Thriving Together

2025 CONFERENCE ON METASTATIC BREAST CANCER

Managing Toxicities of Therapy for Metastatic Breast Cancer

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Getting the right balance

Learning objectives for this talk

- Know what to discuss with your care team
- Understand how we arrive at a dose for cancer treatment
- Understand management of common symptoms *shared by many different therapies*
- Know your resources for getting help

From my patients, on managing symptoms

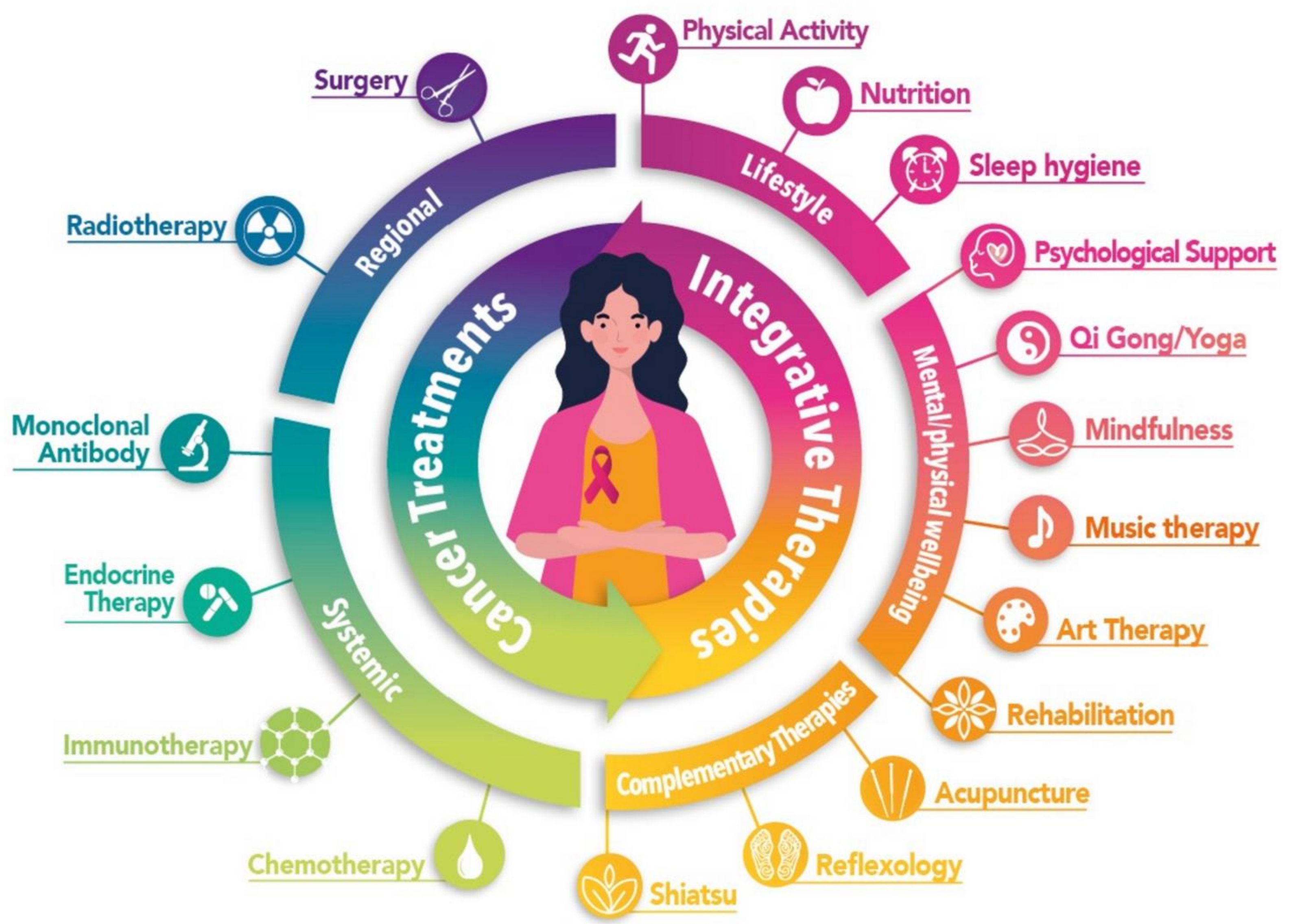
“Wanting to be listened to”

“Kindness and compassion”

“I don't want the side effects to interrupt living my life”

“Faith and a great support system have been essential for my journey”

UNDERSTAND YOUR TOOLKIT



Fabi et al. *Current Oncology Reports*. 2024

The Main Pillar of Proper Management

Clear & Total Communication

- **Enhances likelihood of managing the symptoms**
- **Sometimes a 'side effect' can be a symptom of the cancer**

Components of symptom management

- Supportive care medications
- Lifestyle modifications
- Dose adjustment
- Switching to a different same-class drug
- Switching to a different class drug (if applicable)

