



CHANGING THE PARADIGM OF CHEMOTHERAPY DOSING

How updating dose selection of targeted treatments may result in better outcomes, less toxicity, and less cost.



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TEXAS  ONCOLOGY

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Disclosures

- Pamela Hayes, MD has no conflicts of interest.

Learning Objectives



Review dose selection in oncology drug development



Highlight data limitations for oncology treatments of older or frail populations



Discuss proposed changes in trial design to help optimize treatment doses for efficacy and tolerance.



Case example

Janet is a 50 y/o postmenopausal woman with no significant PMH who has been diagnosed with hormone positive breast cancer. She underwent mastectomy with pathology showing a grade 3, ER/PR+, HER2- infiltrating ductal carcinoma measuring 2.5cm. Two sentinel lymph nodes were removed and noted to be positive for metastatic disease. Staging imaging shows no areas of other metastatic spread.

She is given adjuvant chemotherapy and radiation with good tolerance. She is very nervous about her risk of recurrent disease and wants to know what else can be given to increase her chance of cure.



What should be used?

- Abemaciclib is a CDK4/6 inhibitor.
 - Causes arrest at G1.
- Approved in metastatic ER/PR+ breast cancers or in adjuvant settings in high-risk early stage disease. Typically combined with endocrine therapy.
- Comes in doses of 150mg BID, 100mg BID, and 50mg BID. Recommended starting dose is 150mg.
- Common side effects: diarrhea, nausea, fatigue, neutropenia, and anemia.
- Rare but significant side effects: hepatotoxicity and interstitial lung disease/pneumonitis.

Case example

Janet is a 50 y/o postmenopausal woman with no significant PMH who has been diagnosed with hormone positive breast cancer. She underwent mastectomy with pathology showing a grade 3, ER/PR+, HER2- infiltrating ductal carcinoma measuring 5.1cm. Two sentinel lymph nodes were resected and found to be positive for metastatic disease. The pathology shows no areas of other metastatic spread.

She is given adjuvant chemotherapy and radiation with good tolerance. She is very nervous about her risk of recurrent disease and wants to know what else can be given to increase her chance of cure.

150 mg BID



Case example

Jane is a 70y/o postmenopausal woman with history of HTN, DM, and IBS who has been diagnosed with hormone positive breast cancer. She underwent mastectomy with pathology showing a grade 3, ER/PR+, HER2 - infiltrating ductal carcinoma. Two sentinel lymph nodes were removed and noted to be positive for metastatic disease. Staging imaging shows no metastatic disease.

She declines chemotherapy but is willing to try pills as long as it doesn't impact her ability to play pickle ball.



Case example

Jan is a 70y/o postmenopausal woman with history of CAD, COPD, and CKD who has been diagnosed with hormone positive breast cancer. She underwent mastectomy with pathology showing a grade 3, ER/PR+, HER2 - infiltrating ductal carcinoma measuring 2.5cm. Two sentinel lymph nodes were rechecked and were positive for metastasis.

She was lost to follow up and returns 8 months later with complaints of back pain and imaging showing metastatic disease in her bones and liver.

She is accompanied by her husband. Patient is now motivated to start treatment and is very much hoping she can make it to her 50th wedding anniversary in 2 years.



150 mg BID

Case example

Ja is a 77y/o postmenopausal woman with history of CAD, HTN, CKD, and prior stroke with mobility issues who has been diagnosed with hormone positive breast cancer. She underwent mastectomy with pathology showing a grade 3, ER/PR+, HER2 - infiltrating ductal carcinoma measuring 2.5cm. Two sentinel lymph nodes were found to be positive for metastasis.

She was lost to follow up and returns 8 months later with complaints of back pain and imaging showing metastatic disease in her bones and liver.

She is widowed and lives in an assisted living facility. She has a friend that checks in on her occasionally. Family is estranged.

