Optimizing Dose Selection Strategies in Oncology

Society for Clinical Trials Annual Meeting

May 22, 2023

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AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Contributors

- Laura Levit, JD, American Society of Clinical Oncology (moderator)
- Julia Maues, Patient-Centered Dosing Initiative
- R. Donald Harvey, PharmD, Emory University School of Medicine
- Sumithra Mandrekar, PhD, Mayo Clinic Department of Pediatric and Adolescent Medicine
- Elizabeth Garrett-Mayer, PhD, American Society of Clinical Oncology
- Mirat Shah, MD, U.S. Food and Drug Administration

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#TheRightDose

Drug Dosing: The Patient Perspective

Society for Clinical Trials
Annual Meeting 2023

Julia Maués
Patient-Centered Dosing Initiative

Cancer drug dosing: More is not always better

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- Cancer drugs dosing has historically been determined using phase 1 dose escalation studies, often by moving forward with the MTD
- Based on the premise that higher toxicity ➡ greater efficacy
- Premise not exactly relevant for new treatments: targeted therapies & immunotherapies
- Does not consider long-term treatment-related SEs
- TOLERATED by whom? For how long?

PCDI: Patient-Centered Dosing Initiative

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We are a patient-led initiative questioning the practice of routinely treating Metastatic Breast Cancer patients with the highest tolerable dose.

- MBC isn't curable but can be treated, often for years, in some cases even decades.
- We don't just want to live LONGER, we also want to live WELL – quantity AND quality.
- Evidence suggests that lower allowed doses of some MBC drugs may be as effective as the Recommended Started Dose (usually based on MTD).
- Anecdotally, we have seen that several long-term survivors are on reduced doses of medications for various reasons, and that plays a role in how they have been able to tolerate these treatments.

Patient-Centered Dosing Initiative

Patient Members

Anne Loeser

Martha Carlson

Janice Cowden

Christine Houser

Sheila Johnson

Julia Maues

Advisory Board Members

Aditya Bardia, MD

Mark Burkard, MD

Kevin Kalinsky, MD

Maryam Lustberg, MD

Hope Rugo, MD

PCDI Goal

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When prescribing a medication, and throughout the treatment for Metastatic Breast Cancer, the clinician and patient should discuss drug dosage, considering the patient's personal wishes and unique characteristics such as age, availability of at-home care, history of side effects and more.

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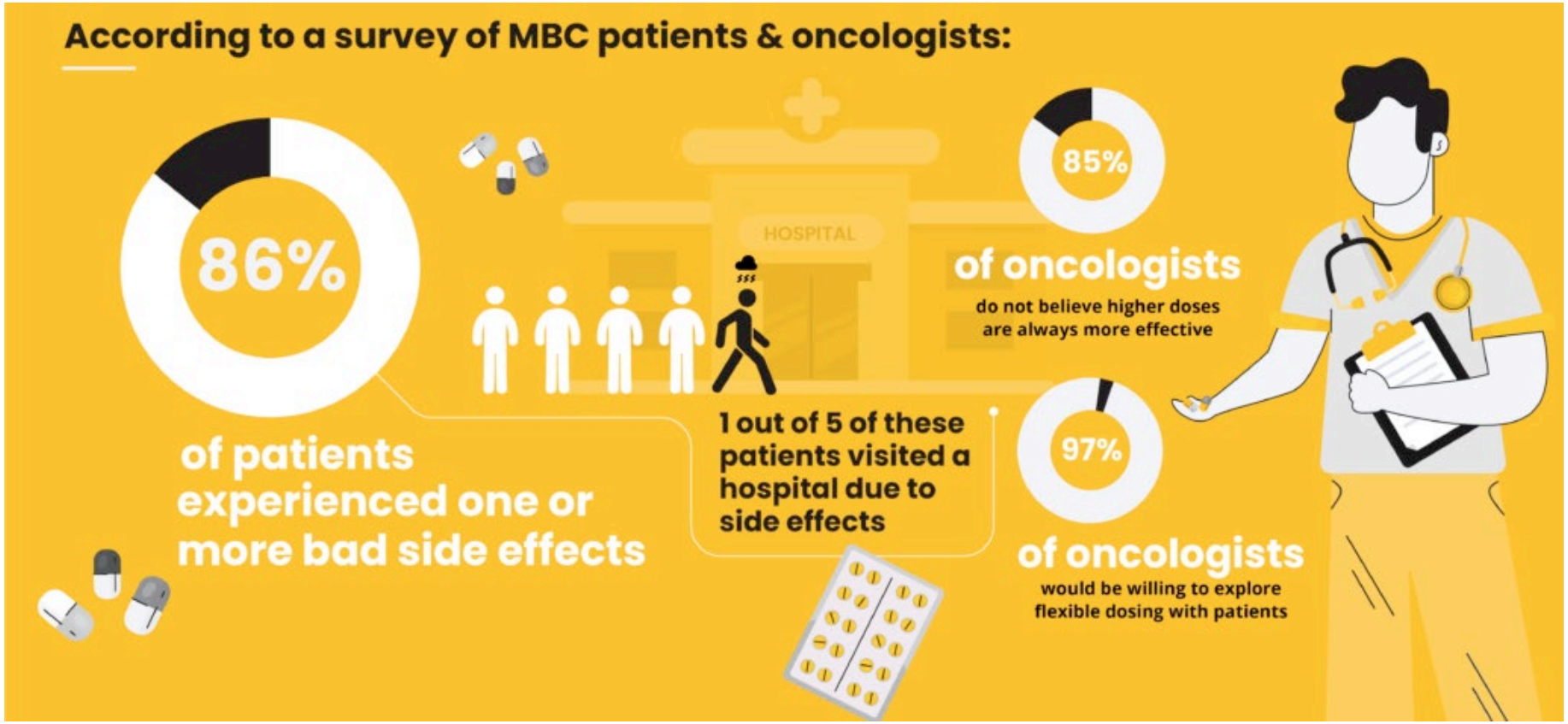
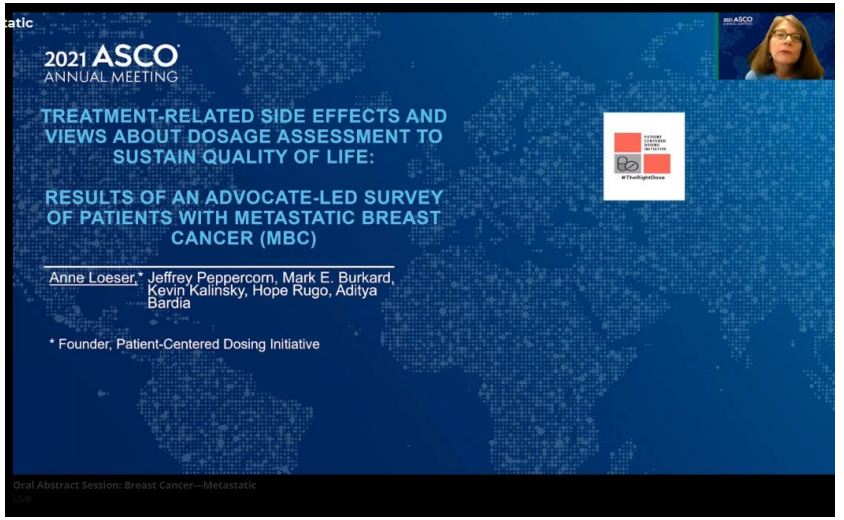
2 Surveys: Patient and Oncologist

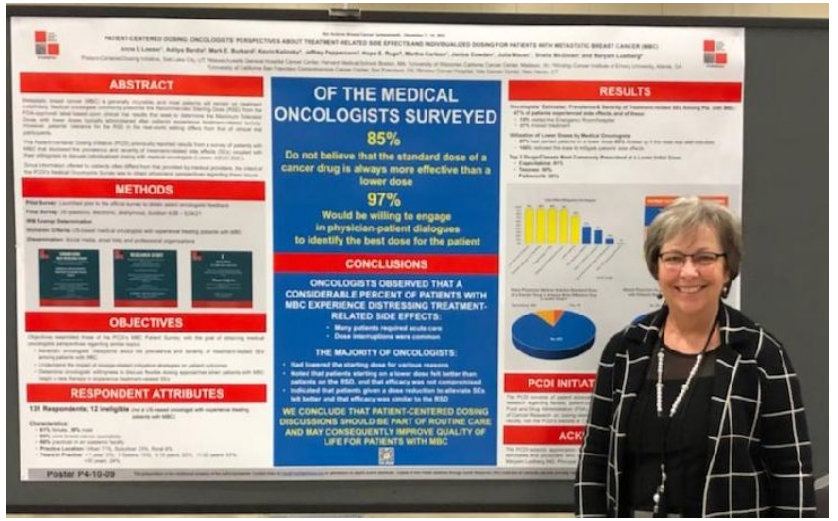
- 1,221 patients with MBC & 119 oncologists participated in the respective surveys



PCDI Exposure

- Patient Survey Results at ASCO ‘21 & two “Best of ASCO” Malaysia & Sri Lanka (oral presentations)
- Pan-Amazonian Oncology Conference ‘21 (oral presentation)
- Friends of Cancer Research Annual Meeting ‘21 (panelist)
- Oncologist Survey at SABCS ‘21 (poster)
- FDA OCE “More Isn’t Always Better: Understanding Cancer Treatment Tolerability,” March ‘22 (panelist)
- FDA & ASCO Workshop “Getting the Dose Right: Optimizing Dose Selection Strategies in Oncology,” May ‘22 (panelist)
- Optimum Cancer Care Alliance ‘22 Annual Meeting (oral)
- AAADV ‘22 (oral)





The idea gained traction with the FDA

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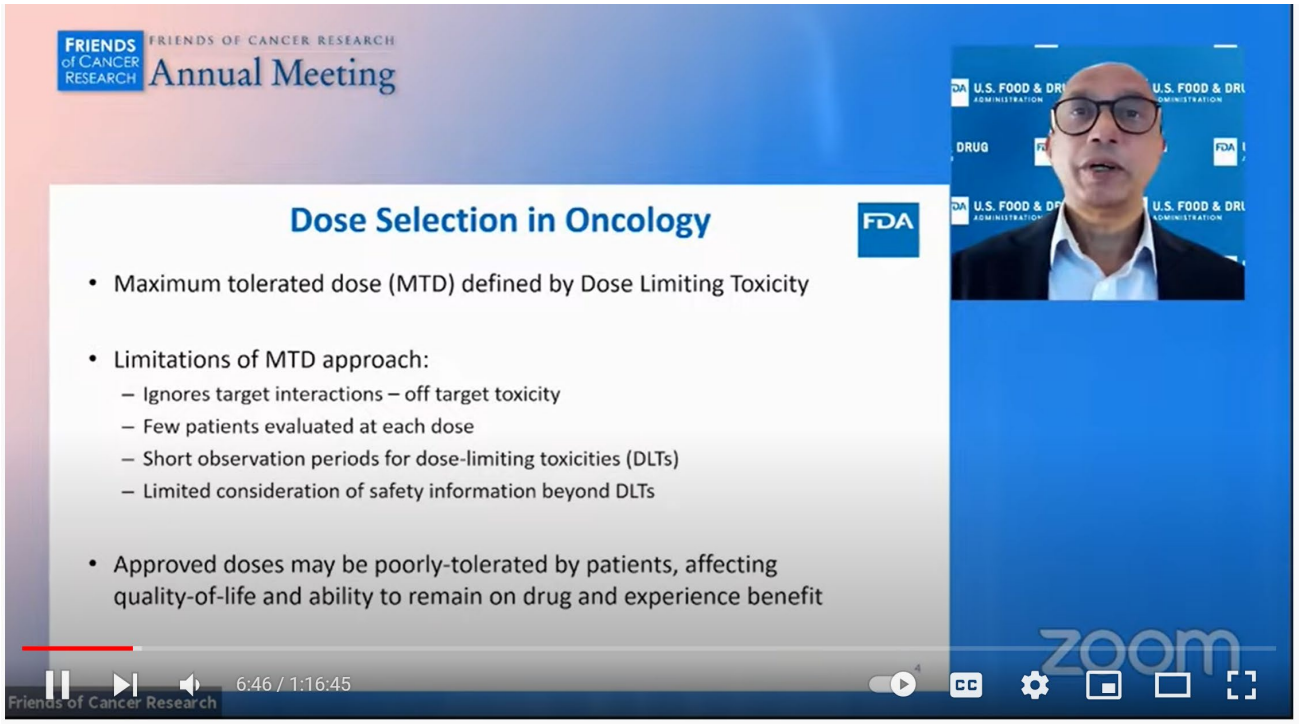
Dr. Atik Rahman, FDA Division Director
Friends of Cancer Research Annual Meeting, Nov. 2021



"It's loud and clear from our patients that the drugs are too toxic… Patients deserve a more tolerable dose."

Real change is happening

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FDA's **Project Optimus** encourages sponsors to evaluate exposure-response, efficacy, and safety data from early trials to inform dose selection instead of automatically selecting the MTD.

When the approved dose and schedule of an approved drug is suboptimal, the FDA may issue **post-marketing requirements (PMRs)** for clinical trials evaluating additional dosages.