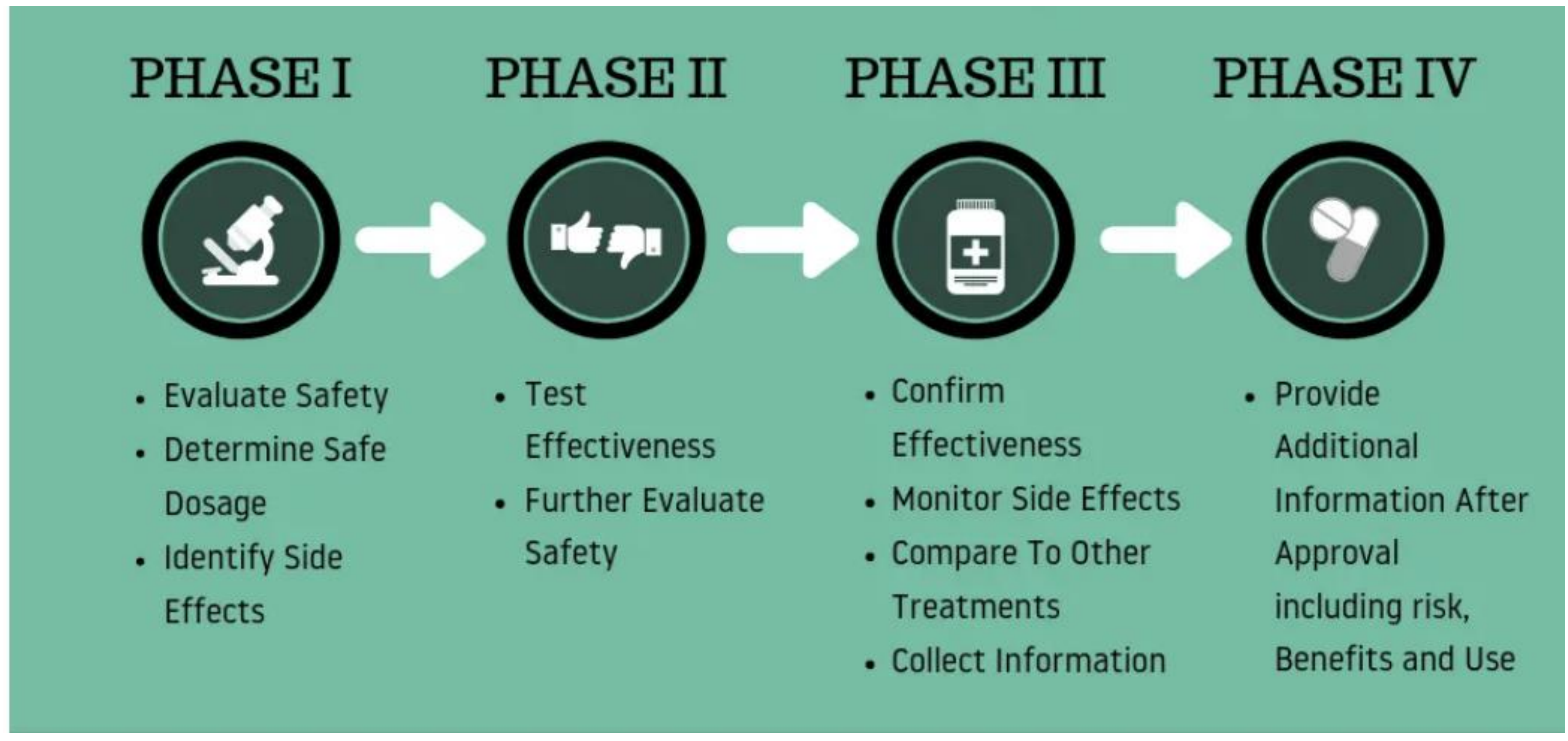
When starting a new therapy, discuss:

- Most common/likely side effects
- Rare but dangerous / life-threatening side effects
- Red flag symptoms to be aware of
- Are there any blood markers of severe toxicity that this drug requires before starting?
- Schedule and dose of the therapy
- Any at-home medications to be prescribed for common side effects
- Any side effects to consider logging (for trending, e.g. neuropathy)
- Is there any flexibility in scheduling (e.g. infusions) for life events like big trips

When side effects arise, discuss:

- Any supportive medications that could help treat?
- Lifestyle modifications?
- Is there a drug in the same class with a different side effect profile that may be a better fit?
- When / should we consider a dose adjustment?

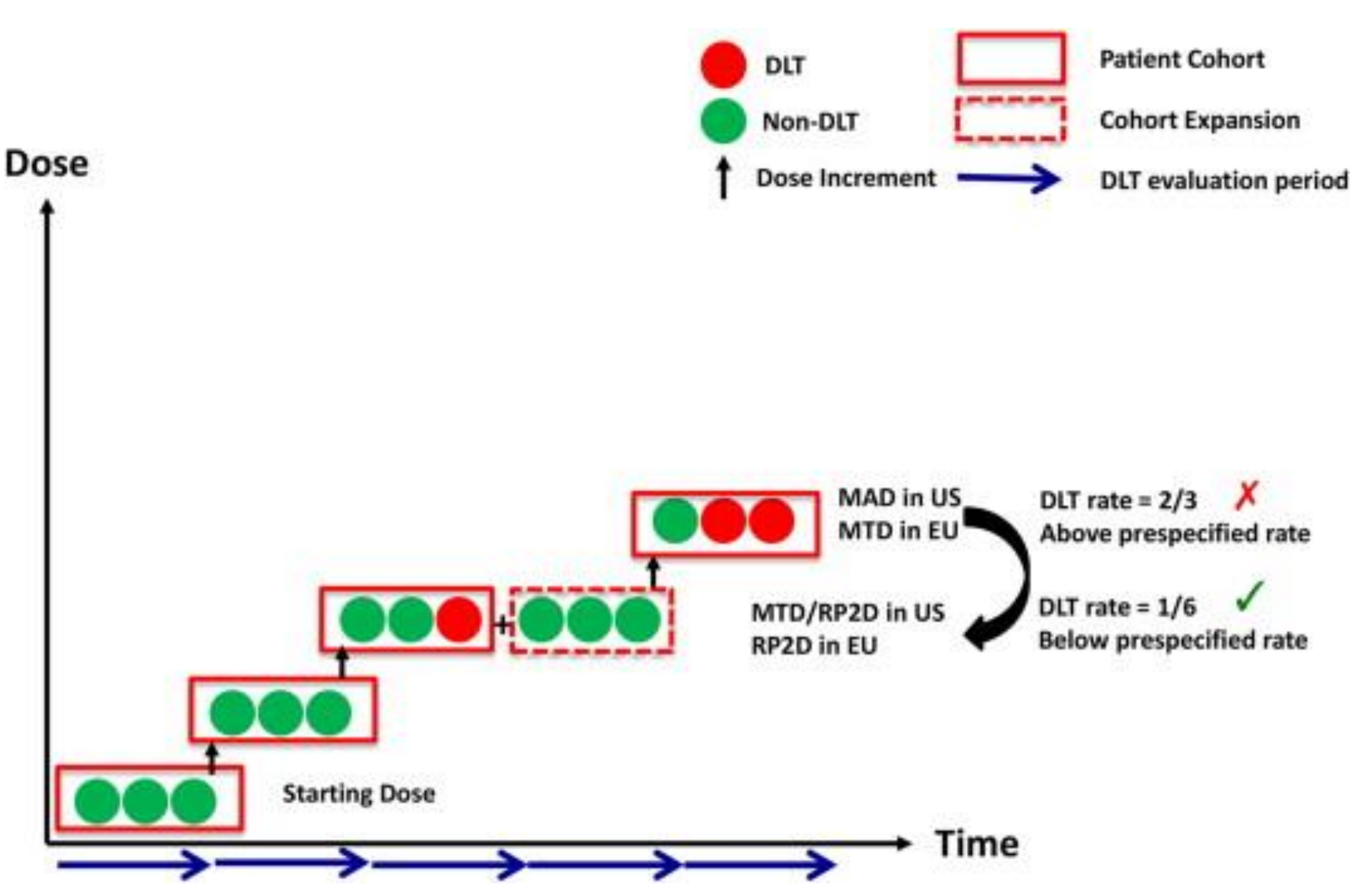
How do we arrive at the FDA-approved dose?