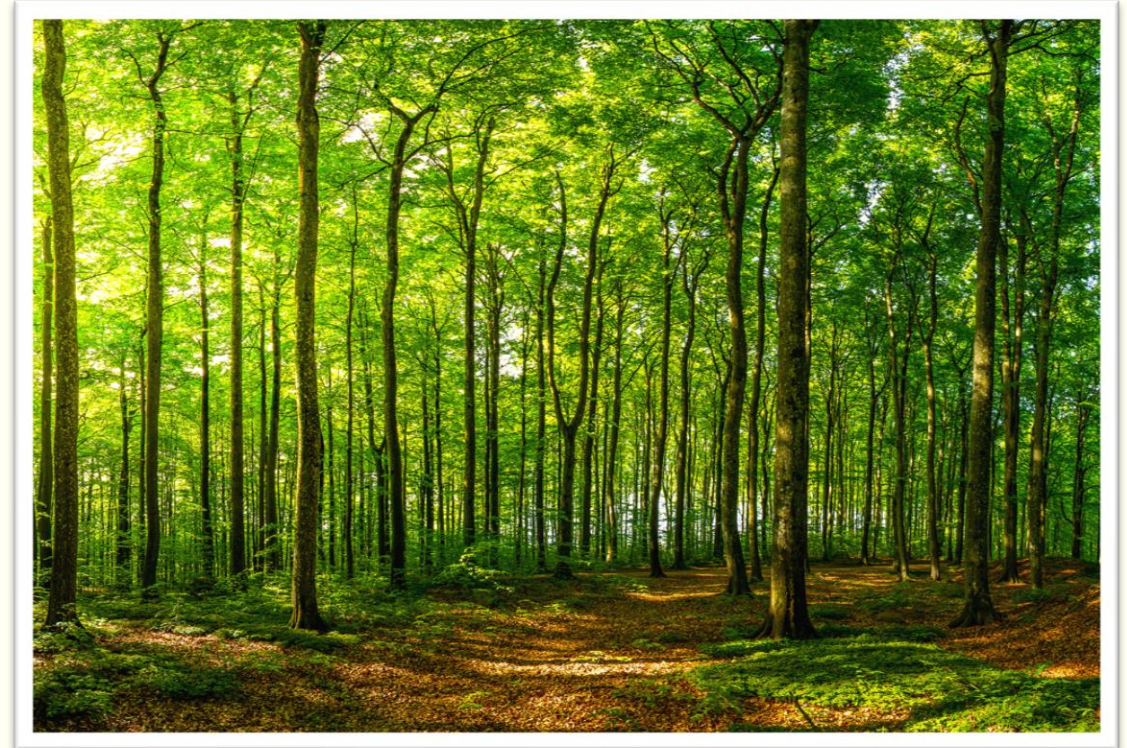
150 mg BID





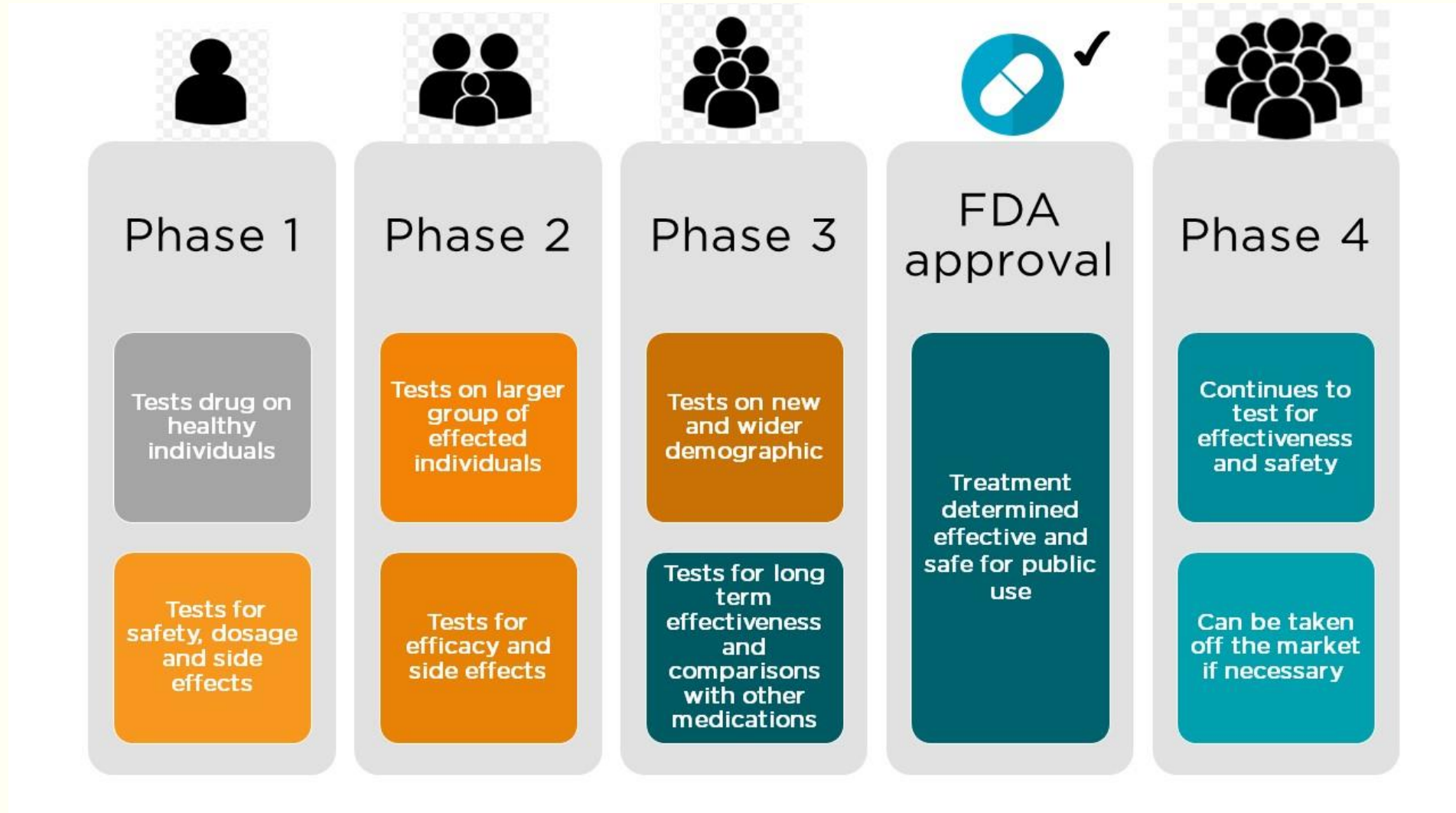
Considerations prior to starting treatment

- Extent of potential benefit
- Baseline functional status
- Baseline goals of care
- Comorbidities
- Social support
- Barriers to compliance/follow up



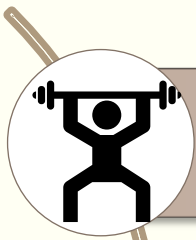
How can I best take care of my patient, not just their cancer?