For the clinic, PCDI encourages **physician-patient discussions about the right dose for the right patient**. This will remain important because:

- Approved drugs currently on the market continue to be prescribed based upon the MTD
- It will take time for drug development to actualize the new paradigm
- Patients' responses in the real world can differ from those clinical trial participants because they are not subject to rigid inclusion/exclusion criteria
- Patients have unique personal attributes (co-morbidities, drug sensitivities, etc.)

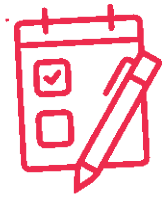
PCDI Patient Education Flyer

Patient-Centered Criteria

Do You Have Stage IV/Metastatic Breast Cancer (MBC)?

MBC IS BREAST CANCER THAT HAS SPREAD BEYOND THE BREAST TO OTHER PARTS OF THE BODY, MOST COMMONLY THE BONES, LUNGS, LIVER, AND BRAIN

IF YOU'RE EXPERIENCING (OR CONCERNED ABOUT) TREATMENT-RELATED SIDE EFFECTS SUCH AS NAUSEA, FATIGUE, RASH, ETC. ***YOU ARE NOT ALONE!***



A SURVEY[1] OF 1,221 PATIENTS WITH MBC FOUND THAT:

86% HAD AT LEAST ONE BAD TREATMENT-RELATED SIDE EFFECT

If you have side effects, speak with your doctor about ways to relieve them.

Your doctor may be able to:

- Prescribe medication for relief
- Adjust your dose
- Revise your treatment schedule
- Recommend a different treatment
- Suggest something else to make you feel better

YOU MAY START THE CONVERSATION WITH YOUR DOCTOR BY SAYING:

"We both want the same things"

"I want to have the longest possible life with the best possible Quality of Life"

"You want that for me too!"

"Let's work together to achieve this!"

YOU AND YOUR DOCTOR MAY WANT TO DISCUSS:

1. Your personal goals, wishes, and desires
2. Your general health situation (other illnesses/conditions)
3. History of side effects from other drugs
4. Current and past blood counts
5. Whether the disease is slow- or fast-growing
6. Whether any organs are severely affected, or the disease is in the brain
7. Your body mass index (level of body fat)
8. Affordability of medications to ease your side effects
9. If you need help at home, is anyone available?

***NEVER** change anything about your treatment on your own; always speak with your doctor!*

[1]Loeser, et all. ASCO Annual Worldwide Meeting, June 2021

Questions/Comments: Visit the Patient-Centered Dosing Initiative at **TheRightDose.org** or email info@TheRightDose.org

The material in this flyer is solely for informational purposes and is not a substitute for professional medical advice or treatment. If you use and/or act upon information in this flyer, you assume full responsibility, and you understand and agree that the Patient-Centered Dosing Initiative and its members are not responsible or liable for any claim, loss, or damage resulting from its use by you or any user. If you have questions about your disease, treatment, and/or side effects, speak with your doctor or other qualified healthcare provider, and never change anything regarding your treatment without obtaining medical advice from your clinician.

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Benefits for Patients

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As a result of fewer toxicity-related side effects, patients may:

- Have less need for emergency care
- Miss fewer treatments
- Potentially remain on a working treatment longer
- Take broader advantage of the full complement of available treatments
- Experience a better Quality of Life

…And possibly,
just possibly,
EVEN LIVE LONGER

Benefits for Oncologists

Medical oncologists want the same things for their patients that patients themselves want: A longer life with better quality.

- "Just because you have cancer and are on treatment doesn't mean you have to be miserable"

  Dr. Eric Winer
  Yale Cancer Center Director & ASCO President

PCDI Patient Member Sheila Johnson and her oncologist of 12 years, Dr. Cynthia Ma.

Benefits for Payers

Cost savings resulting from fewer and less severe patient SEs:

- Fewer specialist visits for side effect mitigation
- Decreased need for palliative medications
- Reduced absenteeism from work
- Less demand for emergency/hospital care

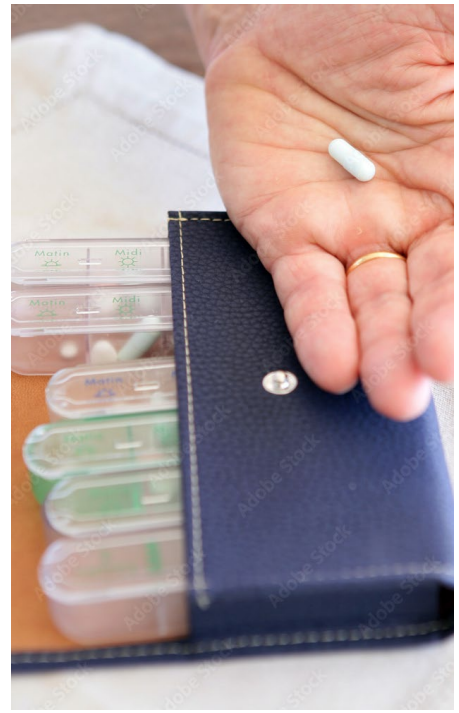
Benefits for Industry

In Clinical Trials:

- Dose optimization early in the drug development process reduces the risk of clinical holds or post-marketing requirements
- If patients can remain on an investigational drug with fewer toxicities, attrition may decrease

In the “Real World”:

- If patients don’t have to stop taking a treatment that is working due to SEs, they can remain on it longer, and sales will increase
- If patients miss fewer treatments due to reduced toxicities, sales will increase



Cancer Drug Dosing: A New Era

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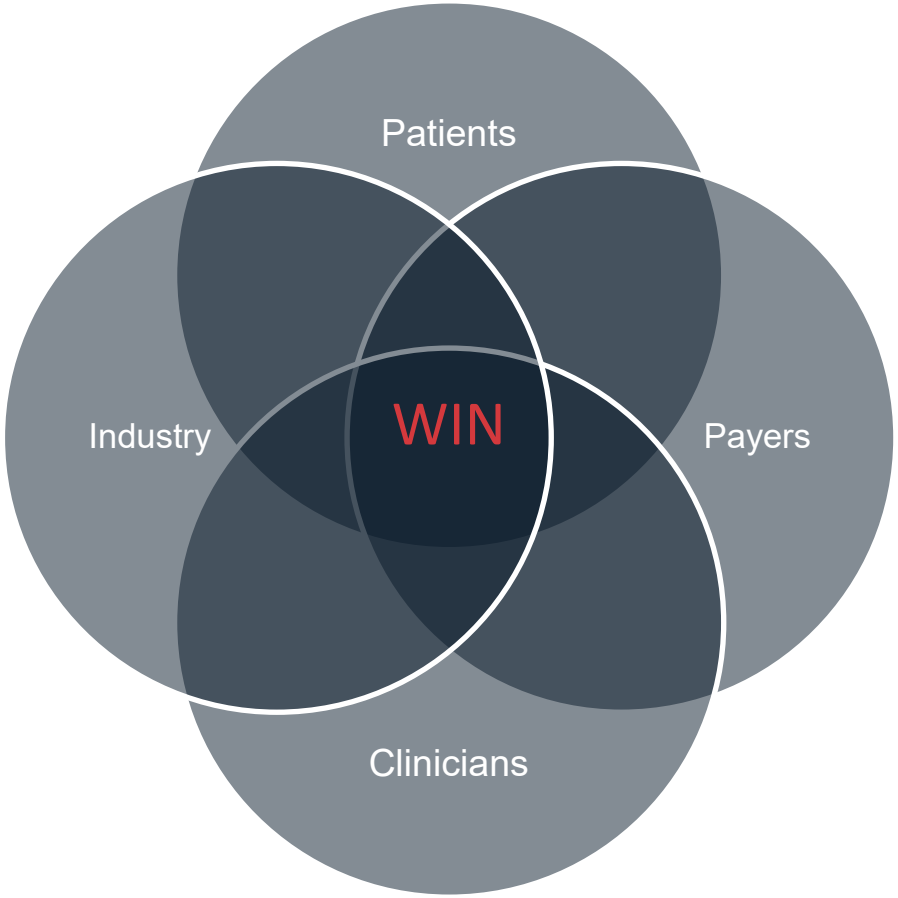

Thank you!

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#TheRightDose

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The Challenges and Opportunities for Dose Optimization in Oncology – How Did We Get Here?

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Medical Director, Clinical Trials Office
Director, Phase I Clinical Trials Section

EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

Disclosures

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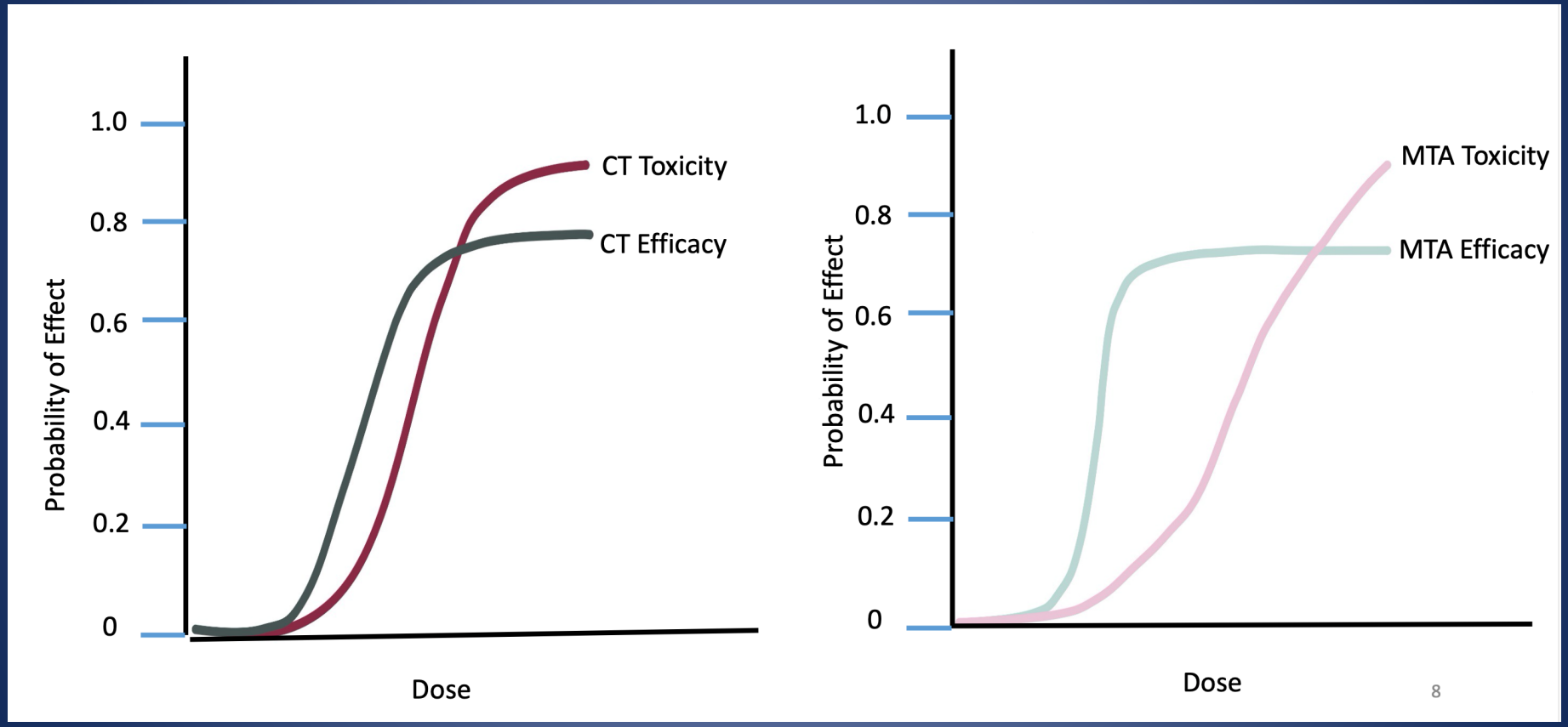
- Consultant: Amgen, Erasca, Janssen

