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# Patient-Centered Dosing

## Komen Greater NYC Metastatic Breast Cancer Conference

Presented by Anne Loeser, followed by Dr. Aditya Bardia

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# TOPICS

THE CANCER DRUG DOSAGE PARADIGM

PHASE 1 CLINICAL TRIAL DOSE ESCALATION

WHY DOSAGE LEVELS MATTER

DOSAGE-RELATED STUDIES

PATIENT-CENTERED DOSING INITIATIVE (PCDI)

QUESTIONS



*Associated with the “Hippocratic Oath” recited by Medical School Students upon graduation*



## “FIRST, DO NO HARM”

If this adage was taken literally, physicians would be reluctant to:

- Allow patients to undergo surgery, even if it was lifesaving
- Order blood tests which can cause pain and bruising
- Recommend CT scans due to cumulative radiation exposure

So the modern interpretation of “first, do no harm” is closer to this:

*“Doctors should help their patients as much as they can by recommending tests or treatments for which the potential benefits outweigh the risks”*

*Robert H. Shmerling, MD, Harvard Health Publishing*



# THE CANCER DRUG DOSAGE PARADIGM

- Dose escalation methods used in Phase 1 Clinical Trials were developed in the era of cytotoxic drugs
- It has been assumed that both efficacy and toxicity\* increase with dose
- These increases are represented by dose/toxicity and dose/efficacy curves, in which toxicity and efficacy increase with higher doses
- Phase 1 Clinical Trials measure **toxicity** as the primary endpoint

*\*Toxicity: a measurement of the dosage needed of a particular substance to damage a living organism*



## “3+3” DOSE ESCALATION IN PHASE 1 TRIALS

3 patients are initially enrolled into a given dose cohort (group)

If there are no Dose Limiting Toxicities (“DLTs” - Severe Adverse Events)

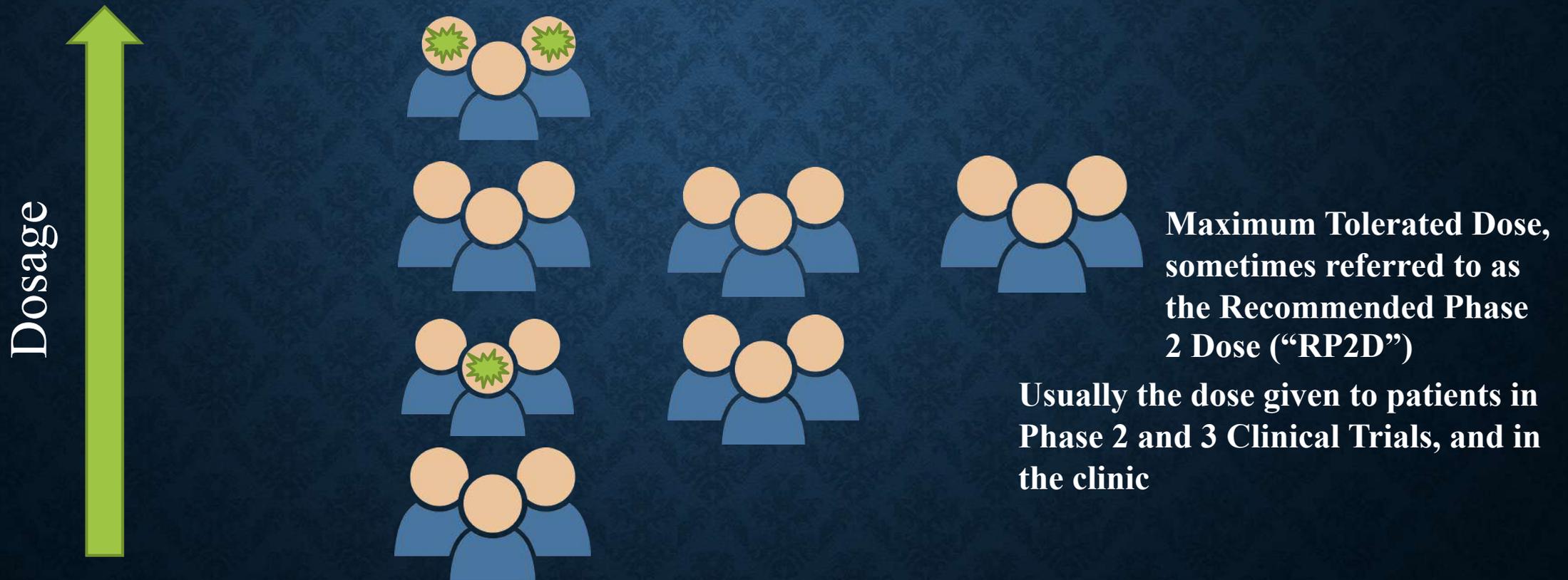
3 new people are enrolled at the next higher dose level