Clinical trials

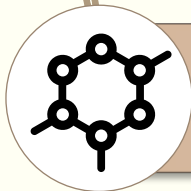


Early phase trials

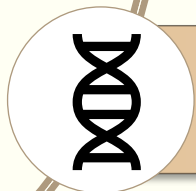
- Phase 1 trials use small numbers of participants to evaluate new medications or dose combinations to determine drug doses and identify major toxicities prior to larger scale studies.



Pharmacokinetics – absorption, distribution, metabolism, and excretion.



Pharmacodynamics – how the medication interacts with its target to produce desired effect.



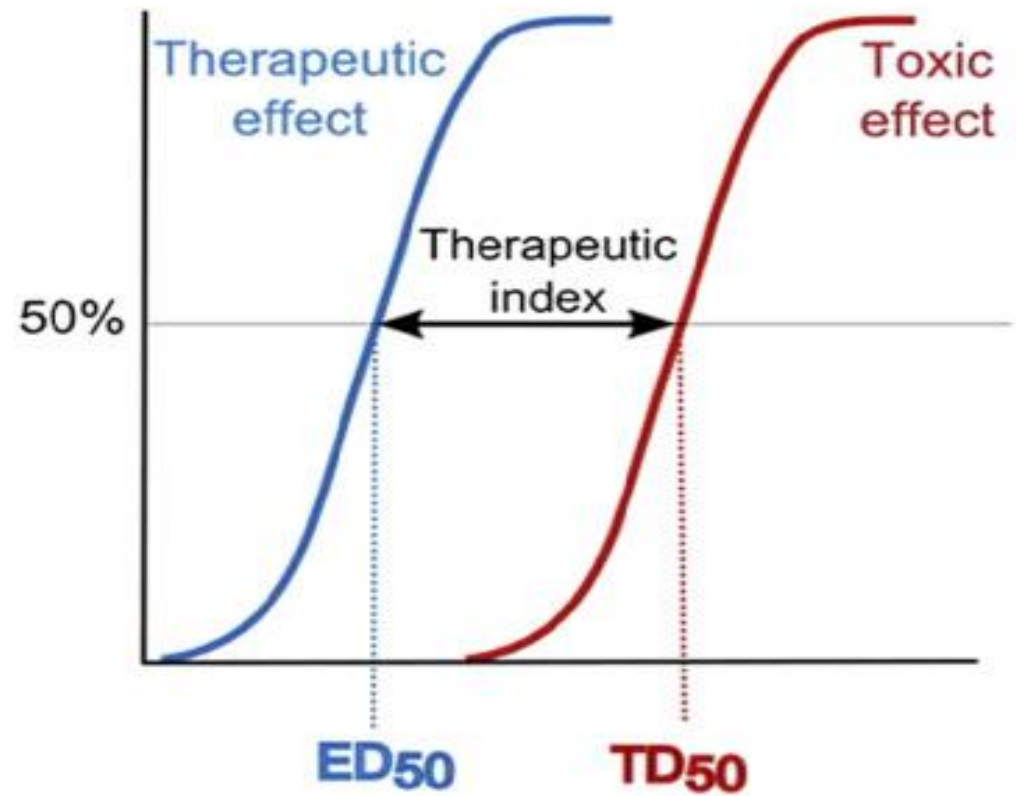
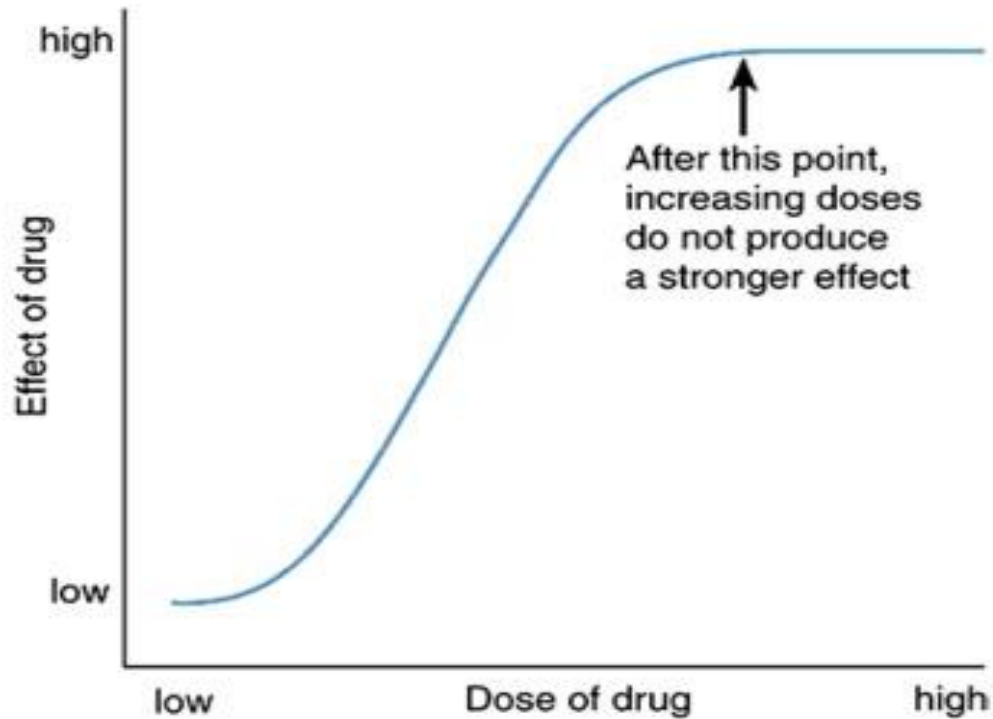
Pharmacogenomics – how genetic variants alter drug efficacy and toxicity