Phase 1 Trial Historical Thinking and Design

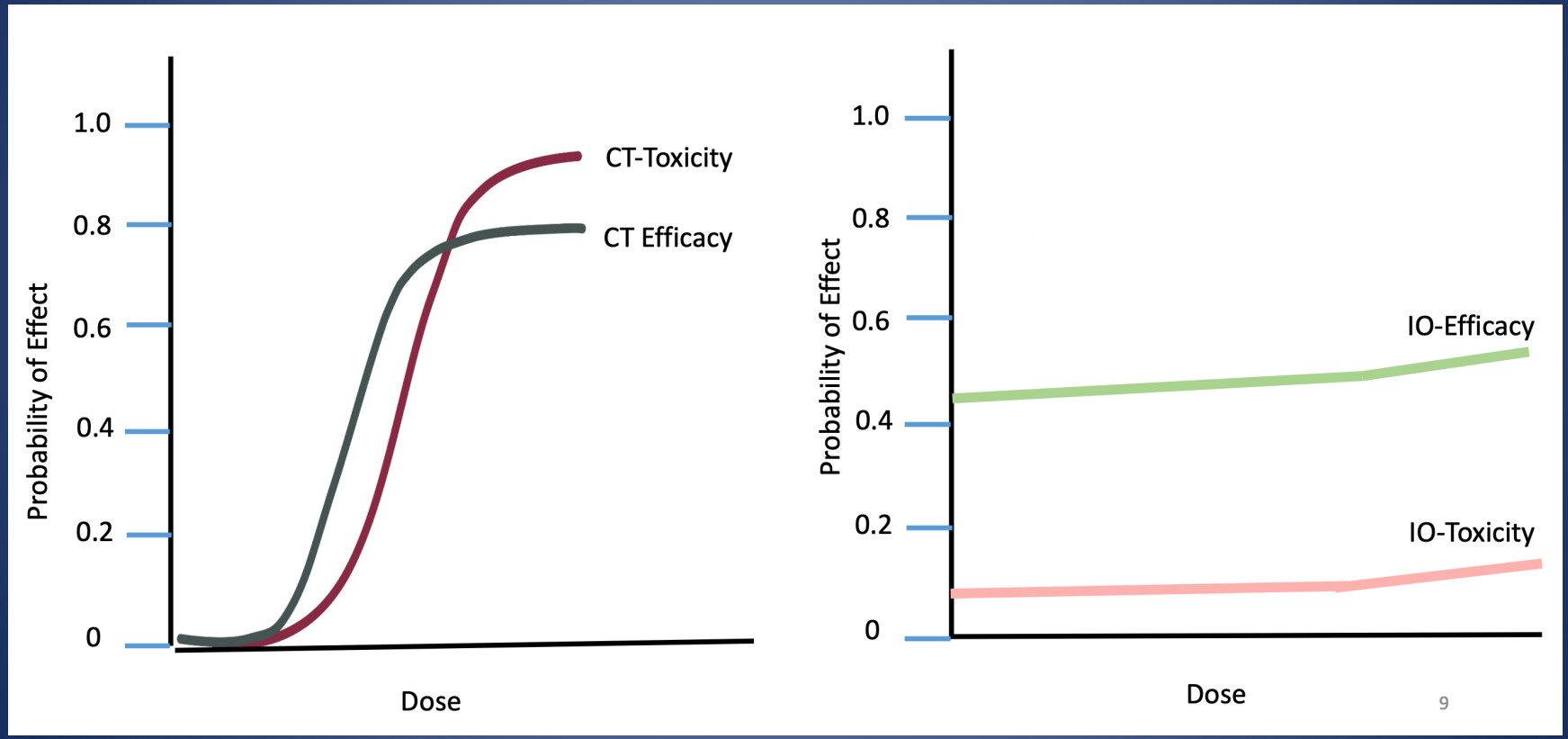
- Solely based on cytotoxic chemotherapy paradigm
  - Dose-response relationships are linear
    - Narrow therapeutic indices
  - The most concerning adverse events are seen in the first 3-4 weeks after treatment initiation (cycle 1)
  - Very few oral, chronically administered agents
  - Treatment duration limited
- Application to novel agents doesn't work

Cytotoxic versus Molecularly Targeted Agents (MTAs)



Slide courtesy of Lillian Siu, MD

Cytotoxic versus Molecularly Immuno-Oncology (IO) Agents



Slide courtesy of Lillian Siu, MD

The Fallacy of Relying Solely on Cycle 1 Toxicity Reporting

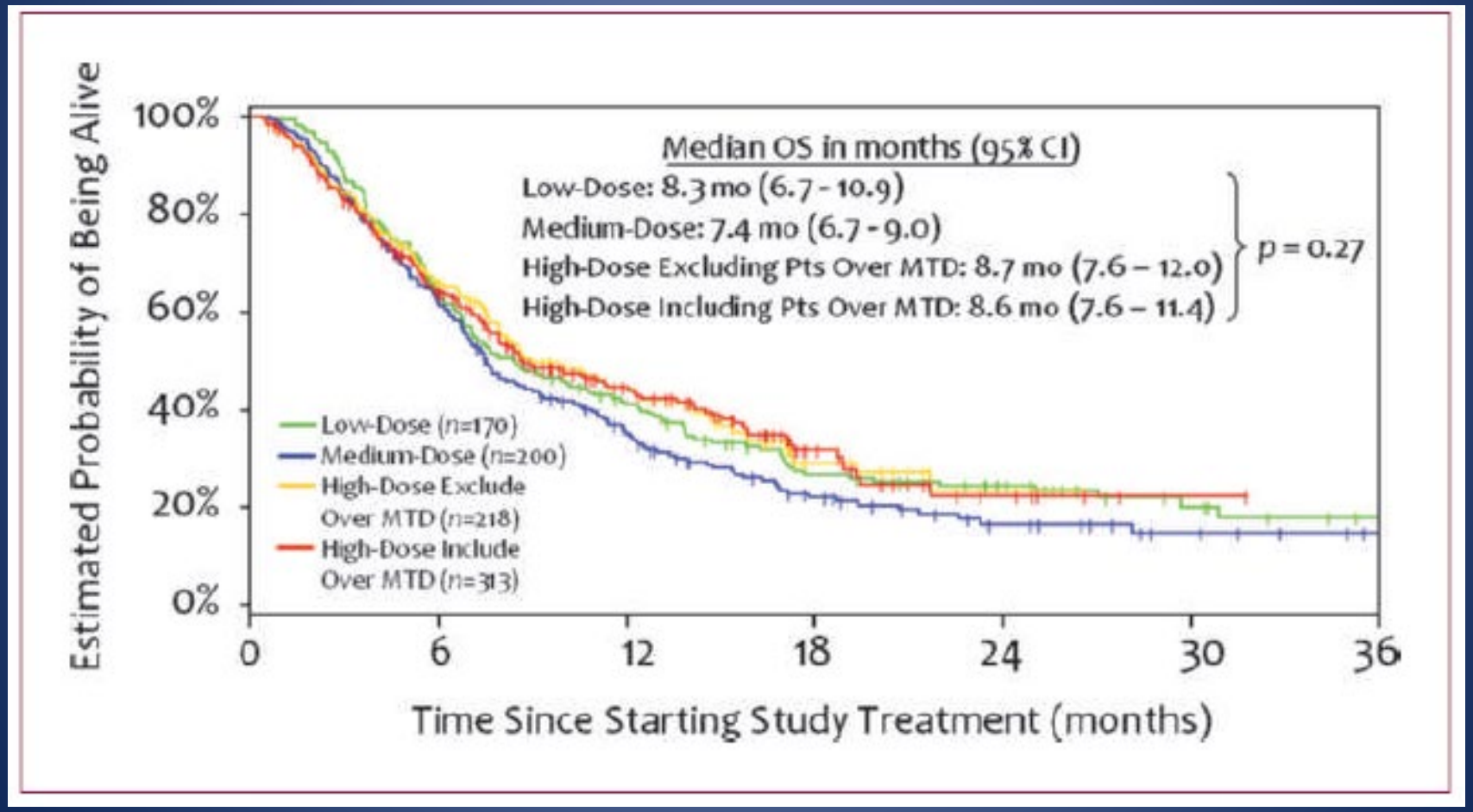
- Recommended phase 2 doses come from cycle 1 grade 3 or higher toxicity measures
- Limitations
  - Adherence to therapy for molecularly targeted agents that yield clinical benefits for prolonged periods
  - Many intolerable chronic grade 2 toxicities not reported
  - Historical example - Capecitabine
    - “In combination with docetaxel, the recommended dose of is 1250 mg/m2 twice daily for 2 weeks followed by a 7-day rest period, combined with docetaxel at 75 mg/m2 as a 1-hour IV infusion every 3 weeks
    - Dosage may need to be individualized to optimize patient management”

Dose-Response Relationships of Targeted Agents

- Evaluation of 683 patients in 24 trials categorized by % of MTD received
  - Low (≤ 25% of MTD)
  - Medium (25-75% of MTD)
  - High (75-100% of MTD)
- Baseline demographics similar among dose levels
  - Age = 55
  - PS = 1 (~ 60%)
  - GI cancer ~ 30%

Jain RK, et al. Clin Cancer Res 2010;16:1289-1297.

Dose-Response Relationships of Targeted Agents



Jain RK, et al. Clin Cancer Res 2010;16:1289-1297.

Causes of Getting the Dose Wrong

- Focus on more rapid, targeted development
  - Smaller sample sizes
- Restrictive eligibility criteria
  - Comorbidities, performance status, organ function, prior lines of therapy
- Limited to no focus on cycle 2+ toxicities for dose selection
  - Chronic grade 2 adverse events

Impact on Patients

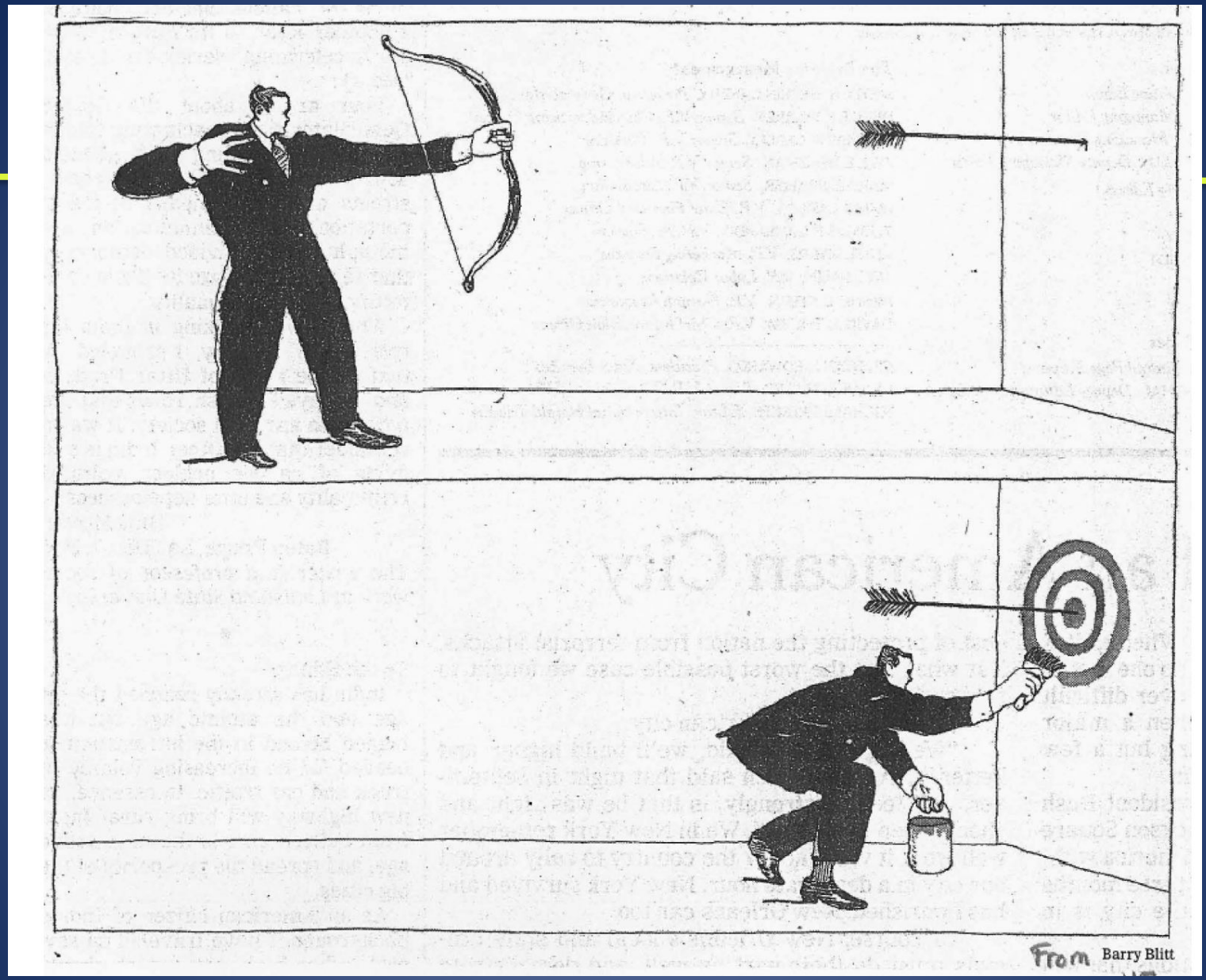
- Toxicity without added disease benefit
  - Quality of life decrements, early discontinuation
- Physician reluctance to use agent in subsequent patients and/or at labelled doses
- More rapid cycling of treatment lines
- Less public trust in the development process

How Do We Correct Course?

Whether?	When?	How?