How do we arrive at the FDA-approved dose?

- Phase 1 Clinical Trial
  - Usually ‘first in human’ trial
  - **Is the drug safe? What is the safe dose to further test?**
- ’Dose escalation’ in small numbers of patients until you find ‘maximal tolerated dose’, which then goes to phase 2, where efficacy is tested

Does NOT necessarily mean that lower doses are not effective



Cook et al. *Molecular Oncology.* 2015.

Clinical Trial Toxicity Grading - **CTCAE**

- ”Common Terminology Criteria for Adverse Events”
- Used to define severity of side effects in clinical trials, which then informs recommendations for future dose modification on label
- **Grade 0**: Normal condition
- **Grade 1**: Mild, asymptomatic, or mild symptoms
- **Grade 2**: Moderate, with minimal or local intervention indicated
- **Grade 3**: Severe or medically significant but not immediately life-threatening
- **Grade 4**: Life-threatening consequences, with urgent intervention indicated
- **Grade 5**: Death due to adverse event

CTCAE example: Diarrhea

- **Grade 1**: Increase of <4 stools per day over baseline
- **Grade 2**: Increase of 4-6 stools per day over baseline
- **Grade 3**: Increase of ≥7 stools per day over baseline; incontinence; hospitalization recommended
- **Grade 4**: Life-threatening consequences, with urgent intervention indicated
- **Grade 5**: Death due to adverse event