Early phase trials

- Phase 1 trials typically enroll patients for whom there is no standard of care or limited effective options.
 - Small chance of benefit may outweigh risk of significant toxicity.
- In oncology trials, it is not uncommon to have limited evaluation of drug doses prior to moving forward with registration trials.
 - Need for rapid evaluation
 - Small number of participants available
 - Pervasive belief that the higher the dose, the more effective the treatment
- Most drug approvals have a burden of proof on efficacy endpoints, so developers favor higher doses in hopes of improving chances of response.

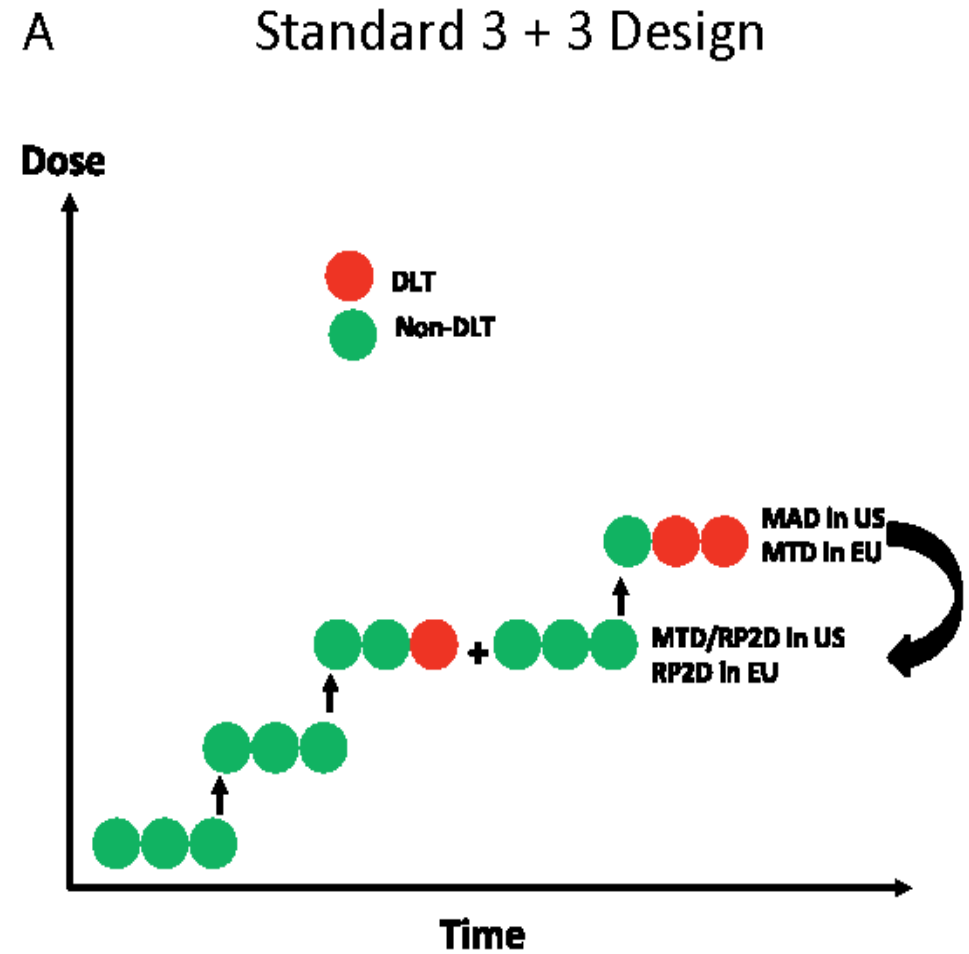
Therapeutic Index

► Dose-Response Curve



How are doses selected?

- Dose is started low based on information from preclinical trials.
- Protocols have set expected toxicities to be seen on treatment and time for occurrence.
 - These events are called dose limiting toxicity (DLT)
 - These events are significant and potentially fatal
 - Typical trial rates for this are set around 20-30%
- Maximal tolerated dose (MTD) is achieved when a certain dose is found to be at or under the determined DLT rate.