• Approved doses of many agents excessive (eg, capecitabine)
• Trial populations ≠ post-approval populations
• Patient perspective rarely included in dose decisions
• Flat dose-response curves for many oral small molecules
	• Activity shown and narrow therapeutic index
	• Earlier
	  • Optimal for development efficiency
	  • May not have large numbers of responses for planning
	• Later
	  • Potential for higher likelihood of confidence in data with ≥2 doses
	  • Potential for even higher numbers of patients receiving suboptimal or toxic dose
		• Assess need by agent and potentially class
		• Include and analyze all data gathered
		• Increase numbers of observations across doses
		• Focus more on defining therapeutic index across clinical and nonclinical data
		• Incorporate time (schedule) into dose decisions
		• Approve a range of doses
		• Utilize therapeutic drug monitoring

J Natl Cancer Inst, Volume 115, Issue 5, May 2023, Pages 485–487, https://doi.org/10.1093/jnci/djad042



Slide courtesy of Merrill Egorin, MD

MAYO CLINIC

Endpoint and Design Considerations for Dose Optimization Trials

Sumithra J. Mandrekar
Professor of Biostatistics and Oncology
Mayo Clinic

SCT Invited Session
Optimizing Dose Selection Strategies in Oncology

May 22, 2023, Baltimore, MD

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No relevant disclosures for this talk

Consulting or Advisory Role

- Flatiron Health
- Harbinger Oncology, Inc

Leadership roles

- Group Statistician and Program Director, Alliance and AFT
- Co-Chair: CTAC SCTWG, NCI SCTIC

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Early Phase Trials: Characteristics

- Small sample size, usually in the range of 20-60 patients
- Extensive data collection
  - Large n (factors) from a small N (patients)
  - Heterogenous (different histology/tumors/markers/dose levels/schedules)
- Data collected:
  - Adverse events: across different body systems, across multiple cycles
  - Attribution or relatedness to study treatment(s)
  - Late-onset and long-term effects
  - PRO, biomarkers, clinical outcomes etc.
- Data used:
  - Binary data points (DLT)
  - Cycle 1 data for dose selection
  - Single/binary efficacy measure

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Trial Optimization: What Does it Entail?

- Endpoints/outcomes
  - Tolerability
    - Unacceptable rate of adverse events
    - Time to all treatment discontinuation
    - Dose delays, interruptions, dose reductions/changes
    - Patient reported adverse events (PRO CTCAEs)
  - Efficacy
    - Biomarker/molecular changes and expression levels
    - Clinical outcomes: Tumor shrinkage, Progression, survival
    - Patient reported outcomes (composite endpoints)
    - Using PK to guide dose escalation
- Design elements
  - Algorithm based, Model Assisted, Model based
  - Dose escalation and Dose expansion (randomized?)
  - Accounting for missing/incomplete data

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Trial Optimization: What Does it Entail?

- Trial Population
  - Heterogenous mix: tumor types, molecular profiles, patient demographics
  - Assess the safety/efficacy within homogenous subgroups
    - biomarker defined
    - tumor/histology focused
    - under-represented populations (minorities, older/frail, gender)
- Streamlining Data Collection
  - Number and frequency
  - Examples:
    - Adverse events
      - Multiple cycles, multiple grades, multiple types of events
      - Long term effects
      - Relationship to study treatment(s)
      - Timing of occurrence of AE
      - PRO CTC AEs
    - Dosing Data: schedule (continuous, intermittent), mode of administration (IV vs. oral); fixed vs. based on body surface area, frailty etc.

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Endpoints

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Adverse Event Burden Score

- AE burden by treatment cycle: weighted sum of the AEs reported in each cycle t.

$$B(t) = \sum_k \sum_g w_{kg} Y_{kg}(t)$$, k = type and g = severity grade

- AE burden overall score: Average (or total) across all treatment cycles

$$TB = \sum_t u_t B(t)$$

- Weight considerations
  - Well defined a priori, and the same weight function must be used if comparing across trials
  - For example: severity grade for grade 1-4 events; and 10 for grade 5 events

Le-Rademacher JG et al. Cancers, 2020; Ruppert AS et al., Leukemia 2021

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Dual Endpoint Design
AE burden score + Efficacy Measure

- A continuous score
- Incorporates multiple AE types and grades
- Incorporates AE data from multiple cycles of treatment for each patient

Novel Treatment Features	Our Design Features
Mild, moderate Toxicities	Lower grade toxicities (grade 1-2) are included.
Late, cumulative Toxicities	Repeated measures of subsequent treatment cycles are included
Non-monotonic relationship of dose and efficacy	Incorporates plateau shape of efficacy

- **Repeated Measures Design**: TTP and continuous efficacy outcome (patient QOL / clinical / biomarker)

Yin J et al. phase1RMD: An R package for repeated measures dose-finding designs with novel toxicity and efficacy endpoints. PLoS One. 2021; 16 (9):e0256391 PMID: 34473708 PMCID: 8412295
Ezzalfani et al., SIM, 2013; Yin et al. SIM 2017; Yu et al., J B Pharm 2019

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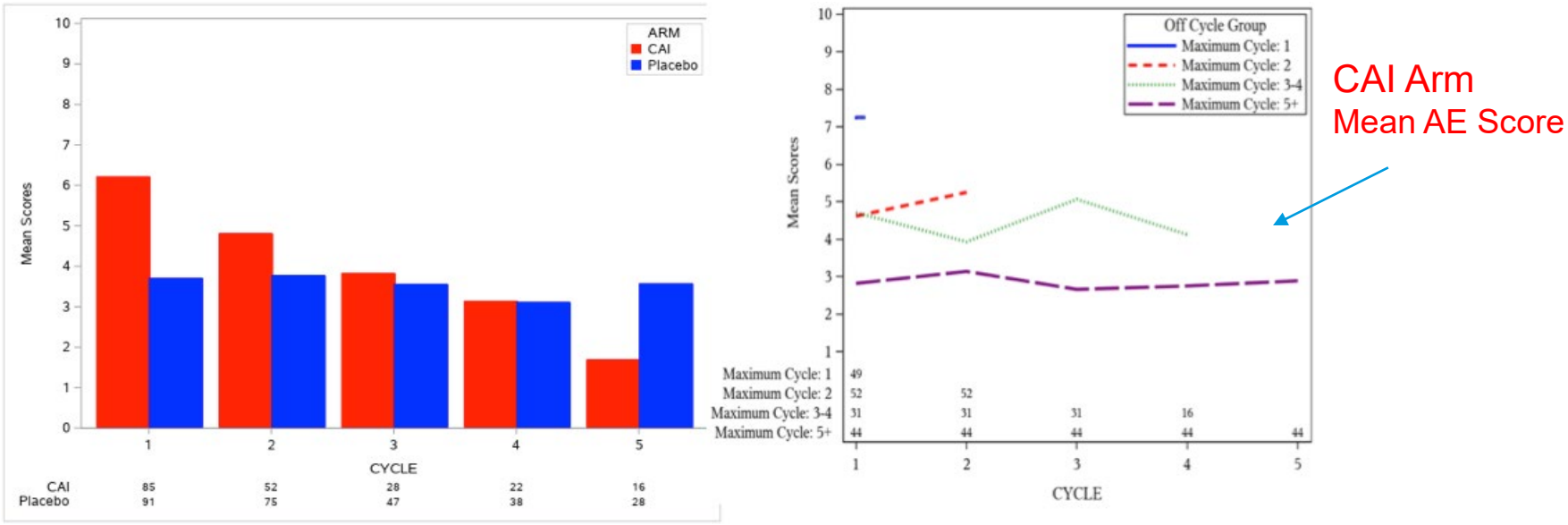
NCCTG 97-24-51 RESULTS



CAI Arm
Mean AE Score

1. AE burden in CAI arm was higher in the early period but decreased over time due to patients going off treatment early due to AEs.
2. AE burden in the placebo arm was relatively flat over the 5 treatment cycles.
3. Patients in CAI with higher AE burden went off treatment early.

cancers

MDPI

Article

Adverse Event Burden Score—A Versatile Summary Measure for Cancer Clinical Trials

Jennifer G. Le-Rademacher [1,*], Shauna Hillman [1], Elizabeth Storrick [1], Michelle R. Mahoney [2], Peter F. Thall [3], Aminah Jatoi [4] and Sumithra J. Mandrekar [1]

A041202 TRIAL RESULTS

IBRUTINIB REGIMENS VERSUS BENDAMUSTINE/RITUXIMAB

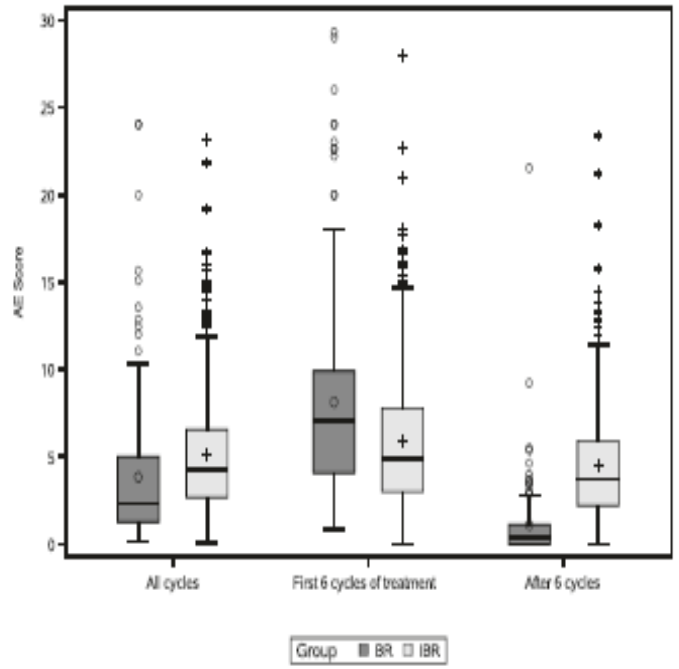


Fig. 2 AE score by treatment group, across all assessments/cycles, the first 6 cycles of treatment, and after 6 cycles of treatment.

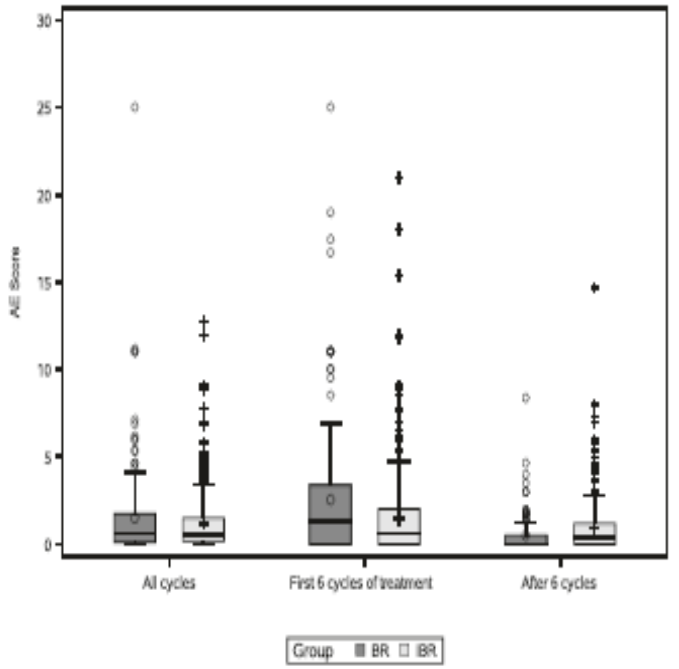


Fig. 3 Limited to grade 3/4 AEs, AE score by treatment group, across all assessments/cycles, the first 6 cycles, and after 6 cycles.

Ruppert et al., Leukemia, 2021

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Design

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TABLE 1. Comparison of Design Characteristics Among Algorithm-Based, Model-Based, and Model-Assisted Phase I Designs

Design Characteristic	Algorithm Based	Model Assisted	Model Based
Transparency and simplicity			
Dose escalation/de-escalation rule can be predetermined and included in the protocol	Yes	Yes	No
Avoids computation-intensive, repeated estimation of the dose-toxicity curve model to make interim decisions	Yes	Yes	No
Flexibility			
Targets any prespecified DLT rate	No	Yes	Yes
Allows decision making when the cohort size deviates from the planned size	No	Yes	Yes
No. of patients treated at the MTD can be > 6	No	Yes	Yes
Sample size can be calibrated to ensure good operating characteristics	No	Yes	Yes
Performance			
Identifies the MTD accurately	No	Yes	Yes
Allocates a high percentage of patients to the MTD	No	Yes	Yes
Provides good overdose control	Yes	Yes	Yes

Abbreviations: DLT, dose-limiting toxicity; MTD, maximum-tolerated dose.

