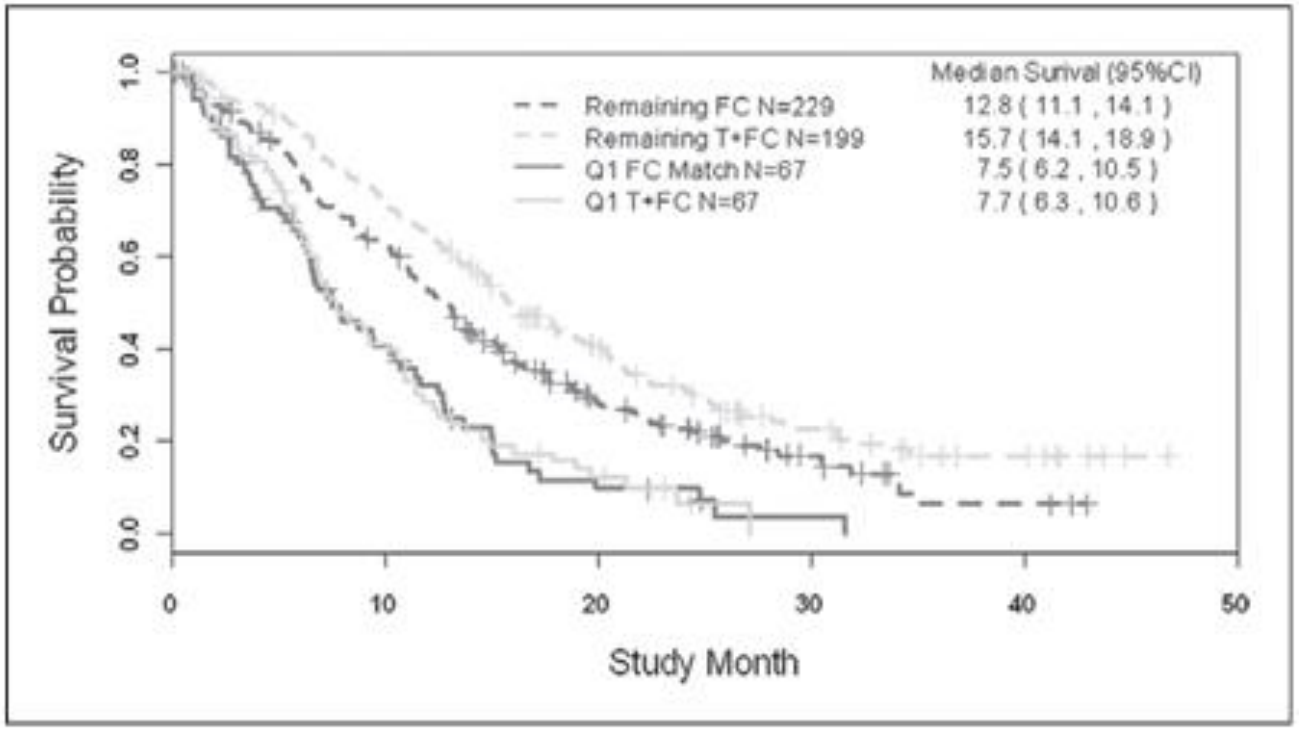


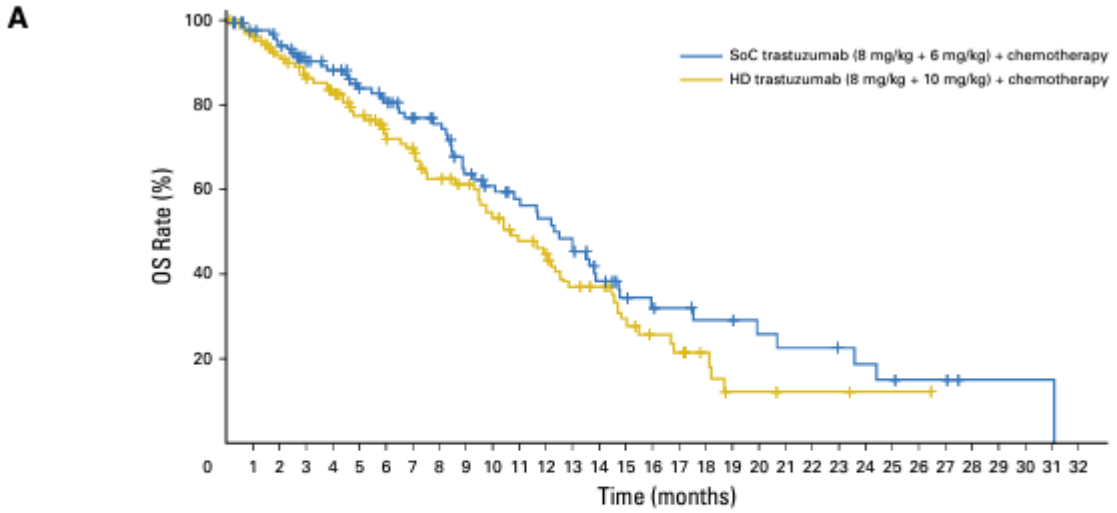

**Figure 2.** Kaplan-Meier curves for the matched subgroups. CI, confidence interval; FC, fluoropyrimidine and cisplatin; Q1, quartile 1; T+FC, trastuzumab in combination with fluoropyrimidine and cisplatin.

[1]Supplemental BLA Approval Letter: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/103792s5250ltr.pdf

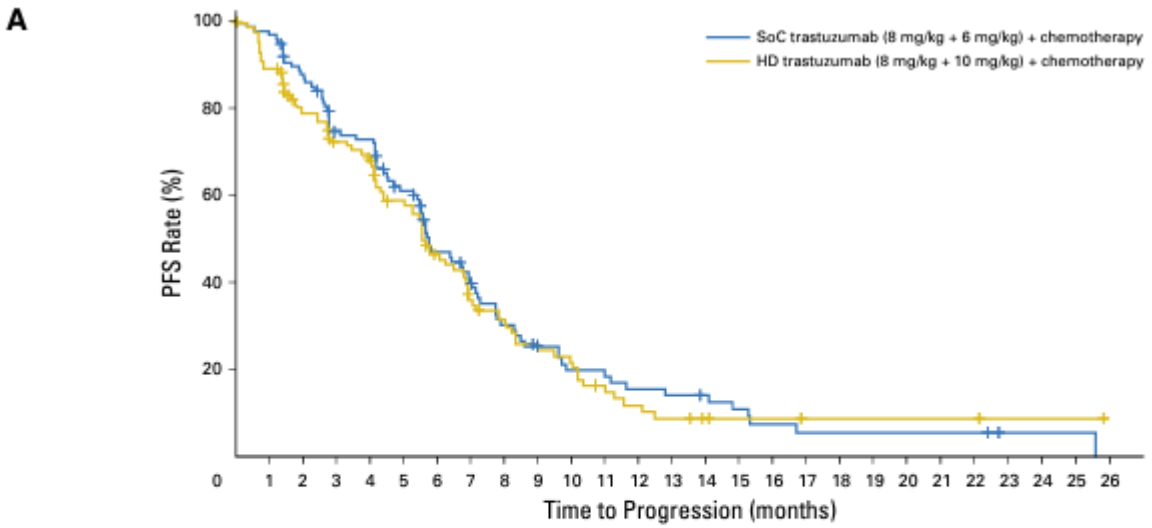
# How Much Do We Know About E-R Relationships?

The HELOISE trial compared standard of care (SoC) trastuzumab + chemotherapy vs. higher dose (HD) trastuzumab + chemotherapy.

- ✓ Higher dose increased concentration
- × No difference in OS or PFS




| | SoC Trastuzumab (8 mg/kg + 6 mg/kg) + Chemotherapy (n = 124) | HD Trastuzumab (8 mg/kg + 10 mg/kg) + Chemotherapy (n = 124) |
|---|---|---|
| OS events, No. (%) | 58 (46.8) | 67 (54.0) |
| Median OS, months | 12.5 | 10.6 |
| Stratified OS HR (95% CI) | 1.24 (0.86 to 1.78); log-rank $P = .2401$ | |