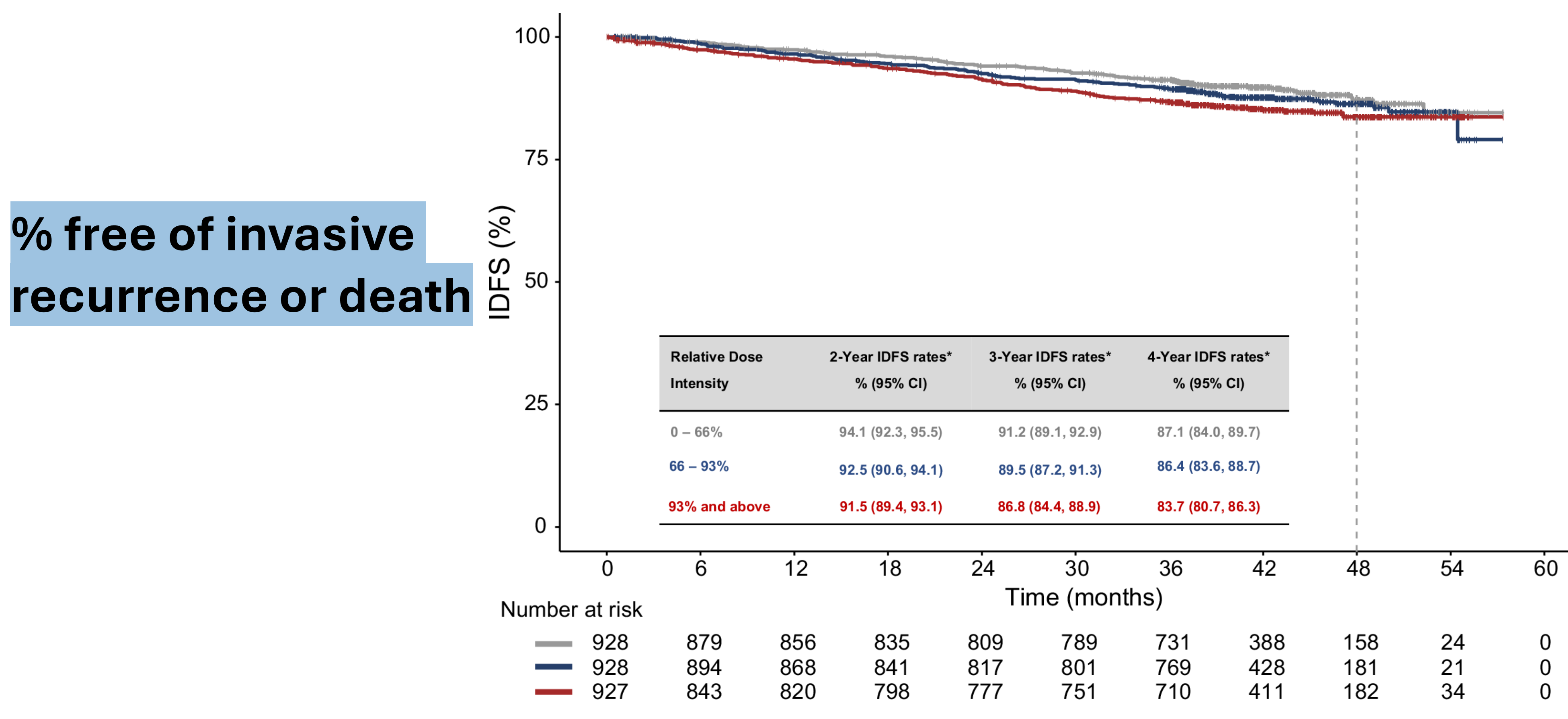
CTCAE example: Diarrhea

Table 3: VERZENIO Dose Modification and Management — Diarrhea

At the first sign of loose stools, start treatment with antidiarrheal agents and increase intake of oral fluids.	
CTCAE Grade	**VERZENIO Dose Modifications**
Grade 1	No dose modification is required.
Grade 2	If toxicity does not resolve within 24 hours to ≤Grade 1, suspend dose until resolution. No dose reduction is required.
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to ≤Grade 1. Resume at *next lower dose*.
Grade 3 or 4 or requires hospitalization	Suspend dose until toxicity resolves to ≤Grade 1. Resume at *next lower dose*.

- **Hence label suggests lower the dose if Increase of ≥7 stools per day over baseline or recurrent 4-7 stools above baseline**
- **Are 3 daily episodes of diarrhea compatible with everyone's lifestyles?**

No difference by dose level for Abemaciclib in adjuvant ER+ HER2- breast cancer



Relative Dose Intensity	2-Year IDFS rates* % (95% CI)	3-Year IDFS rates* % (95% CI)	4-Year IDFS rates* % (95% CI)
0 – 66%	94.1 (92.3, 95.5)	91.2 (89.1, 92.9)	87.1 (84.0, 89.7)
66 – 93%	92.5 (90.6, 94.1)	89.5 (87.2, 91.3)	86.4 (83.6, 88.7)
93% and above	91.5 (89.4, 93.1)	86.8 (84.4, 88.9)	83.7 (80.7, 86.3)

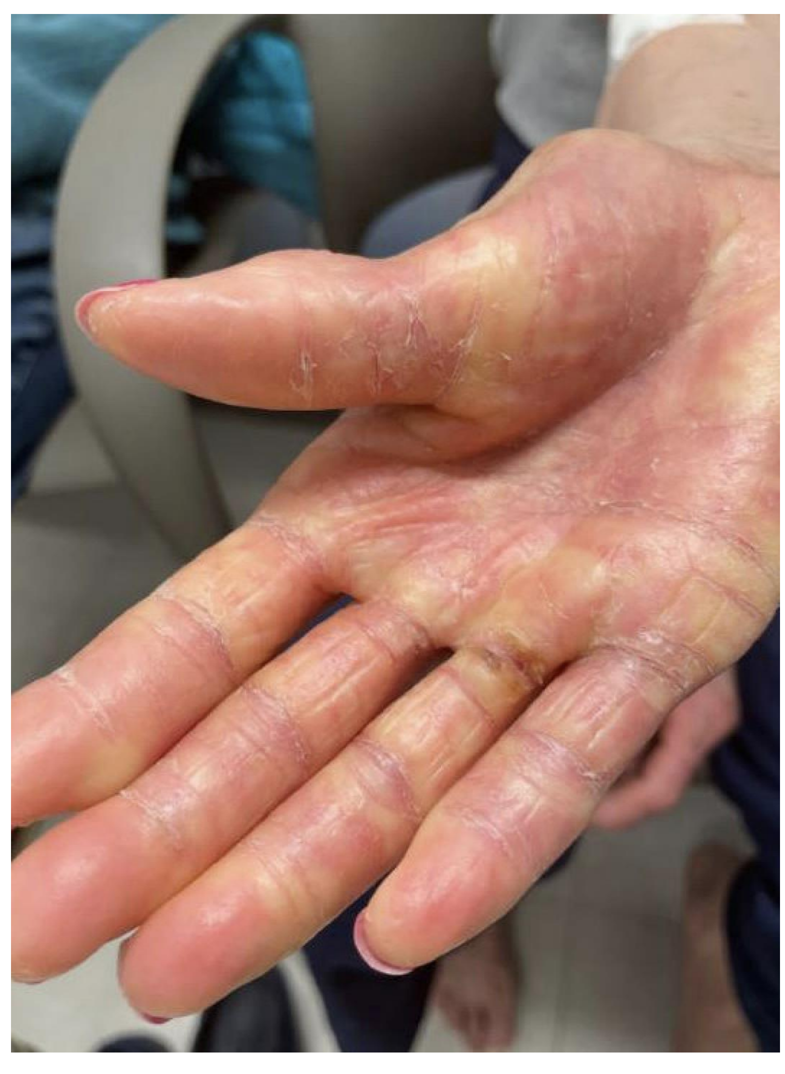
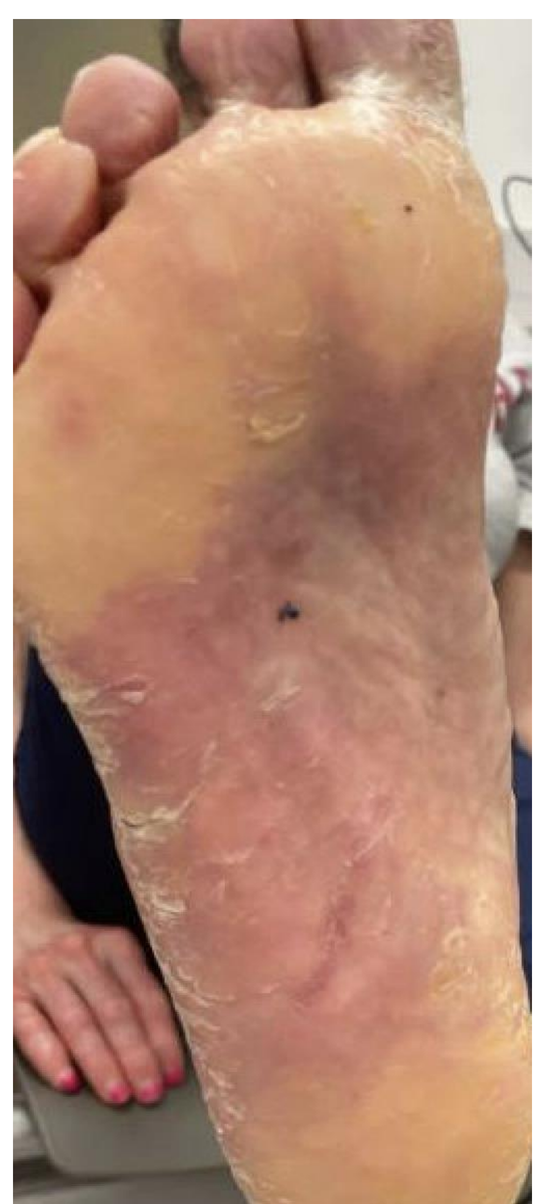
Time in Months