Benefits

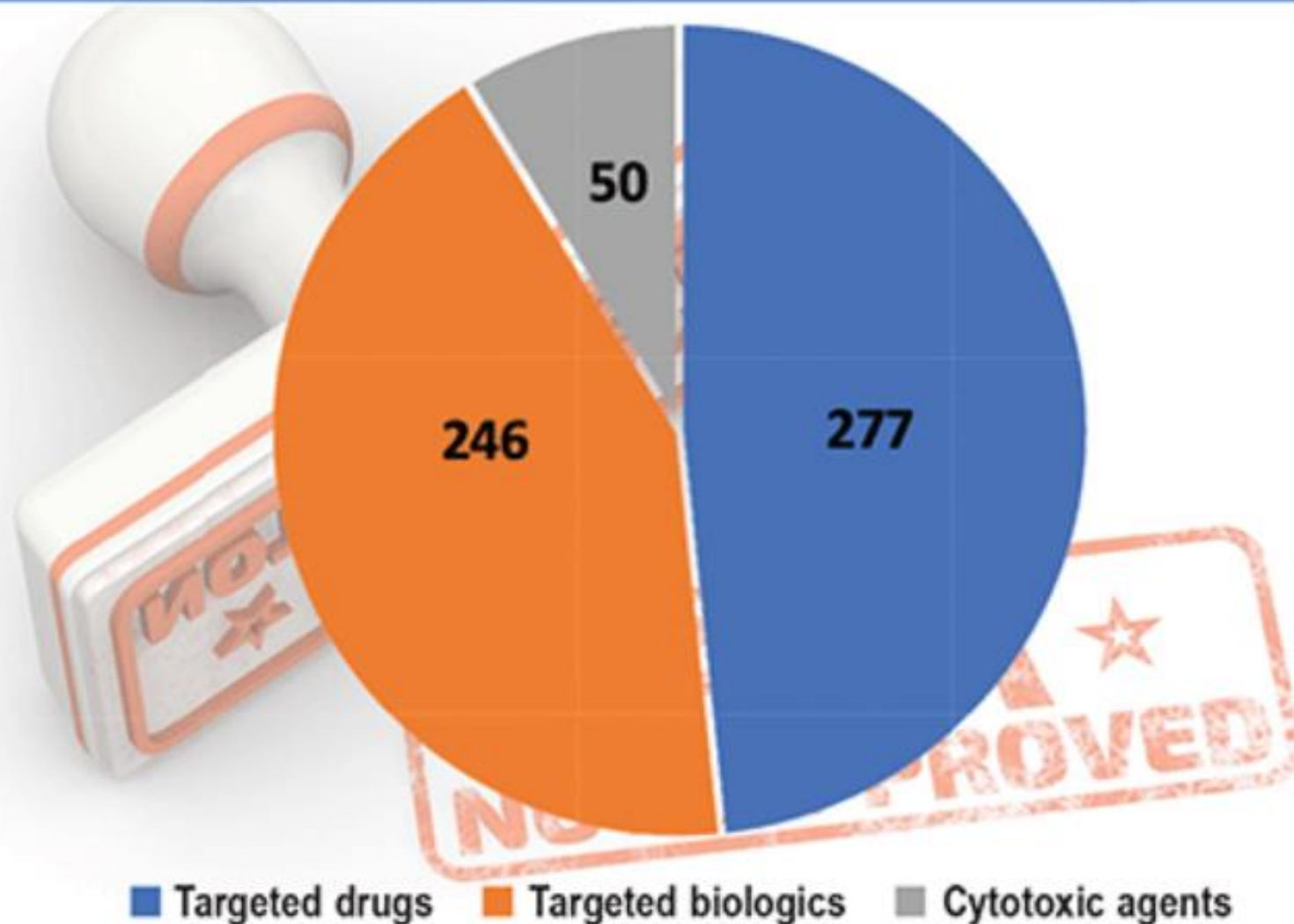
- Fast
- Cost effective
- Small numbers of patients exposed to untested drug/side effects



Limitations of this dose strategy

- “Acceptable” toxicity level set at a high level
- Dose strategies are focused on short-term toxicities
- Some drugs don’t have a clear MTD
- Depending on post-marketing trials for dose optimization is not ideal
 - are the testing groups equivalent
 - are the endpoints the same
 - are current patients getting overly toxic doses

FDA Approvals for Oncologic Diseases (January 2000–October 2022)



Source: Nature Reviews, 2023.

Changes in oncology therapies

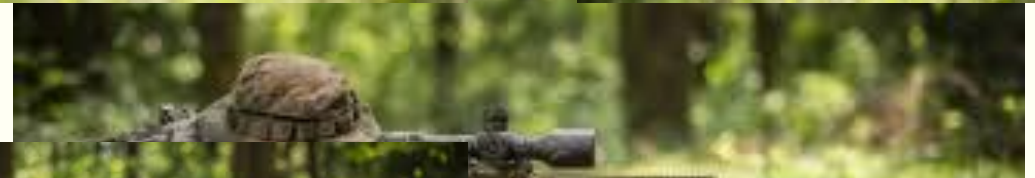
Cytotoxic Therapy

- Cytotoxic chemotherapy disrupts natural processes within the cell resulting in arrest or apoptosis.
- All cells are potentially affected.
- Generally, there is a set duration (number of cycles) prior to needing stop for toxicity.