Yuan et al, *JCO Precis Oncol*, 2019

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Yuan et al, *JCO Precis Oncol*, 2019

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Simulation Considerations: Trial Conduct and Design Elements

- Components of the design
  - Plausible Scenarios for dose-toxicity/dose-efficacy
    - Number of patients to treat at a dose level
    - Unacceptable toxicity threshold/acceptable efficacy bounds
  - Accrual patterns and rates
    - Missing data, treatment/schedule compliance
  - Patient characteristics
  - Patient outcomes
- Decision rules for escalation and expansion
  - Timing, maturity of data to use in dosing decisions
  - Pre-specified adaptations: randomization ratios; inclusion/exclusion; dose selection; adding/dropping arms; subgroup selection
- Final summary
  - Operating characteristics; dose range recommendations

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Trial Population

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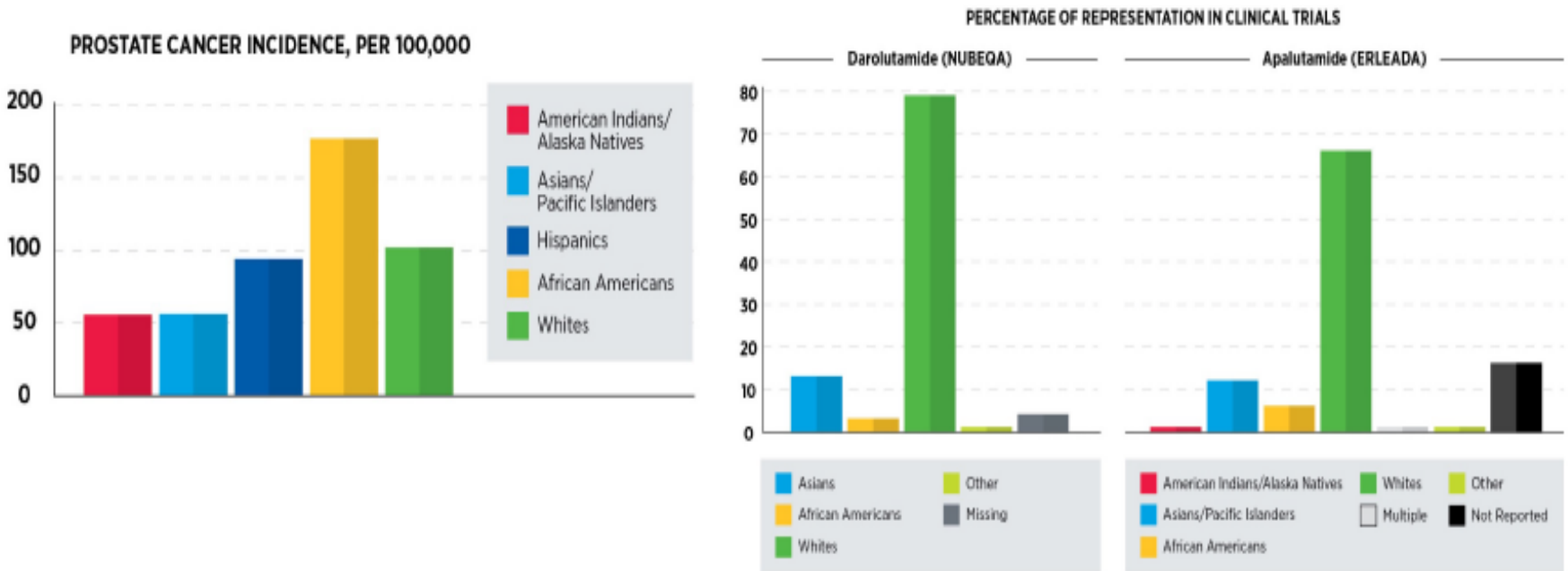
Inadequate Representation in Clinical Trials…

- Perpetuates inequities in healthcare
- Limits the generalizability of clinical trial results
  - Biomarker expression may differ by race or ethnicity
- Contributes to the efficacy-effectiveness gap

Phillips et al. Cancer. 2020 Apr 15;126(8):1717-1726.

Racial and Ethnic Minorities and Other Medically Underserved Populations are Underrepresented in Oncology Clinical Trials



AACR Cancer Disparities Progress Report, 2020

Table 4. Race/ethnicity of US patients in Phase I clinical trials in oncology compared with US demographics and cancer incidence.

Race/ethnicity	US patients (%)	US Census[†] (%)	SEER data[‡]: 2013–2017 age-adjusted cancer incidence per 100,000
White/Caucasian	84.2	76.5	452.1
Black/African-American	7.3	13.4	440.4
Asian	3.4	5.9	302.0[§]
Native Hawaiian/Pacific Islander	0.1	0.2	NR[§]
American-Indian/Native Alaskan	0.1	1.3	310.1
More than one race	0.0	2.7	NR
Other/unknown	3.7	–	NR
Hispanic/Latino	2.8	18.3	348.4

[†]Source: US Census Bureau. Population Estimates, July 2019 (https://www.census.gov/quickfacts/fact/table/US).

[‡]Source: Surveillance, Epidemiology and End Results (SEER) Program. 5-Year age-adjusted incidence rates, 2013–2017 for all cancers (https://seer.cancer.gov/explorer/).

[§]Hawaiian/Pacific Islander included with Asian.

NR: Not reported; SEER: Surveillance, Epidemiology and End Result.

Camidge DR et al., Future Oncology, 2021

Streamlining Data Collection

©2012 MFMER

Candidate Data Categories to Streamline

- Adverse events
  - Low-grade
  - Attribution and start/stop times
- Laboratory data
  - Beyond standard of care
  - Unrelated to study endpoints or safety monitoring
  - Unused components of panels
- Imaging
  - Beyond standard of care
- History and Physical
  - Concomitant medication, start dates for concomitant medications not linked to protocol eligibility or safety
  - Start dates for histories not linked to protocol eligibility or safety
  - Patient position and resting status for vital signs

https://deainfo.nci.nih.gov/advisory/ctac/1122/Meropol-Mandrekar2.pdf

MAYO CLINIC

Thank you for your attention

mandrekar.sumithra@mayo.edu

Society for Clinical Trials Annual Meeting

May 2023

Randomized Dose Finding Studies

Elizabeth Garrett-Mayer, PhD
Vice President
Center for Research and Analytics (CENTRA)
American Society of Clinical Oncology (ASCO)
Alexandria, VA

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Disclosures for Elizabeth Garrett-Mayer

- I am a full-time employee of the American Society of Clinical Oncology, a non-profit organization

- I have no financial interests to disclose

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Revisiting Dose Finding Objectives

- Maximum tolerated dose is not optimal in modern oncology drug development
- Trials should be designed to target an 'optimal dose' characterized by both SAFETY AND EFFICACY
- Some proposals for change:
  - *Phase I and II should be merged using a coherent approach for optimal dosing*

    Co-primary endpoints: SAFETY and EFFICACY
  - *Phase I identifies a set of SAFE doses to be assessed for EFFICACY in phase II.*

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There are a many integrated safety and efficacy based designs

- Short list of simultaneous or semi-sequential model-based approaches to address both toxicity AND efficacy
  - Thall and Cook, Dose-Finding Based on efficacy-toxicity trade-offs. Biometrics (2004)
  - Wages et al. Tailoring early-phase clinical trial design to address multiple research objectives. Cancer Immunology, Immunotherapy (2020)
  - Chiuzan et al. An adaptive dose-finding design based on both safety and immunologic responses in cancer clinical trials. Statistics in Biopharmaceutical Research (2018).
  - Jin and Yin. CFO: Calibration-free odds design for phase I/II clinical trial. Statistical Methods in Medical Research (2022).
  - Zhou et al. TITE-BOIN12: A Bayesian phase I/II trial design to find the optimal biological dose with late-onset toxicity and efficacy. Statistics in Medicine (2022).
  - …….
- Unfortunately, these are infrequently employed

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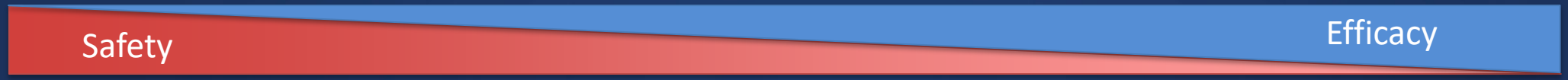
Integrated dose finding design example



1. Dose escalation; Collect efficacy

Dose 1

Dose 2

Dose 3

Dose 4

Dose 5

2. Randomize to dose levels for efficacy outcomes; continue safety monitoring

Dose 2

Dose 3

Dose 4

3. Complete accrual for efficacy outcomes; continue safety monitoring

Dose 2

Dose 3

4. Estimate efficacy parameters among safe doses.

Chiuzan et al. An adaptive dose-finding design based on both safety and immunologic responses in cancer clinical trials. Statistics in Biopharmaceutical Research (2018).

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Integrated toxicity and efficacy designs

- Many designs exist that integrate outcomes for dose finding.
- But uptake has been poor.

- Why?
  - Newer designs take longer to develop, require specialized expertise
  - Newer designs require more patients to get a “phase I” answer
  - Simple designs are simple!

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Sequential dose finding approach

Part 1: Toxicity-based dose finding

→ Identify a set of doses with acceptable toxicity

Similar to traditional phase 1

Part 2: Dose selection study

→ Assess efficacy and toxicity in small number of doses (usually 2 or 3)

→ Randomized design

→ Might be adaptive?

→ Select dose level with better performance

Similar to traditional single arm phase 2

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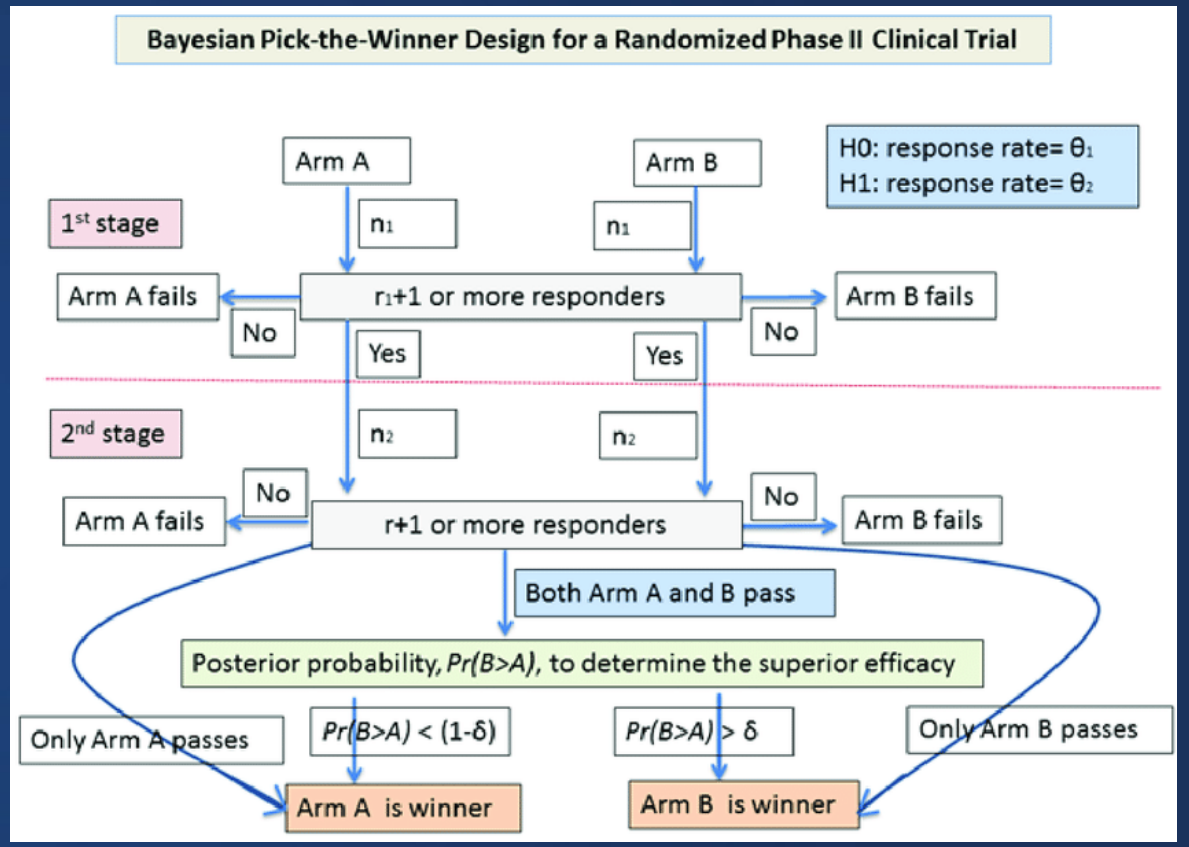
Characteristics of dose selection studies

- Objective: Identify **optimal** dose of treatment from a set of doses
- Relatively small sample sizes per dose arm – not designed for a direct comparison.
  - Compare each arm with a historical rate of success
  - Select N to achieve a level of precision of parameter estimate
- "Pick the winner" designs

  Simon et al (1985): only 29-37 patients per arm will yield 90% power to detect a regimen that has response rate superior by 15%, in a two-arm study
- Designs motivated by precision of estimates
  - Select N to provide level of precision (e.g., confidence interval width)
  - Select N to exclude boundary based on assumed rate
    - Similar to hypothesis testing.
- Not always a prescribed "selection rule" or "Go vs. No-Go"



Chen, Huang, et al. Oncotarget 2017.