Goetz et al. *NPJ Breast*. 2024

Cases from the clinic

Case 1: A case for dose reduction

- **62-year-old woman with metastatic ER+ HER2- breast cancer presents second opinion**
- **On adjuvant anastrozole treatment until 2019, when she had recurrence of her breast cancer to the bones. Genomic testing was negative.**
- **Began Fulvestrant + Palbociclib**
- **4 years later, switched to Abemaciclib due to progression in bones / lung**
- **Six months later, switched to Capecitabine due to progression in the liver; she was initially started on 2000mg twice daily for 14 days on and 7 days off**
  - **Follow up PET/CT 12 weeks later showed a complete response to therapy; however, she endorsed worsening skin changes in the palms and soles of her feet**

Case 1: Capecitabine Dosing

- Standard dose of capecitabine for MBC is 1,250mg/m2 in twice daily doses, 14 days on, 7 days off
  - With average BSA for adult woman **= 2,125mg twice daily**
    - **Up to 41% of patients require dose reduction; 16% discontinue**
- Randomized trial comparing ***fixed dose 1500mg twice daily for 7 days on, 7 days off*** against standard dose showed:
  - NO difference in effectiveness
  - SIGNIFICANTLY LOWER rates of side effects
    - **Grade 2-4 diarrhea 7.5% vs 37%**
    - **Grade ≥3 Hand Foot Syndrome 0 vs 20.5%**
    - **Grade 2-4 Mouth Ulcers: 2.5 vs 13.7%**

Khan et al. *JCO Oncology Advances*. 2025

Case 1: A case for dose reduction

- She was recommended to reduce the dose to 1500mg twice daily 7 days on, 7 days off
- Also was recommended to initiate topical diclofenac gel twice daily

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

ORIGINAL REPORTS | February 27, 2024

Topical Diclofenac for Prevention of Capecitabine-Associated Hand-Foot Syndrome: A Double-Blind Randomized Controlled Trial

Authors: Akhil Santhosh, MD, DM, Atul Sharma, MD, DM, Sameer Bakhshi, MD, Akash Kumar, MD, DM, Vinod Sharma, MD, DM, Prabhat Singh Malik, MD, DM, Raja Pramanik, MD, DM, ... SHOW ALL ... on behalf of the D-TORCH Trial Investigators | AUTHORS INFO & AFFILIATIONS

Rate of Hand Foot Syndrome 3.8% vs 15%, with fewer dose reductions in the diclofenac arm

- Skin improved significantly, as did energy levels

Santhosh et al. *JCO.* 2024

Summary For Capecitabine

- Newer dosing guidelines recommend 1500mg twice daily flat dose, 7 days on, 7 days off for metastatic breast cancer
- Similar effectiveness
- Improved quality of life
- Consider prophylactic topical diclofenac gel twice daily to palms/soles to prevent onset of Hand Foot Syndrome
- Ensure skin stays moisturized
- Additional point: Ensure DPYD Enzyme checked at treatment start

Summary For Dose Reductions

- Standard doses are not necessarily a ‘biologically effective dose’
- Individuals have unique metabolisms and tolerate drugs differently at same doses
- A lower dose does NOT automatically mean it is less effective
- A lower dose may often significantly reduce toxicity, improve quality of life, and maintain efficacy

Case 2

- 65-year-old woman presents for routine follow up prior to her regularly scheduled infusion with trastuzumab deruxtecan for metastatic ER-HER2+ breast cancer
- She began therapy in April 2024 after progression of disease in the liver, and achieved a complete response on subsequent PET scans
- She has been receiving therapy at the standard 5.4mg/kg dose
- She reports minimal nausea, normal bowel movements, but has been noticing increasing fatigue over the past 2 months
- She now has limiting fatigue for the first two weeks, and feels normal during the third week only