Targeted Therapy

... proteins that ... at is ... w or



Challenges in the treatment of older adults

- Over 50% of cancers occur in patients over the age of 65 and this is expected to further increase over the next ten years.
- Increased rates of comorbidities may complicate medication dosing.
 - poor nutrition, less marrow reserve, liver dysfunction, renal insufficiency, reduced performance status, less social support, cognitive issues.
- Commonly used functional status such as ECOG or Karnofsky can be limited.

Challenges in the treatment of older adults

- Patients over the age of 70 are chronically under-represented in clinical trials which makes extrapolating trial data challenging
- Adverse events are under-reported in older patient
 - Monalissa-2 trial looking at abemaciclib previously reported no difference in toxicity based on age
 - Subsequent pooled analysis showed higher rates of adverse events, dose reductions, and reduced QOL in patients >75 years
- Geriatric patients often focus on quality-of-life goals, but trials often only assess survival and progression endpoints.

Do older patients do as well on clinical trials?

- As age and dose increases, so does risk of toxicity
 - Hematologic, liver, and renal toxicity rates are generally similar across ages
- Overall, there are similar response rates and treatment-related mortality rates when compared to younger cohorts.
- Elderly participants enrolled in phase I trials had improved survival rates compared to matched patients who did not receive treatment.
- Higher rate of self-withdrawal from protocol

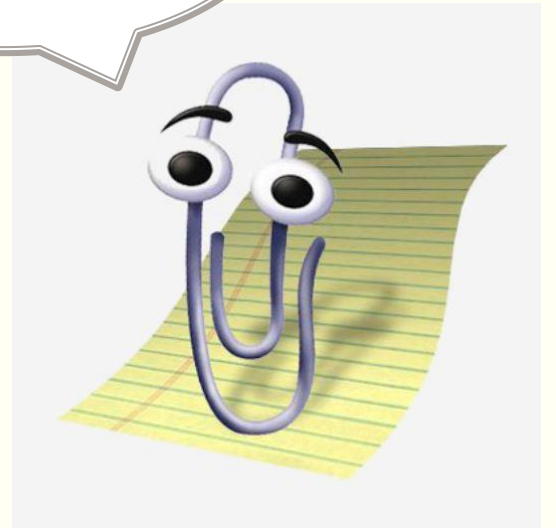
Barriers to enrollment in trials

- Common comorbidities such as cardiac history, renal insufficiency, and hematologic abnormalities may prohibit enrollment.
- Cognitive decline
- Transportation, travel distance
- Physicians are less likely to offer or discuss enrollment in elderly patients

GAP70+ Trial

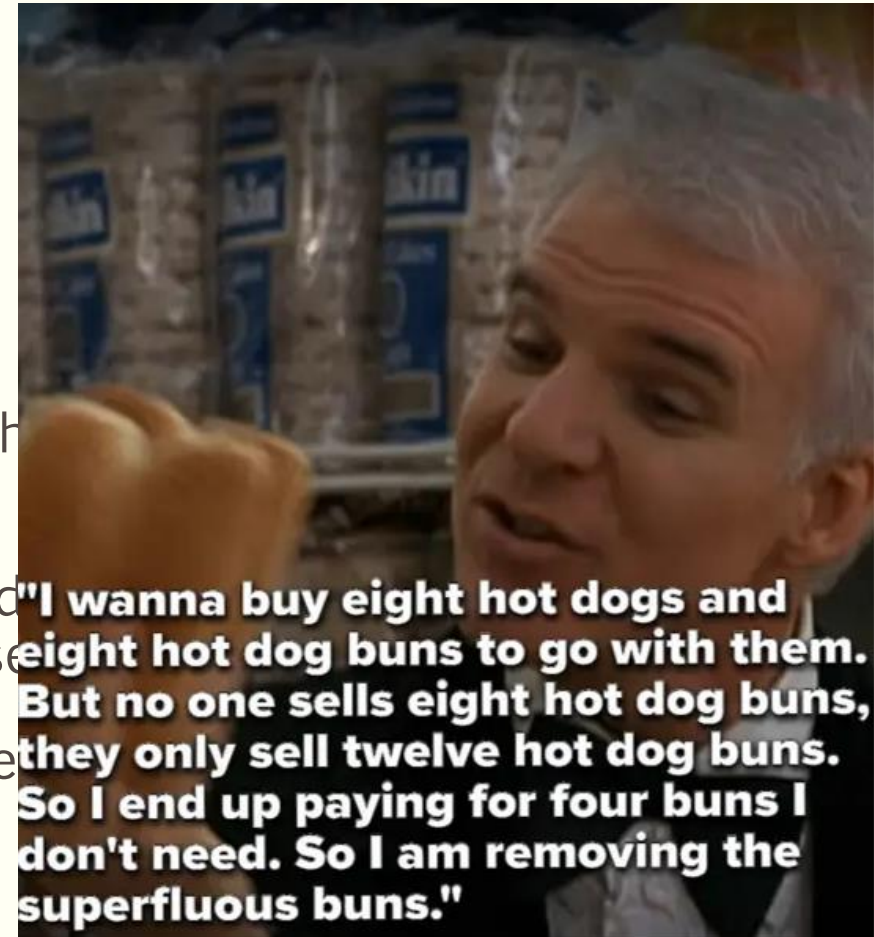
- 718 patients over age of 70 with terminal cancers.
- Oncologist were randomized to receive a geriatric assessment with recommendations vs. usual care.
- Chart reviewers were blinded to intervention.
- Patients with geriatric assessments had lower doses of chemo, less toxicity, less fall incidents.
- OS at 6 months was the same.