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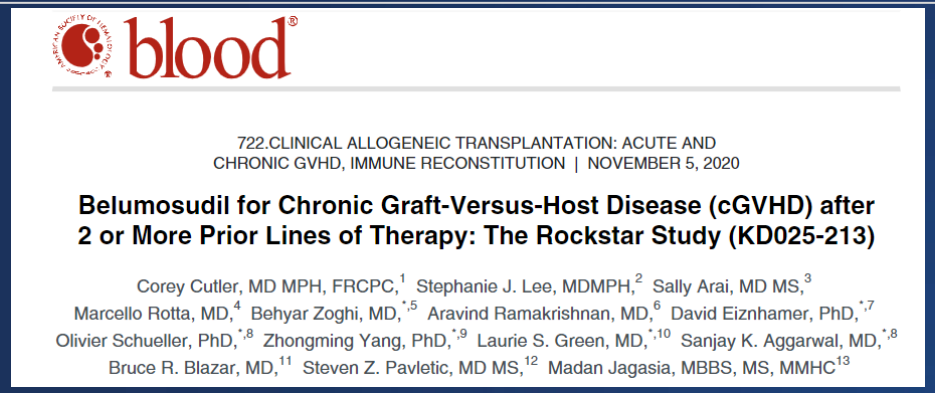
Targeted therapy randomized phase II selection design



blood

722.CLINICAL ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION | NOVEMBER 5, 2020

Belumosudil for Chronic Graft-Versus-Host Disease (cGVHD) after 2 or More Prior Lines of Therapy: The Rockstar Study (KD025-213)

Corey Cutler, MD MPH, FRCPC,[1] Stephanie J. Lee, MDMPH,[2] Sally Arai, MD MS,[3] Marcello Rotta, MD,[4] Behyar Zoghi, MD,[*,5] Aravind Ramakrishnan, MD,[6] David Eiznhamer, PhD,[*,7] Olivier Schueller, PhD,[*,8] Zhongming Yang, PhD,[*,9] Laurie S. Green, MD,[*,10] Sanjay K. Aggarwal, MD,[*,8] Bruce R. Blazar, MD,[11] Steven Z. Pavletic, MD MS,[12] Madan Jagasia, MBBS, MS, MMHC[13]

Belumosudil may effectively treat patients with chronic graft-versus-host disease (cGVHD), a major cause of morbidity and late non-relapse mortality after an allogeneic hematopoietic cell transplant*

Belumosudil arms:

Arm 1: 200 mg daily	Arm 2 200 mg twice daily

*Belumosudil mechanism of action: oral kinase inhibitor, inhibits ROCK1 and ROCK2.

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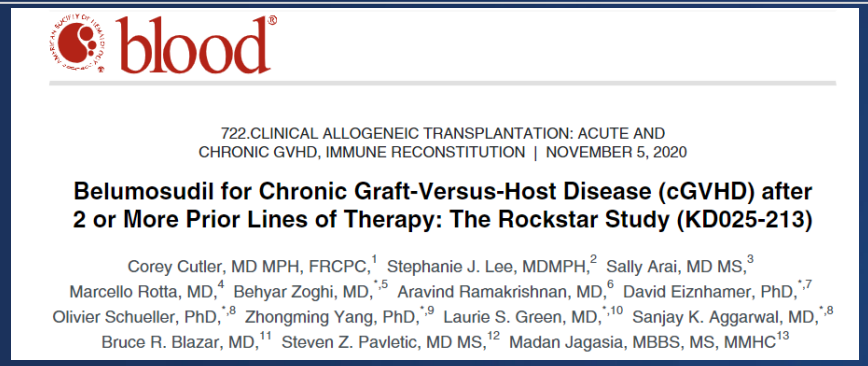
ROCKSTAR Study design



blood

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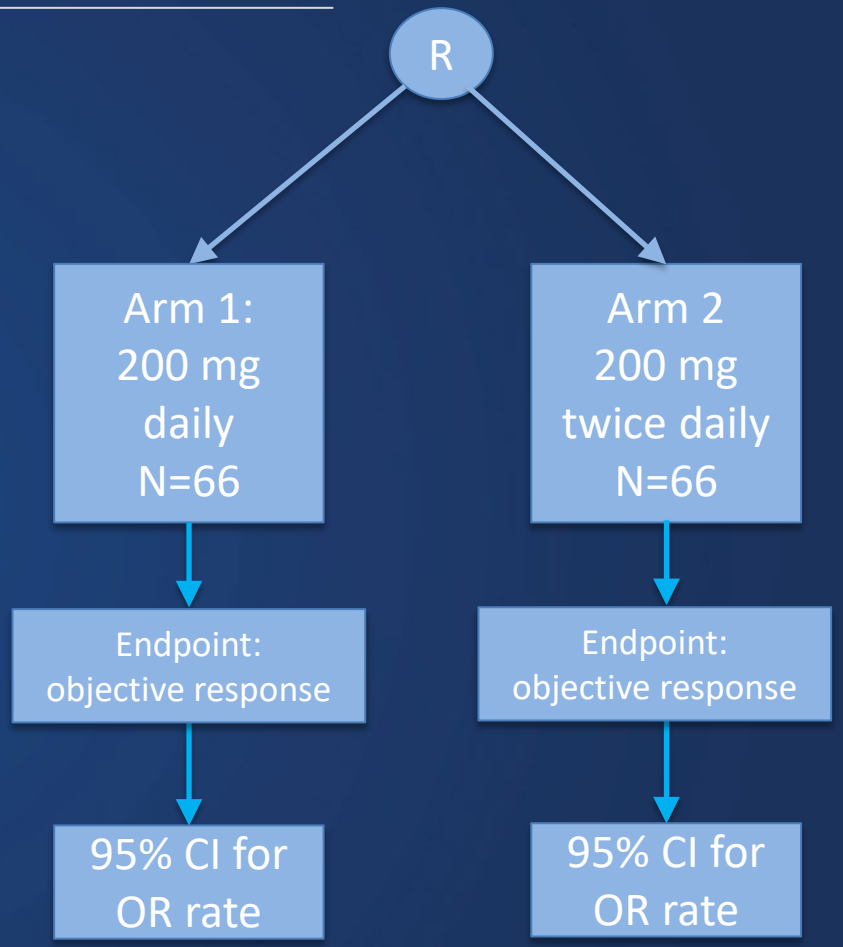
- Primary outcome: objective response (OR) (partial or complete response)
- 1:1 randomization
- Expected OR rate: 55%
- Sample size: With 66 patients in an arm, each arm has 90% power to exclude 30% OR rate as lower bound
- Other endpoints also included to assess tolerability



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ROCKSTAR Results

blood

722.CLINICAL ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION | NOVEMBER 5, 2020

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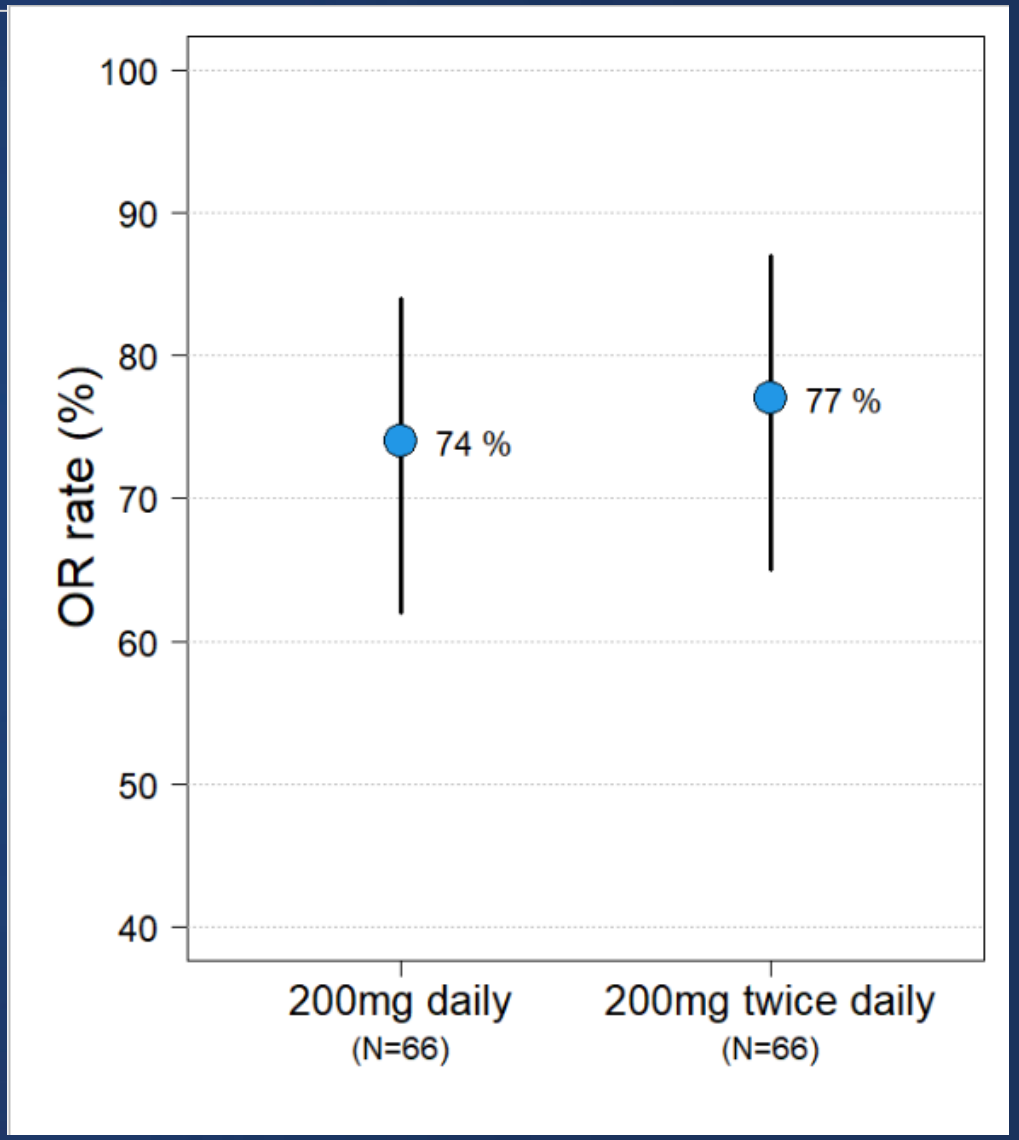
- Both arms demonstrated sufficient efficacy.
- Slightly higher response rate in the twice daily arm
- Adverse event rates were similar across arms
- "Based on the similar efficacy and safety observed in this study, **200 mg daily is the preferred dosage for the treatment of SR cGVHD**. Although the 200-mg twice-daily dose showed higher responses in certain organs, such as the skin, and slightly fewer AEs, the difference compared with the 200-mg daily dose was not deemed significant. "

Objective response rate with 95% CI

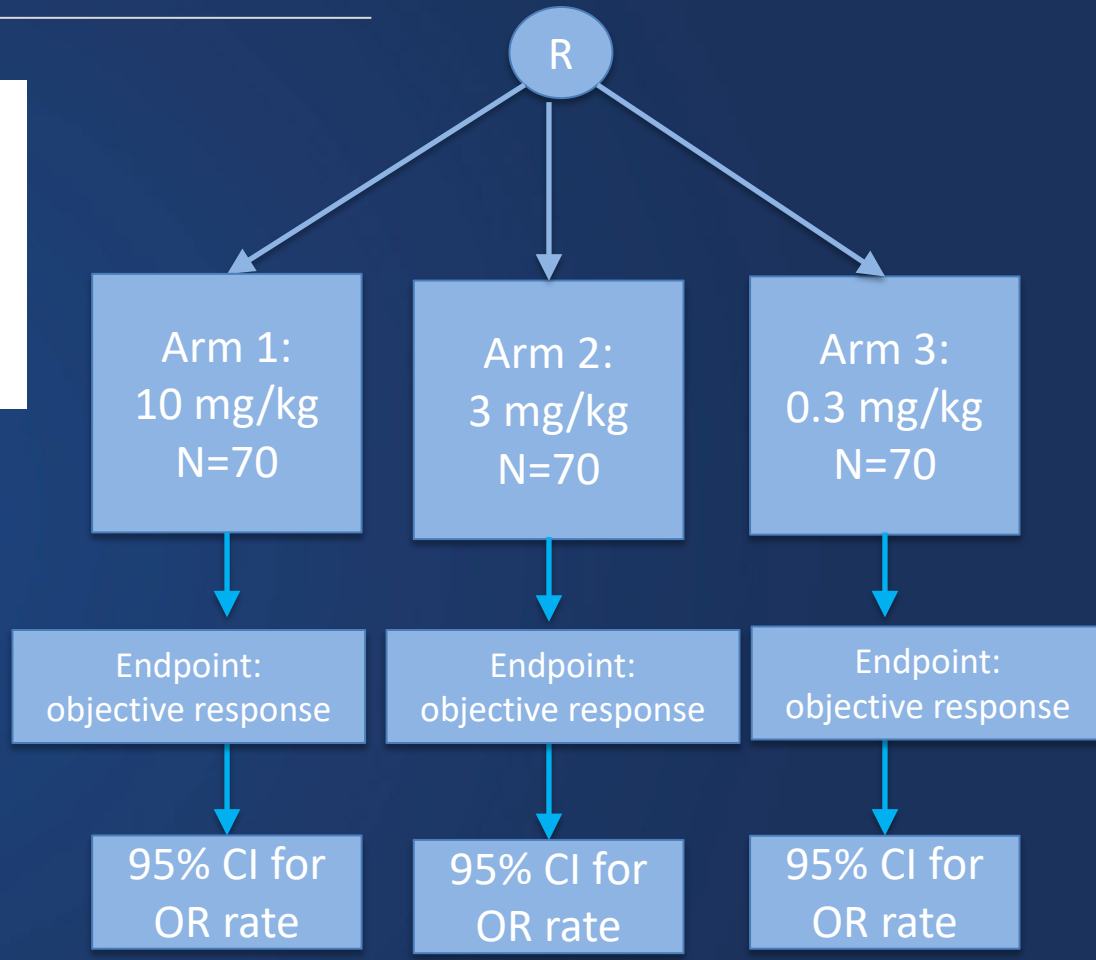


Immunotherapy randomized phase II selection design

Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study

Jedd D Wolchok, Bart Neyns, Gerald Linette, Sylvie Negrier, Jose Lutzky, Luc Thomas, William Waterfield, Dirk Schadendorf, Michael Smylie, Troy Guthrie Jr, Jean-Jacques Grob, Jason Chesney, Kevin Chin, Kun Chen, Axel Hoos, Steven J O'Day, Celeste Lebbé

Lancet Oncology. 2010, 11: 155- 64



Design: Patients with previously treated stage III (unresectable) or stage IV melanoma; fixed injection dose of ipilimumab every 3 weeks for four cycles followed by maintenance therapy every 3 months

Sample size: Target N = 210 (~ 70 per group)

Primary endpoint: Objective response (partial or complete response)

Ipilimumab mechanism of action: Monoclonal antibody that binds to CTLA-4, augments T –cell activation and proliferation.