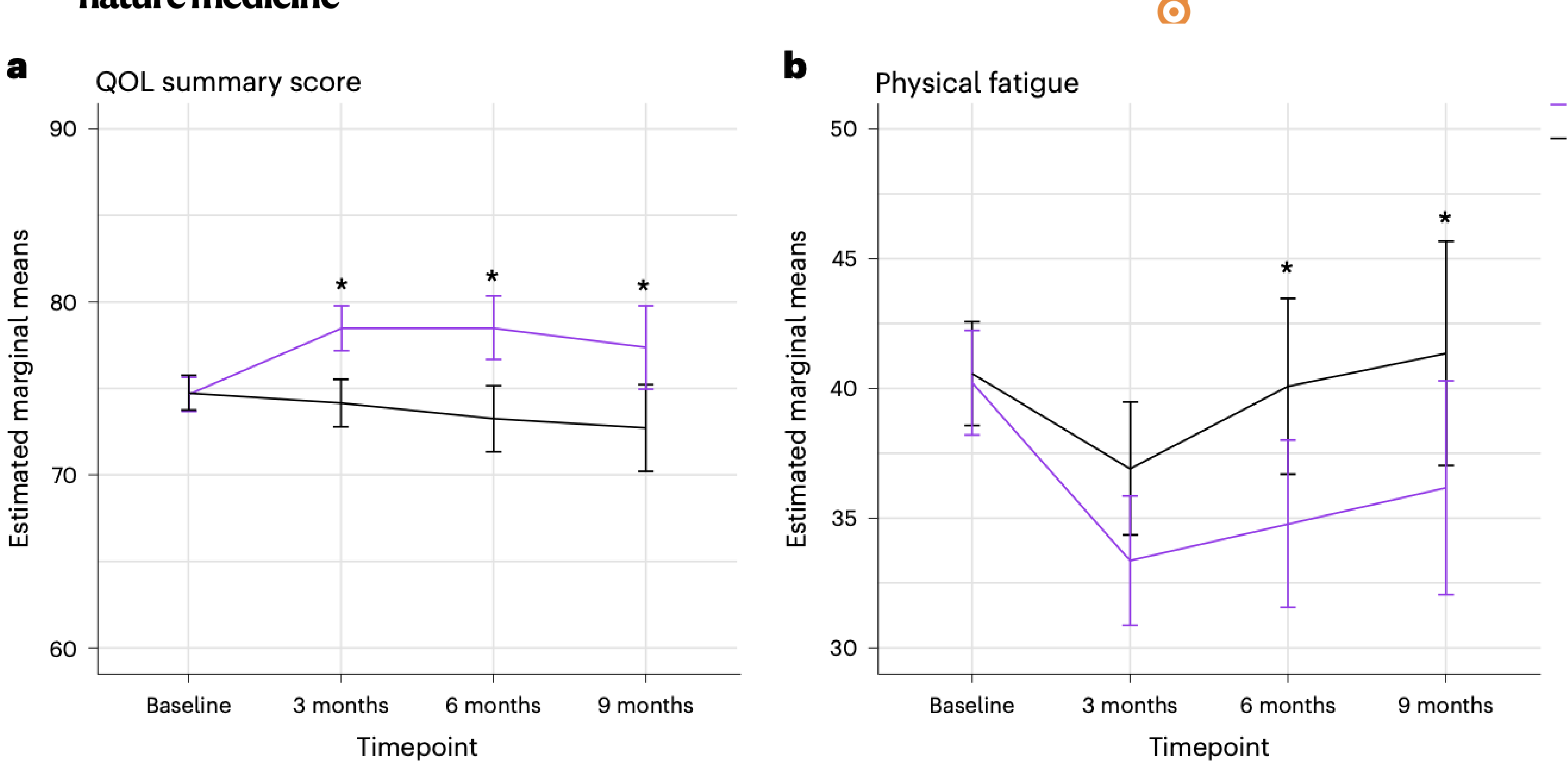
Case 2

- In discussion, she endorses 8 hours of sleep nightly, and takes 2-3 naps during the day
- Has been more sedentary due to fatigue
- Recent thyroid studies were normal
- She maintains a balanced diet
- She is interested in any complementary therapies that might help with her fatigue

Fatigue

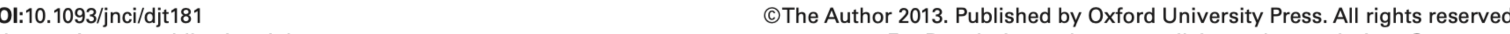
- Feeling of tiredness or weakness in terms of physical, cognitive, and emotional symptoms
- Extremely common with systemic therapies, particularly chemotherapy
- Can also be due to the cancer, inflammation, stress
- Can be cumulative in intensity, interfere with daily functioning and significantly impact overall quality of life
- Dose and/or schedule modifications can be helpful
- Stimulants like methylphenidate have very mixed data for effectiveness (not routinely recommended as first line)
- Mind-Body Interventions such as Qigong have shown intriguing improvements in cancer fatigue in early pilot studies

Case 2: Fatigue



Hiensch et al. *Nature Medicine*. 2024.

Case 2: Fatigue


DOI:10.1093/jnci/djt181
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MFSI-SF general subscale

50
40
30
20
10
0

P = .07

P = .003

Ginseng
Placebo
4 weeks

Ginseng
Placebo
8 weeks

Change from baseline

Barton et al. *JNCI*. 2013.

Summary for Fatigue

- Very common among patients with cancer undergoing chemo and other therapies
- Exercise combats fatigue in metastatic breast cancer
- Wisconsin Ginseng has randomized-level data supporting its use
  - **Make sure to check with your oncologist / pharmacist to ensure no drug-drug interactions with current therapies**
- Dose reductions of systemic therapy can also be very helpful in mitigating fatigue
- Additional approaches: cognitive behavioral therapy, qigong, meditation, proper sleep hygiene

Case 3

- A 56-year-old woman with ER+ HER2-low metastatic breast cancer presents for cycle 2 of trastuzumab deruxtecan
- Overall tolerated well, but had significant nausea first 4 days including 3 episodes of vomiting
- Otherwise, she reports good energy, and no shortness of breath or cough

Case 3: Nausea

- Nausea is very common among various chemotherapies, and *particularly common* for Trastuzumab-deruxtecan
  - ~75% frequency of ‘any-grade’ nausea
  - ~45% frequency of vomiting, across clinical trials
- Common infusional chemotherapies with high frequency of nausea:
  - AC
  - Carboplatin
  - Sacituzumab Govitecan
- Nausea is managed both ***preventatively*** with both pre- and post (take home) meds, and ***reactively*** for breakthrough nausea
- Get ahead of the nausea! Don’t wait until it gets severe