Would you like help limiting that toxicity?



FDA: Starting the shift

- Sotorasib
 - Targeted treatment for KRAS G12C – approved in 2021
 - Treatment of locally advanced or metastatic lung cancer
- Recommended dose is 960mg (8 pills of 120mg tablets).
- 45% of patients noted a significant adverse event & 9% had discontinued medication due to toxicity
- Early phase testing looked at doses of 180, 360, 720, and 960mg to determine drug levels, saturations, and response rates between doses
- Preclinical data suggested a minimal effective dose range of 360-720mg



FDA: Starting the shift

- FDA asked to do further testing to compare 960mg dose to 240mg dose
- Higher dose did show better efficacy, but at risk of toxicity
- Response rate 33% vs 25%, Overall survival 13 vs 11.7 months
- Toxicity grade ≥ 3 37% vs 20%
 - “Serious” AE 14% vs 8%
- Cost of month supply (240 tablets)
 - \$22,245



2024

Corolla

\$22,050

Base MSRP *

32/41

Est. MPG *

Balancing risks with benefits

- Standard dosing may lead to worse outcomes.
 - High risk of toxicity may lead to discontinuation and refusal to try medication at a lower dose.
 - Delays in care due to hospitalizations, rehabilitation placement.
- Statistical improvement and clinical improvement may not be the same.



"If a cat sits on a hot stove, that cat won't sit on a hot stove again. That cat won't sit on a cold stove either. That cat just don't like stoves."