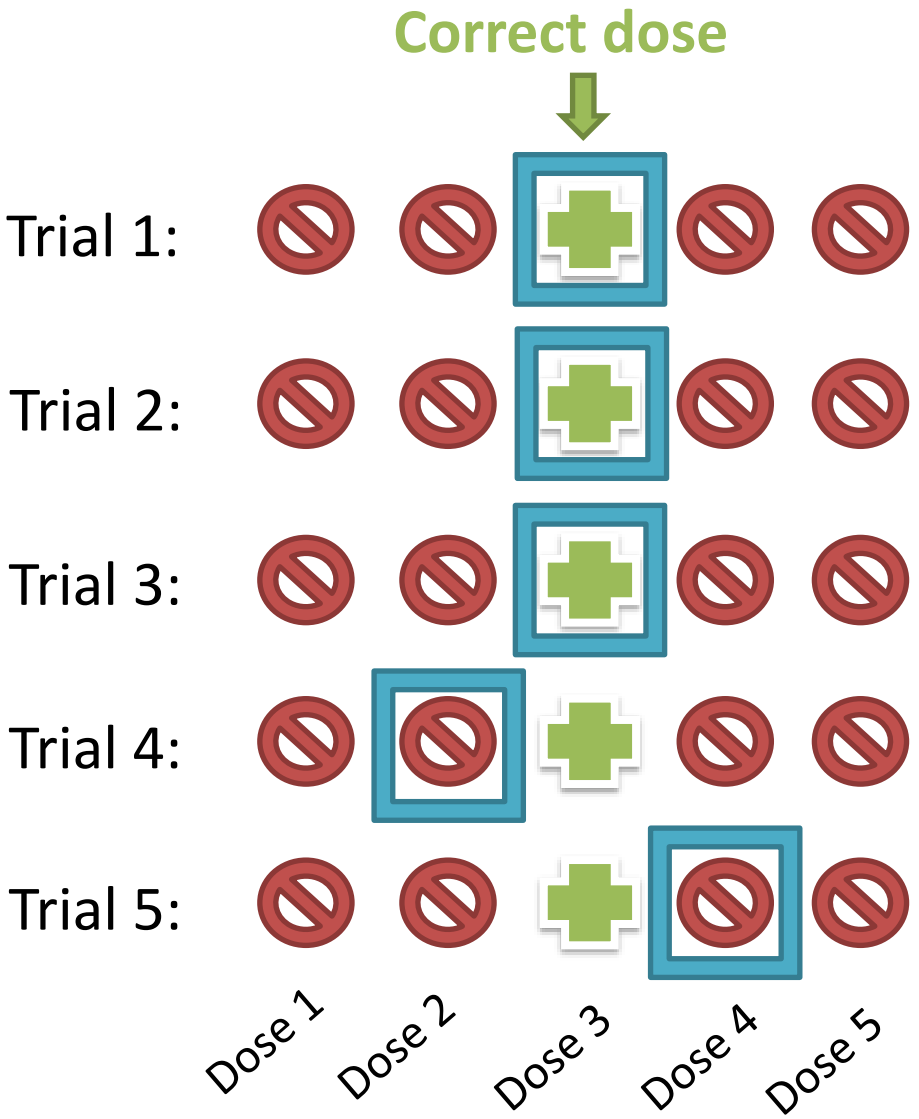



| | SoC Trastuzumab (8 mg/kg + 6 mg/kg) + Chemotherapy (n = 124) | HD Trastuzumab (8 mg/kg + 10 mg/kg) + Chemotherapy (n = 124) |
|---|---|---|
| Median PFS, months | 5.7 | 5.6 |
| Stratified PFS HR (95% CI) | 1.04 (0.76 to 1.40); log-rank $P = .8222$ | |

Shah (2017)

# How Much Do We Know About the MTD?

- Typical dose-finding designs treat ~6-20 patients at the MTD
- Comparative simulations often report that correct selection of MTD is moderate (~40-70%)
  - Doses above ≥33% DLT rate can be incorrectly selected
- After MTD declared, dose often not reassessed



# High Frequencies of Dose Modifications at Approved Doses

Selected targeted agents approved by FDA in 2019

| Drug | Drug Class | Dose Discontinuation % | Dose Reduction % | Dose Interruption % |
|---|---|---|---|---|
| Erdafitinib | Kinase inhibitor | 13 | 53 | 68 |
| Alpelisib | Kinase inhibitor | 21 | 55 | 66 |
| Selinexor | Kinase inhibitor | 27 | 53 | 65 |
| Polatuzumab vedotin | Antibody-drug conjugate | 27 | 4 | 49 |
| Enfortumab vedotin | Antibody-drug conjugate | 16 | 34 | 64 |
| Fam-trastuzumab deruxtecan | Antibody-drug conjugate | 9 | 18 | 33 |

drugs@FDA

## We Can Do Better!

# Growing Calls for Change

FDA

TARGETED THERAPIES

## Redefining the primary objective of phase I oncology trials

*Mark J. Ratain*

Cytotoxic agents are conventionally dosed on the basis of the maximum tolerated dose defined in phase I trials. A study assessing adverse events in over 2,000 patients treated with molecularly targeted agents suggests a need to redefine criteria for dosing of molecularly targeted agents, which should be based on randomized, dose-ranging phase II trials.