Case 3: Managing Nausea – the Toolkit

- **Common pre-meds used to *prevent* nausea/vomiting**
  - 5-HT3 antagonists: Ondansetron, Palonosetron
  - Steroids: Dexamethasone
  - NK1 antagonists: Fosaprepitant
  - Olanzipine
- Common ‘post-meds’ after infusion
  - Dexamethasone for 1-4 days post chemo infusion
  - Olanzipine at bedtime (can be for duration of typical nausea period)
- For breakthrough nausea/vomiting
  - Sublingual ondansetron
  - Compazine
- Anticipatory nausea: Lorazepam
- Additional remedies
  - Ginger (raw, or in tea)

Summary for Nausea

- Ask your care team about your list of pre-meds for your chemo
  - Depending on baseline risk of nausea, you may be started with less or more pre-meds
- If nausea develops, consider:
  - Adding additional pre-meds before infusion (steroids, aprepitant)
  - Consider adding olanzapine at bedtime for the first few days to week of cycle
- If refractory to maximal pre-meds:
  - Talk to care team about dose reduction

Case 4

- Our 56-year-old patient on Trastuuzmab-deruxtecan experienced significant relief in nausea with addition of fosaprepitant pre-med and olanzapine at bedtime for days 1-5
- 10 weeks later, she presents with a new mild cough that has lasted 5 days
- No recent sick contacts
- No shortness of breath
- A CT scan shows inflammatory changes concerning for pneumonitis
- Trastuzumab deruxtecan is discontinued and she initiates prednisone 60mg
- Repeat CT chest in 1 month shows resolution of inflammatory changes and her cough has resolved

Case 4: Pneumonitis / Interstitial Lung Disease

- pathophysiology is poorly understood, but consists of inflammation damaging the lungs
- Pneumonitis / Interstitial Lung Disease (ILD) can be caused by several therapies including:
  - Trastuzumab deruxtecan (T-DXd)
  - Chemotherapies: Gemcitabine, Paclitaxel
  - Pembrolizumab
  - CDK4/6 inhibitors (e.g. Palbociclib, Ribociclib, Abemaciclib)
- For patients on T-DXd:
  - 10-13% overall rate of pneumonitis
  - 1-2% of severe pneumonitis requiring hospitalization
  - Can be fatal

Case 4: Pneumonitis / ILD

- **Know the warning signs**
  - **New shortness of breath that progressively worsens from exertion to rest**
  - **New cough, often dry**
  - **New fevers**
  - **Drop in oxygen saturation (measured on pulse oximeter)**
- Notify your care team *RIGHT AWAY*
- A high-resolution CT chest will be done to evaluate

Management

- If suspected on routine scans *without symptoms*
  - T-DXd will be held for up to 4 weeks, with or without steroids, and then repeat CT chest to ensure resolution; T-DXd may be restarted if resolved
- If symptom + CT findings:
  - Permanently discontinue T-DXd
  - High dose steroids
  - Consider hospitalization if worsening shortness of breath and low oxygen levels
  - Pulmonary consultation

Summary for Pneumonitis

- An inflammatory reaction in the lungs
- Can be picked up on routine scans without symptoms
- Can cause shortness of breath and/or dry cough
- Management includes stopping the drug and starting steroids
- ***Can be life-threatening if not picked up early, so crucial to reach out to your care team if new onset cough or shortness of breath!***

Case 5

- A 45-year-old woman with recently diagnosed ER+ HER2- metastatic breast cancer to the bones is started on ribociclib, letrozole, and leuprolide (ovarian suppression)
- Repeat CBC on day 14 shows a white blood cell count of 3.5, and absolute neutrophil count of 2.0
- Repeat CBC on Cycle 2 Day 1 shows a white blood cell count of 2.3, with an absolute neutrophil count of 1.1
- Do you need to reduce the dose?

Low White Blood Counts (Leukopenia)

- White blood cell (WBC) count comprises several types of white blood cells
- Neutrophils, the bacteria-fighting cells, are important to monitor
- Low neutrophils (Neutropenia) is *VERY* common for CDK4/6 inhibitors (palbocilib, ribociclib, less so with Abemaciclib)
- Considered an ‘on-target’ effect (CDK4 in Neutrophils)
- Have been shown to be a ‘biomarker’ of response (those whose neutrophils decrease do *better* with cancer control)*
- Unlike chemotherapy, which kills the white blood cell stem cells, CDK4/6 inhibitors do *not*, hence risk of infection is much lower
  - Frequency of low neutrophils: 80%; risk of infection severe infection, 0%**

*McAndrew et al. *Br J Cancer*. 2020
**Finn et al. NEJM 2016

Case 5: Low White Blood Counts

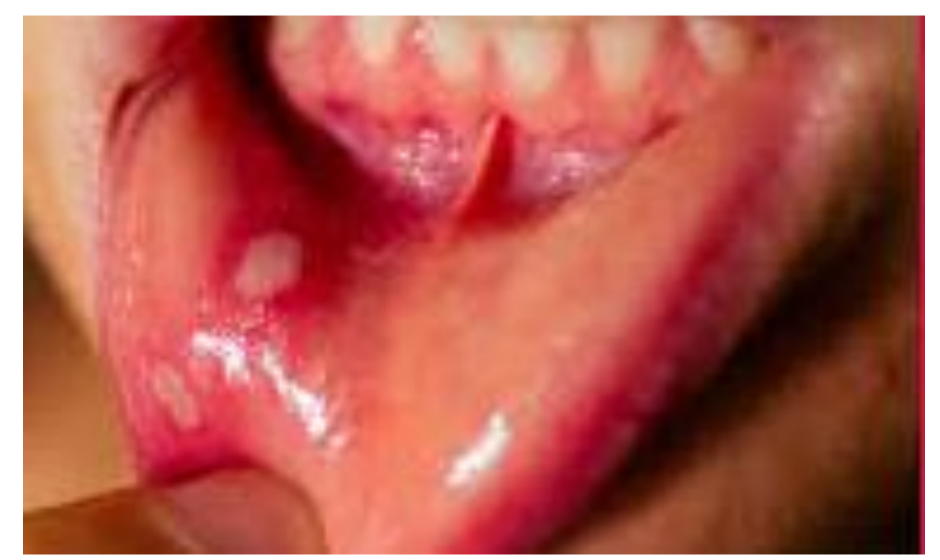
- Goal for neutrophils is >1.0 (or 1,000 depending on units)
- Dose reduction does *NOT* seem to impact outcomes
- Consider dose reduction if neutrophils consistently <1.0 (Grade 3)
- Unlike with chemotherapy, growth factors are *NOT* indicated here