If 1 person develops a DLT

3 new people are enrolled in that same dose level

Development of DLTs in more than 1 of 6 patients in a specific dose cohort suggests that the Maximum Tolerated Dose (“MTD”) has been exceeded so the next-lower dose is considered the MTD

# PHASE 1 CLINICAL TRIAL “3+3” DOSE ESCALATION



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## LIMITATIONS OF “3+3” DOSE ESCALATION

- Based upon the premise that higher toxicity = greater efficacy
- Has small, fixed cohort sizes
- Does not take into account long-term treatment side effects
- Ignores levels of drug efficacy (Minimal Effective Dose)

## QUESTIONING THE DOSAGE PARADIGM

- In the 1990s, more than 41,000 breast cancer patients underwent High-Dose Chemotherapy + Autologous Bone Marrow Transplant (HDC-ABMT)
- In 2000, the New England Journal of Medicine reported the results of a major randomized HDC-ABMT trial for MBC patients. No survival advantage compared with standard-dose chemo, corroborating the results of 4 other randomized trials

<https://www.healthaffairs.org/doi/full/10.1377/hlthaff.20.5.101>



# WHY DOSAGE LEVELS MATTER

- Patients with MBC are treatable but not curable, and most will remain on treatment indefinitely
- As a result of toxicity-related side effects, patients with MBC have been known to:
  - visit the Emergency Room/hospital
  - be rendered incapable of receiving treatment on schedule
  - experience a reduced Quality of Life
- Although more data is needed, recent evidence suggests that allowed lower doses of some MBC therapies may be as effective as the MTD with less severe side effects
- Lower doses may allow patients to remain on therapy for a longer period of time

# ALLOWED LOWER MBC DRUG DOSAGES

- Endocrine (hormonal) therapies are available in one dose only
- Most other MBC therapies have multiple dosages
- Number of possible dose reductions: 0 - 3
- Percent of original dosage can be as low as 25%
- Example: Abemaciclib/Verzenio (when taken as monotherapy):
  - Starting Dose = 200 mg twice daily (standard dose, or MTD)
  - First dose reduction = 150 mg twice daily (allowed lower dose)
  - Second dose reduction = 100 mg twice daily (allowed lower dose)
  - Third dose reduction = 50 mg twice daily (allowed lower dose)



# MBC DOSAGE EFFECTIVENESS STUDIES

**Verzenio lower starting dose:** A Phase 2 study randomized 234 HR+, HER2- MBC patients previously treated with chemotherapy to receive either: Verzenio at 150 mg twice daily plus Tamoxifen once daily, or as monotherapy at either 150 mg or 200 mg twice daily. Median Overall Survival (OS) results:

- 24.2 months OS on the combination
- **20.8 months OS** on the 150 mg twice daily monotherapy dose
- **17.0 months OS** on the 200 mg twice daily monotherapy dose (*200 mg. twice daily is the current FDA-approved monotherapy dose*)
- Treatment-related Adverse Events were slightly lower on the 150-mg monotherapy dose than on the 200 mg dose (97.5% vs. 98.7%)

<https://www.onclive.com/view/abemaciclib-tamoxifen-shows-os-benefit-in-hr-her2-metastatic-breast-cancer?fbclid=IwAR2C9gFP-XTtvE6cAqeRMp4X07hexSRr5bvnJlZkJMvJOsFgJBXLX2JoRnc>

**Ibrance lower starting dose:** A Phase 2 study randomizing 72 HR+ HER2- MBC patients previously treated with chemotherapy to receive Ibrance in either a 125 mg or 100 mg dose in combination with physician's choice of Faslodex or Tamoxifen concluded that:

- **Progression Free Survival (PFS) and clinical benefit were the same** in both groups
- The 100 mg dose was associated with a lower rate of grade 3 or 4 neutropenia

<https://www.targetedonc.com/news/reduced-palbociclib-dose-associated-with-lower-rate-of-neutropenia-in-hr-metastatic-breast-cancer>

**Xeloda dose reduction:** An analysis of dose modification and outcomes from four monotherapy trials, one combination trial, and an analysis of 113 MBC patients who received Xeloda outside of a clinical trial concluded that:

- **Time to progression and OS were similar among patients who received the lower vs. full-dose** in all studies reviewed
- Reduced Xeloda doses were associated with a lower incidence of treatment-related Adverse Events

[https://www.clinical-breast-cancer.com/article/S1526-8209\(11\)00111-X/fulltext](https://www.clinical-breast-cancer.com/article/S1526-8209(11)00111-X/fulltext)