Ratain, M. J. *Nat. Rev. Clin. Oncol.* **11**, 503–504 (2014); published online 5 August 2014; corrected online 9 September 2014; doi:10.1038/nrclinonc.2014.135

AP WORLD U.S. ELECTION 2024 POLITICS SPORTS ENTERTAINMENT BUSINESS SCIENCE FACT CHECK ...

Israel-Hamas war Nevada primary King Charles Marvel crewmember dies Taylor Swift's jet

HEALTH

## As cancer treatment advances, patients and doctors push back against drugs' harsh side effects

PATIENT CENTERED DOSING INITIATIVE

About Us Patients Oncologist Surv

#TheRightDose

Advocating for a better quality of life for people living with Metastatic Breast Cancer through Patient-Centered Dosing.

Learn More

2021 ASCO ANNUAL MEETING

TREATMENT-RELATED SIDE EFFECTS AND VIEWS ABOUT DOSAGE ASSESSMENT TO SUSTAIN QUALITY OF LIFE:

RESULTS OF AN ADVOCATE-LED SURVEY OF PATIENTS WITH METASTATIC BREAST CANCER (MBC)

Anne Loeser,* Jeffrey Peppercorn, Mark E. Burkard, Kevin Kalinsky, Hope Rugo, Aditya Bardia

* Founder, Patient-Centered Dosing Initiative

FRIENDS of CANCER RESEARCH

A FRIENDS OF CANCER RESEARCH WHITE PAPER

## Optimizing Dosing in Oncology Drug Development

Friends of Cancer Research Annual Meeting 2021

December 23, 2019 | 14 min read SAVE

## Cancer drug doses: More is not always better

ADD TOPIC TO EMAIL ALERTS

Historically, the goal of cancer treatment has been to destroy as many cancer cells as possible through chemotherapy or radiation.

# Right Time for Dosage Optimization = Prior to Approval

- Improves decision-making for the drug development program
- Prevents avoidable toxicity → increases uptake and improves adherence
- More efficient, more feasible
- **Allows for more rapid development of new indications and combination therapies**

**"Dose is the foundation of drug development. Having the wrong dose is like building a house on quicksand."**

- Rick Pazdur

# Patient and Clinician Experience (Metastatic Breast Cancer)

## Patients (Loeser 2024)

| Question | No. (%) |
|---|---|
| Do you believe that the highest approved dose of a cancer drug is always more effective than a lower approved dose of the same drug? | N = 1,221 |
| Yes | 237 (19.4) |
| No | 651 (53.3) |
| Don't know | 333 (27.3) |
| Would you be willing to discuss approved MBC drug dosing options with your doctor based upon your unique characteristics (such as other illnesses you may have, your body mass index, your reactions to previous therapies, and your personal goals and wishes)? | N = 1,221 |
| Yes | 1,127 (92.3) |
| No | 11 (0.9) |
| Don't know | 83 (6.8) |

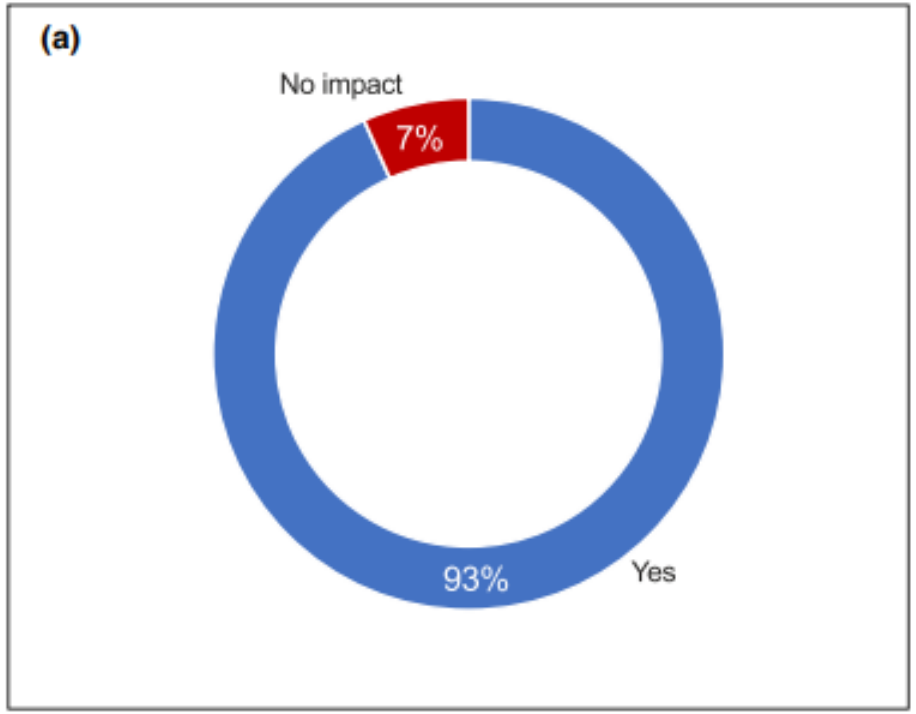
## Oncologists (Loeser 2022)