Case 5: Low White Blood Counts

- Regardless of type of therapy (CDK4/6i or Chemotherapy), **call your provider right away if fever develops**
    - Causes
        - Drug-related
        - Viral
        - Bacterial
        - Tumor-fever
        - Blood clots
- Depending on scenario, antibiotics and infectious workup may be recommended

Mouth ulcers associated with Neutropenia

- Mouth ulcers often present with onset of neutropenia
- As neutrophils rebound, ulcers tend to resolve
- Can be painful
- Supportive care includes:
  - Baking soda / Salt Water rinses
  - Viscous lidocaine-based solutions (e.g. Magic Mouthwash)
  - Oral steroid (Dexamethasone) rinses



Case 6

- A 45 year old woman with ER+ HER2- metastatic breast cancer recently began Abemaciclib (a CDK4/6 inhibitor) along with letrozole and leuprolide as first-line treatment
- Shortly after starting, she developed several episodes of diarrhea (loose watery stools)
- She described 4 stools daily, mostly brought on by food, as well as stomach spasms
- She is a physician and the diarrhea has been very disruptive to her daily work

Case 6: Diarrhea

- A very common side effect of systemic therapies in breast cancer
- Both chemotherapy and targeted therapies
- Important to consider other cause (e.g. C.diff)
- For therapies with high risk of diarrhea, important to have at-home meds ready
  - Loperamide (Imodium) is frequently first-line anti-diarrheal therapy
  - Can take 2 capsules (4mg) up front, followed by 2mg with each subsequent diarrheal episode
- If loperamide not helping, ask care team about other medicines:
  - Diphenoxylate / Atropine (Lomotil)
- Dose modification may be necessary

Case 6: Diarrhea

- For our patient, diarrhea brought on by meals was terminated with single dose of Imodium
- She was recommended to take a dose of Imodium before each meal, which stopped the diarrhea from happening
- Other considerations can include dietary modification, avoiding highly fatty or acidic foods that irritate the GI tract
- For stomach spasms, another common side effect of Abemaciclib, dicyclomine (Bentyl) often helpful

Case 7

- A 63-year-old woman with metastatic ER+ HER2- breast cancer just begun therapy with ribociclib and letrozole
- On follow up visit, she notes significant joint stiffness, particularly when getting up from seated position, and after long periods of inactivity, as well as mild swelling in her fingers
- The joint pains, which include wrists, knees, and hips are impacting her daily functioning

AI-Induced Musculoskeletal Symptoms (AIMSS)

- *Very* common, with reported incidence as high as 75%
- Presentation: joint stiffness (morning or after periods of inactivity), carpel tunnel syndrome, trigger finger, fatigue, reduced grip strength
- Can involve any joint (shoulders, hips, knees, wrists, elbows, etc.)
- Risk factors not well understood but may include time from last menstrual period, BMI
- Pathology: Decrease in estrogen levels associated with increased inflammatory markers and altered pain sensitivity
  - *Less movement* => build up of inflammation -> symptoms

Gupta et al *JCO Practice* 2020

Case 7: AIMSS Management

- Movement!
  - Exercise (aerobic, strength training)
  - Daily stretching
  - Yoga
  - Qigong
- Acupuncture
- Taking a short holiday -> switching to a different AI
  - Letrozole, Anastrozole = non-steroidal AI vs Exemestane steroidal AI
  - All three equally effective hence no concern about loss of efficacy
- Omega-3 Fatty Acids
- For carpel tunnel syndrome -> night time splint, steroid injections, carpel tunnel release surgery

Gupta et al *JCO Practice* 2020

Know your resources!

- Huge repository of information about all aspects of metastatic breast cancer
- Support groups
- Conferences (like this one!)
- Limited need-based financial support for cost of care

NCCN Patient Guidelines

NCCN.org

Guidelines for Supportive Care

Anemia and Neutropenia - Low Red and White Blood Cell Counts
Version: 2021

Blood Clots and Cancer
Version: 2023

Distress During Cancer Care
Version: 2024

Fatigue and Cancer
Version: 2024

Graft-Versus-Host Disease
Version: 2021

Immunotherapy Side Effects: CAR T-Cell Therapy
Version: 2024

Immunotherapy Side Effects: Immune Checkpoint Inhibitors
Version: 2024

Nausea and Vomiting
Version: 2022

Palliative Care
Version: 2023

Quitting Smoking
Version: 2024

Survivorship Care for Cancer-Related Late and Long-Term Effects
Version: 2024

Survivorship Care for Healthy Living
Version: 2024

Wellness MBC Extended Passport Program

Members will learn about the benefits of integrative therapies and create a personal care plan for incorporating these services into their treatment, including:

- Acupuncture*
- Exercise
- Reiki
- Meditation and Mindfulness
- Nutrition (grocery gift cards, counseling, cooking classes, meal and vegetable deliveries)
- Oncology Massage Therapy*
- Professional Counseling
- Sexual Health Counseling
- Yoga

Each member receives a curated care box with a renewable Wellness Passport valued at **$2,000** of integrative therapies and services.

Passports are renewable every six months for life.

These services are only available in PA, NJ, and DE

Your care team!

- Oncologist
- NP/PA
- Clinic Nurse
- Oncology Pharmacist
- Infusion Nurses
- Social Worker (counseling, financial resources)
- Oncology Nutritionist

Thank you!