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Ipilimumab Efficacy Results

Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study

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Lancet Oncology. 2010, 11: 155- 64

	Ipilimumab 0·3 mg/kg (n=73)	Ipilimumab 3 mg/kg (n=72)	Ipilimumab 10 mg/kg (n=72)
Best overall response			
Complete response	0	0	2
Partial response	0	3	6
Stable disease	10	16	13
Progressive disease	43	41	36
Unknown (progressive disease by clinical observation only)	20	12	15
Best overall response rate*	0% (0·0–4·9)	4·2% (0·9–11·7)	11·1% (4·9–20·7)
Disease control rate†	13·7% (6·8–23·8)	26·4% (16·7–38·1)	29·2% (19·0–41·1)

Ipilimumab Safety Results

Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study

Jedd D Wolchok, Bart Neyns, Gerald Linette, Sylvie Negrier, Jose Lutzky, Luc Thomas, William Waterfield, Dirk Schadendorf, Michael Smylie, Troy Guthrie Jr, Jean-Jacques Grob, Jason Chesney, Kevin Chin, Kun Chen, Axel Hoos, Steven J O'Day, Celeste Lebbé

Lancet Oncology. 2010, 11: 155- 64

	Ipilimumab 0·3 mg/kg (n=72)	Ipilimumab 3 mg/kg (n=71)	Ipilimumab 10 mg/kg (n=71)
Immune-related adverse events†			
Any grade	19	46	50
Grade 3–4	0	5	18

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Ipilimumab Randomized Design

Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study

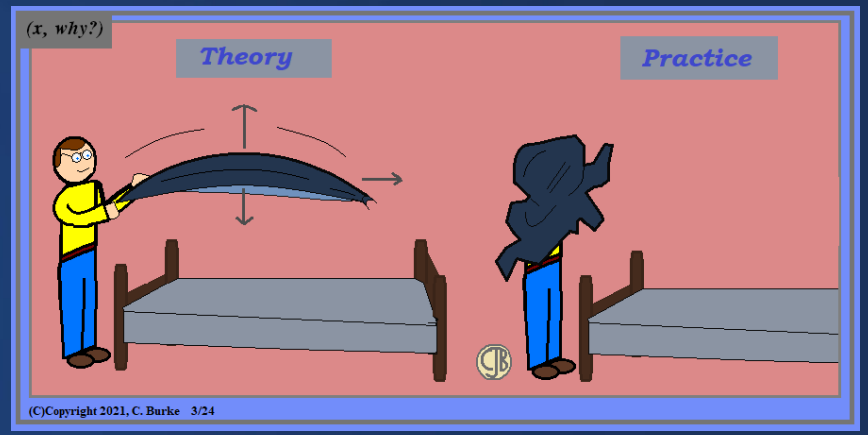
Jedd D Wolchok, Bart Neyns, Gerald Linette, Sylvie Negrier, Jose Lutzky, Luc Thomas, William Waterfield, Dirk Schadendorf, Michael Smylie, Troy Guthrie Jr, Jean-Jacques Grob, Jason Chesney, Kevin Chin, Kun Chen, Axel Hoos, Steven J O'Day, Celeste Lebbé

Statistical justification of sample size:

"We calculated that 70 patients should be randomly allocated to every treatment group, whereby the maximum width of the exact 95% CI for best overall response rate at 10 mg/kg, 3 mg/kg, and 0·3 mg/kg would be about 18%, 15%, and 12% if the true best overall response rate lay in the anticipated 10–15%, 6–9%, and 2–5% ranges, respectively. ***We did not select the sample size to achieve a prespecified power for a particular statistical test***."

Confidence in correct dose?

- Statistically: How large is large enough?
  - What is an appropriate level of precision?
  - Can be motivated by power calculation



- Practically: What defines correct dose?
  - Consider agent type
    - Examples are targeted therapy and IO drugs in cancer
  - Efficacy vs. toxicity trade-off
  - Patient tolerability – not always grade 3+ adverse events
    - Persistent grade 2 toxicities are not acceptable!
  - Rules for dose selection may be imprecise due to competing priorities for patient benefit
  - Important to include 2ndary endpoints to understand trade-offs

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Key points for design consideration

- Dose selection designs provide more realistic assessment of toxicity than traditional phase I designs
  - Traditional MTD based dose finding focuses on cycle 1
  - Dose selection design allows longer exposure to assess AEs in later cycles
- Patient populations (i.e., eligibility) often differ in traditional phase I and phase II studies.
  - Impacts choice of integrated vs. sequential design approach
- Patient heterogeneity
  - Randomized designs allow stratification to account for some prognostic factors
  - Larger sample sizes provide evidence vs. more anecdotal information from dose finding cohorts with 3 patients

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Summary: Incorporating randomization in oncology dose finding studies

- In the era of targeted and immunotherapies, traditional toxicity-based dose finding misses the mark
- Lower grade toxicity (grade 2) are often unacceptable, depending on type and number of cycles of treatment
- Collaboration between research team members is critical.
- **Thoughtful dose optimization yields better patient outcomes!**

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Project Optimus

Changing the Dosing Paradigm for Cancer Drugs

Mirat Shah, MD
Medical Oncologist, Breast and Gynecologic Malignancies
Clinical Lead, Project Optimus
U.S. Food and Drug Administration

Disclosures for Mirat Shah, MD

- 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

Oncology Center of Excellence

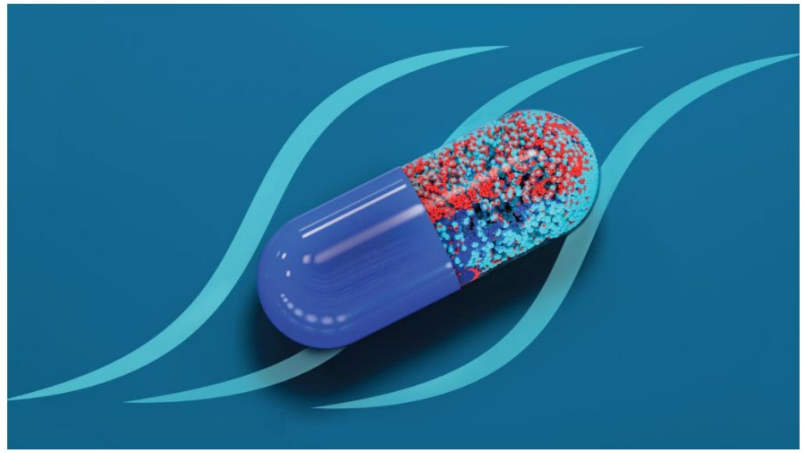
Project Optimus

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



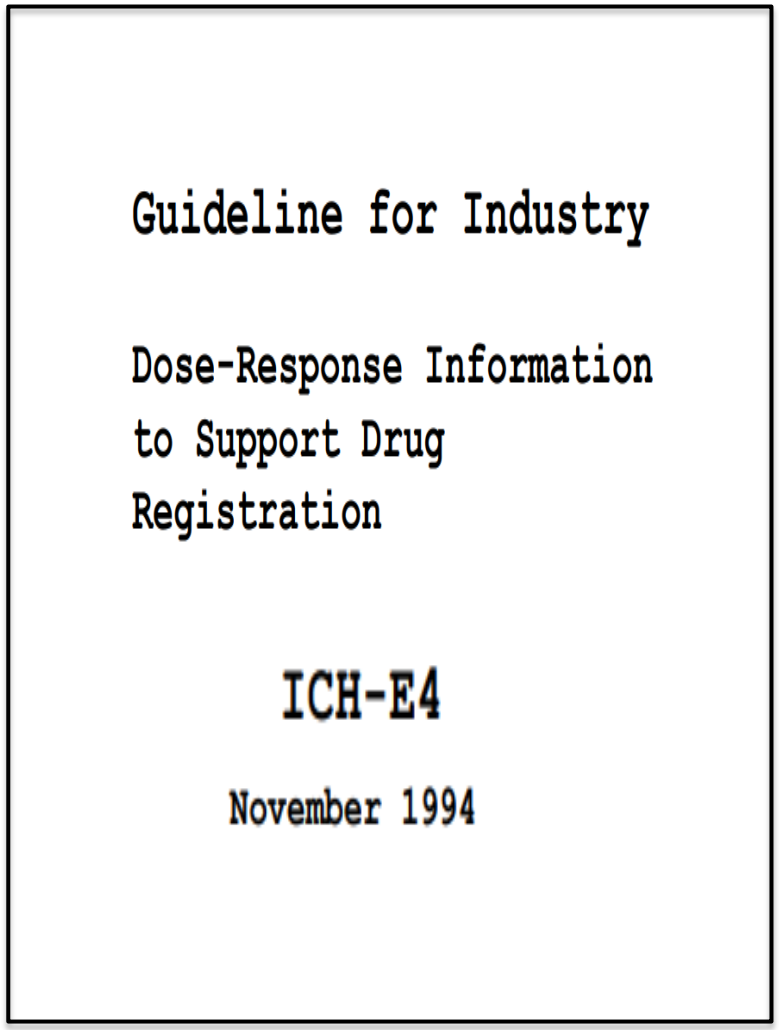
Right Time for Dosage Optimization = Prior to Approval

- 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

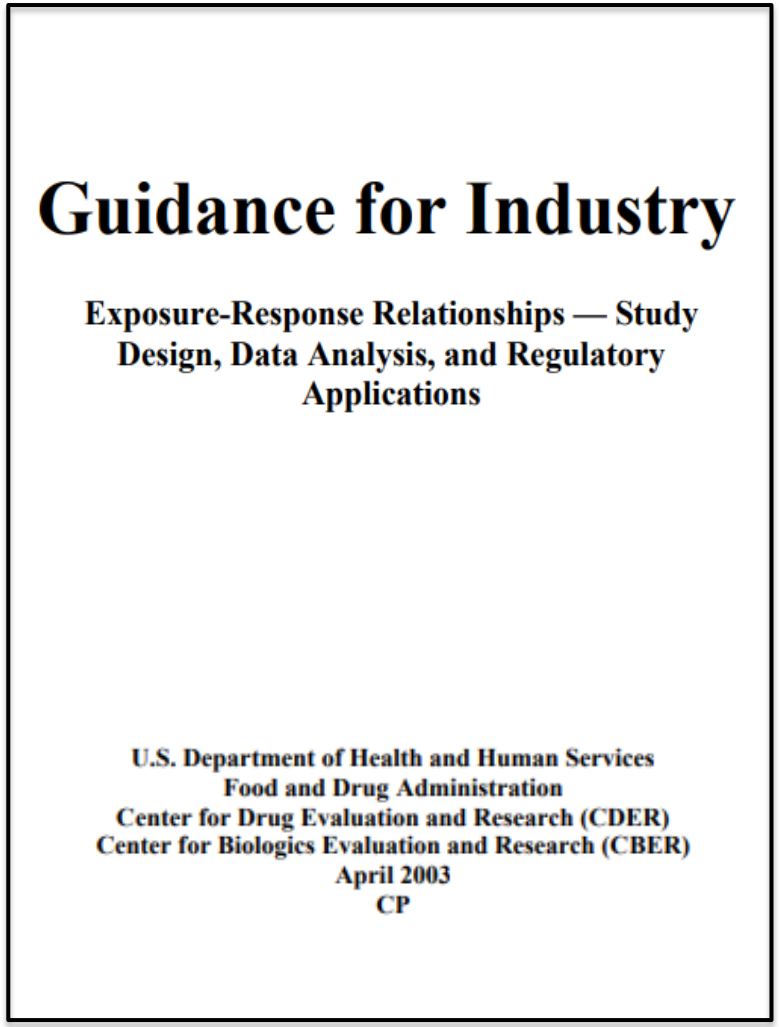
"Dose is the foundation of drug development. Having the wrong dose is like building a house on quicksand."