| Question | No. (%) |
|---|---|
| Do you believe that the standard dose (Maximum-Tolerated Dose) of a cancer drug is always more effective than an allowed lower dose of the same drug? | N = 119 |
| Yes | 6 (5) |
| No | 101 (85) |
| Don't know | 12 (10) |
| Irrespective of whether you have done so in the past, would you be willing to discuss allowed MBC drug dosing options with your patients in future based upon their personal characteristics? | N = 119 |
| Yes | 115 (97) |
| No | 3 (2) |
| Don't know | 1 (1) |

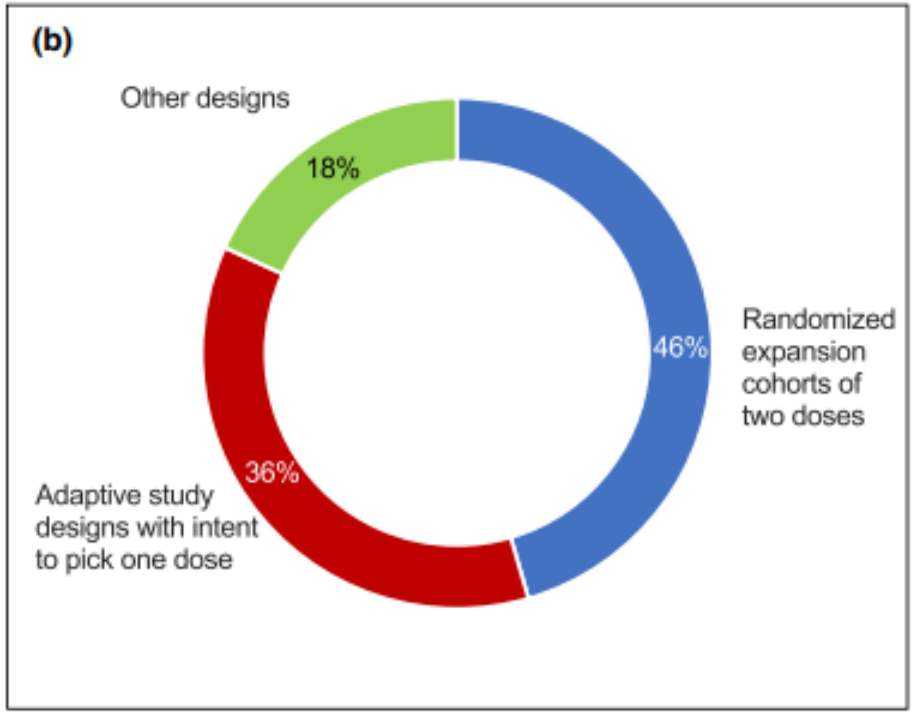
Adapted from Loeser (2022) and Loeser (2024), which surveyed patients and oncologists about their views on treatment-related effects and dosing.

# Industry Perspective

"Has the Project Optimus initiative at OCE-FDA impacted recent strategies for dose optimization?"




"Project Optimus recommends conducting randomized dose finding studies…share your preference on potential study designs."




Adapted from Samineni (2024), which surveyed 18 member companies of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium).

# Conclusions

- Premarket dosage optimization offers benefits to patients, drugmakers, and oncology overall
- It is important to consider the totality of data at each step of dosage selection
- Randomized trials support selection of a dosage optimized for benefit-risk
- One size doesn’t fit all oncology product development programs
- FDA is committed to engaging with stakeholders to realize the promise of this new dosing paradigm in oncology

# Acknowledgements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- Richard Pazdur
- All members of the Project Optimus team


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ADMINISTRATION

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