## WHAT PATIENTS CAN DO!

- Communicate openly with your doctor about how you are feeling on treatment
- Make your doctor aware of your personal wishes and priorities
- If you are having treatment-related side effects, speak with your doctor about the options to relieve them (reducing the dosage or changing treatment frequency may be possibilities)
- Make a collaborative decision with your doctor about what you can do to feel better

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- **NEVER reduce your dosage or alter anything regarding your treatment on your own - speak with your doctor before making any treatment changes!**



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# PATIENT-CENTERED DOSING INITIATIVE (PCDI)

## **Mission:**

To enhance quality of life

while maintaining therapy effectiveness

by enabling patients with MBC & their physicians

to identify the optimal allowed dosage of treatment

based upon each patient's unique physical, circumstantial,  
and psychological factors



# PCDI TEAM MEMBERS



Lesley Glenn

Anne Loeser, Founder



Kimberly Parekh



Flori Hendron

Sheila McGlown



Chawnte Randall



Julia Maues



Natalia Padron

Sandra (Sandi) Spivey



## ADVISORY BOARD MEMBERS



Aditya Bardia, M.D., MPH

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# MBC PATIENT-CENTERED DOSING SURVEY

## Purpose:

The PCDI sought to obtain a greater understanding about MBC treatment-related side effects and the approaches used to manage them - in lieu of making assumptions

- ✓ Questions pertained to treatment-related experiences, quality of patient-physician communication, and level of support provided by physicians whose patients experience treatment-related side effects
- ✓ Responses are enabling the PCDI patient advocate team and the medical professionals supporting this initiative to identify opportunities for future improvements regarding side effect mitigation

## SURVEY RESULTS

- 1,221 patients with MBC responded over a 15-day period
- 86% reported having one or more bad side effects from treatment
  - 20% of these patients visited the Emergency Room/hospital
  - More than 2 of 5 these patients (43%) missed at least one treatment
- 98% reported discussing their side effects with their physician!

## SURVEY RESULTS (CONT'D)

- Of the patients who experienced treatment-related side effects and reported them to their physicians, 66% were prescribed a reduced treatment dosage
- 83% of patients whose dosage was reduced reported feeling better, at least initially
  - 64% of these patients required only one dosage reduction to feel better
  - 28% needed two dosage reductions
  - 8% required three dosage reductions
- 53% of patients felt that a higher dose of a cancer drug is not necessarily more effective than a lower dose, whereas 20% hold the opposite belief (27% were undecided)
- **The vast majority of patients (92%) would be willing to discuss allowed MBC drug dosing options with their physician based upon their unique characteristics**



# PATIENT-CENTERED DOSING CRITERIA

1. The Patient's Personal Goals and Wishes
2. Patient's Performance Status (*co-morbidities/medications, mobility and agility, current & past health situation, age, etc.*)
3. Patient's History of Side Effects from Prior Drugs
4. Patient's Current & Historical Blood Count Levels
5. Whether the Patient's Disease is Aggressive or Indolent
6. Whether the Patient has Organ Dysfunction or Central Nervous System Metastasis
7. Patient's Body Mass Index (BMI)
8. Patient's Race/Ethnicity (*potential variability in response to drugs*)
9. Patient's Financial Situation (*if additional medications are needed for side effect mitigation, is the patient able to afford them?*)
10. Availability of the Patient's At-Home Care (*if the patient's side effects are severe, is there anyone available at home to assist?*)

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## WHAT WILL “REAL-WORLD” SUCCESS LOOK LIKE?

- Patients’ dosages (and potentially frequency of administration) will be based upon collaborative physician-patient assessment of the patient’s unique characteristics and circumstances
- Patients’ Quality of Life may improve, and they may potentially remain on treatment longer due to lower toxicities



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According to Dr. Christine Thang, a graduate of the School of Medicine at UCLA

the Hippocratic oath...

*...is a reminder that a physician's job is to treat not just the diseases physicians encounter, but to think of each individual patient as a whole person*

***The Patient-Centered Dosing Initiative is focused on advancing this premise***

# QUESTIONS?



*For additional information, visit [therightdose.org](http://therightdose.org) or email [info@therightdose.org](mailto:info@therightdose.org)*

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## CO-PRESENTER: DR. ADITYA BARDIA



Aditya Bardia, M.D., MPH is a board-certified medical oncologist and an Attending Physician at Massachusetts General Hospital.

Dr. Bardia led the clinical development of the newly-approved antibody drug conjugate Trodelvy (Sacituzumab Govitecan), and is working on an investigational oral estrogen receptor degrader (SERD) called Elacestrant for patients with metastatic breast cancer.

Dr. Bardia is especially interested in optimal biological drug dosage adaptations to maximize quality of life and maintain treatment efficacy, and has received numerous research awards.