- Rick Pazdur

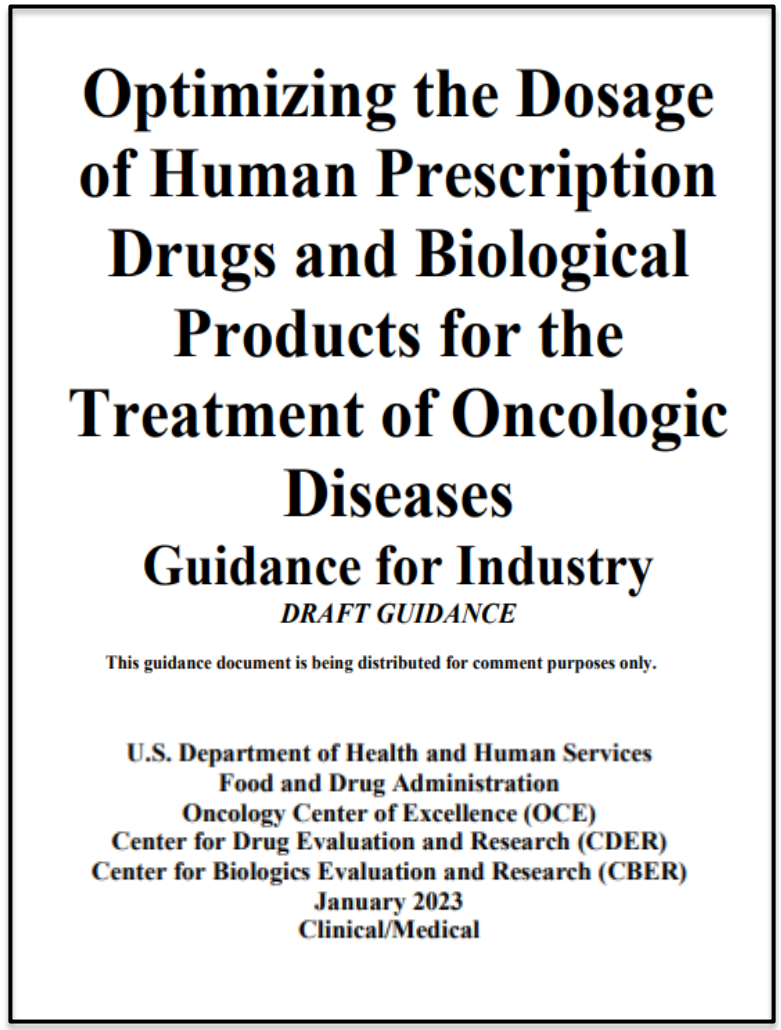
Guidance Documents



1994

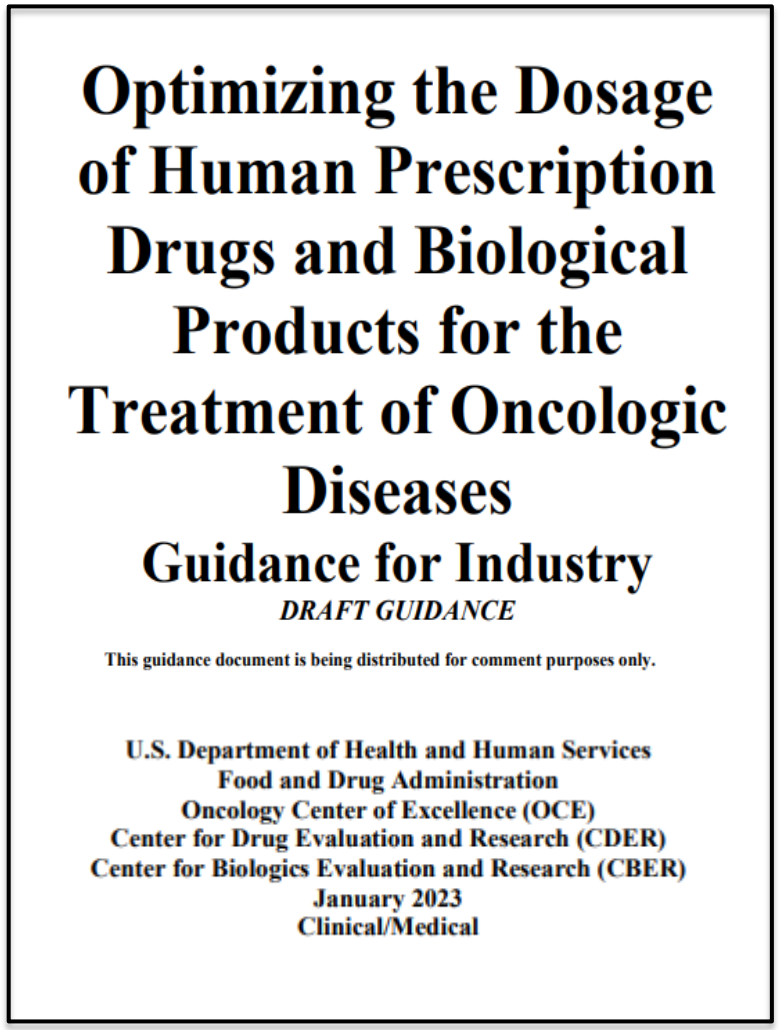


2003



2023

Oncology Dosage Optimization Draft Guidance

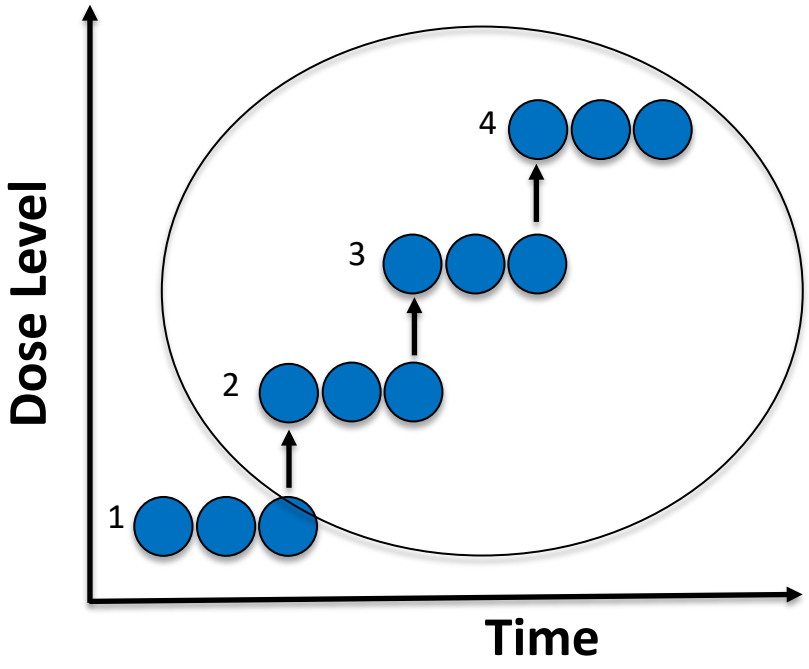


2023

- Dosages must have justification appropriate to the stage of development
- Use the totality of data for dosage selection
  - Including dose- and exposure- response relationships for efficacy and safety
- Randomized comparisons support identification of optimized dosage(s) → more on next slides
- Safety assessments should include low-grade symptomatic toxicities which affect tolerability
- Meet with FDA early to discuss plans

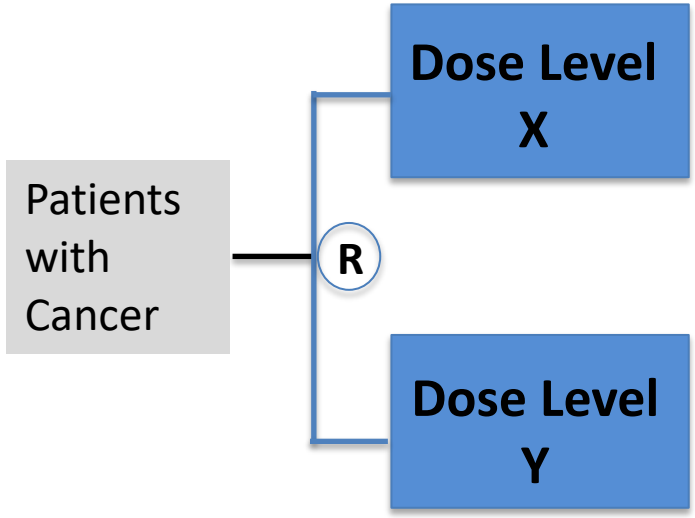
Updated Dosage Selection Strategy

Dose Escalation



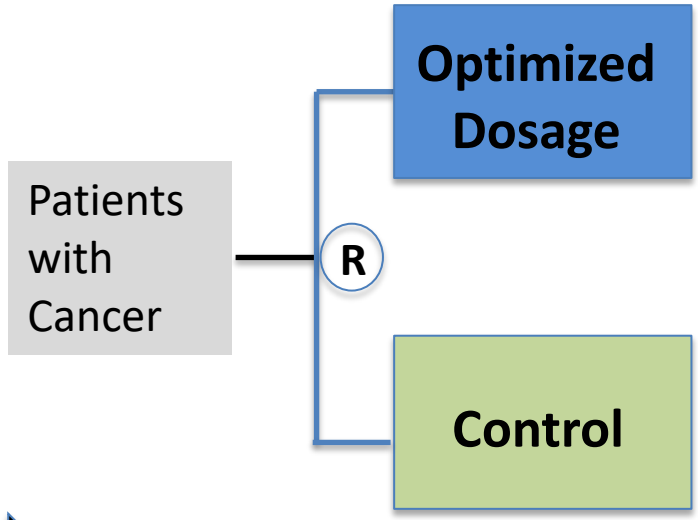
Select Several Dosages

Dosage Optimization



Further Evaluate Dosages

Registration



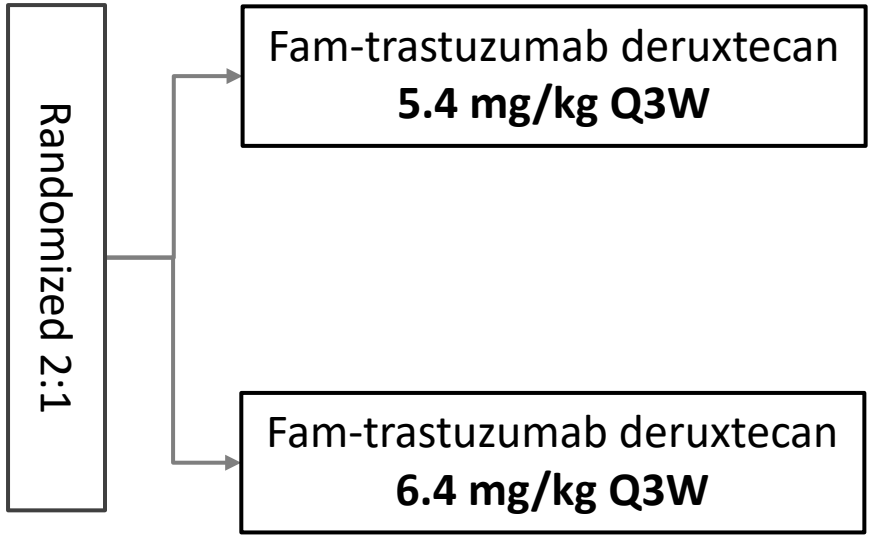
Compare to Standard of Care

Example: Fam-Trastuzumab Deruxtecan

DESTINY-Lung02

Key Eligibility Criteria

- Metastatic Non-Small Cell Lung Cancer (NSCLC)
- Activating *HER2* mutation
- No history of interstitial lung disease



Key Endpoints

- Overall response rate (ORR)
- Duration of response (DOR)

DESTINY-Lung02: Efficacy and Safety

Efficacy	5.4 mg/kg* (N=52)	6.4 mg/kg** (N=28)
Overall Response Rate % (95% CI)	**58** (43, 71)	**43** (25, 63)
Duration of Response (months), median (95% CI)	8.7 (7.1, NE)	5.9 (2.8, NE)

Toxicity	5.4 mg/kg* (N=101) %	6.4 mg/kg** (N=50) %
ILD/Pneumonitis	6	14
Drug Discontinuation	8	16

*From USPI drugs@FDA
**From ESMO 2022

Conclusions

- Traditional oncology dosage selection strategies need to be updated
- Failure to optimize the dosage has lasting consequences to patients and overall drug development
- It is important to consider the totality of data at each step in dosage selection
- Randomized trials support selection of a dosage optimized for benefit-risk
- One size doesn’t fit all oncology product development programs

Acknowledgements

- Laleh Amiri-Kordestani
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- Joyce Cheng
- Stacy Shord
- Atik Rahman
- Marc Theoret
- Richard Pazdur
- All members of the Project Optimus team

Dosage Optimization Resources

Multi-Stakeholder Meetings

- Friends of Cancer Research Annual Meeting 2021
- Friends of Cancer Research White Paper 2021
- FDA- ASCO Workshop: “Getting the Dose Right”

Publications

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

Guidance Documents

- ICH E4: Dose-Response Information to Support Drug Registration
- Exposure- Response Relationships
- Optimizing the Dosage for Treatment of Oncologic Diseases