- Mark Twain

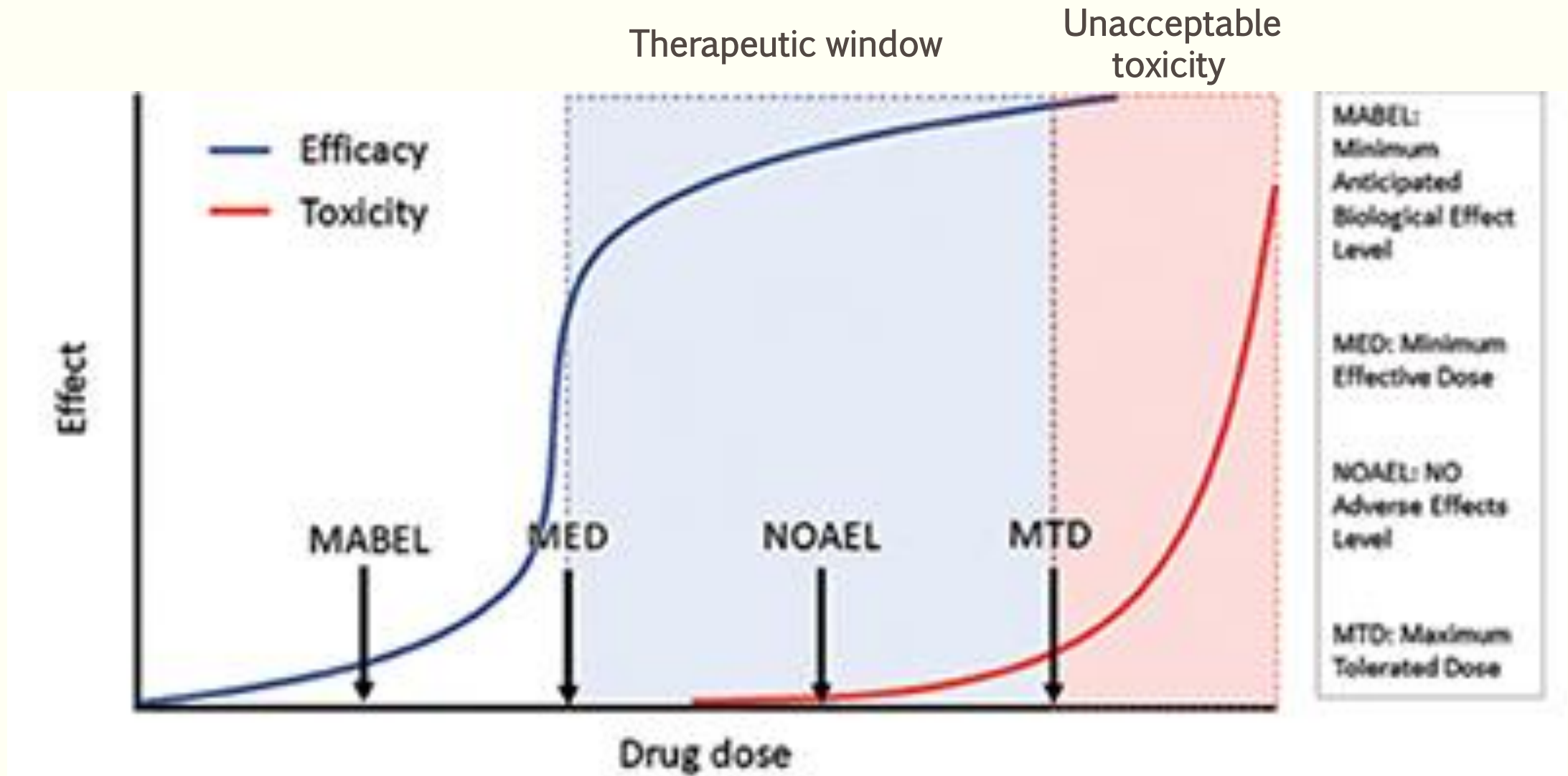


FIGURE 2: THE THERAPEUTIC INDEX

Project Optimus

- FDA initiative developed by the Oncology Center of Excellence in 2021.
- “Develop strategies for dose finding and dose optimization that leverages nonclinical and clinical data in dose selection, including randomized evaluations of a range of doses in trials.”
- Aim to start dose optimization as early as possible in trials.
- Drugs that have not undergone prior dose optimization but are already approved or are in later stages of development may be asked perform additional testing.



Dose optimization

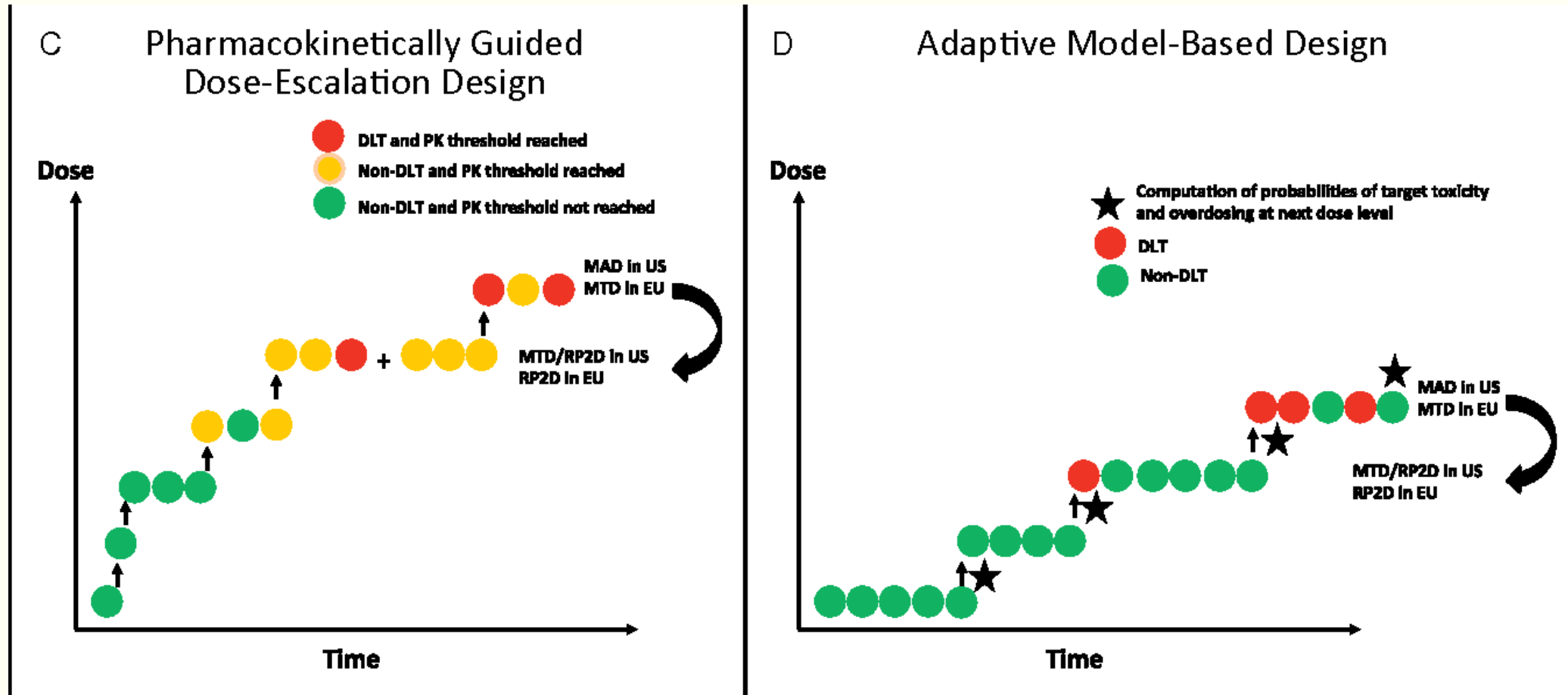


Fig 1 (A) Schematic of the standard 3 + 3 design. (B) Schematic of the rule-based accelerated titration design. (C) Schematic of the pharmacokinetically

Initiatives with Optimus

- Using more PK/PD data and disease biomarkers to guide dosing.
- Increased emphasis on diversity of patients in trial participation.
- Looking at more quality of life metrics in drug development.
- Encourages dosing schedules that are easier.
 - Improve compliance
 - Reduce drug cost and infusion cost
- Retained efficacy with less toxicity.

Challenges

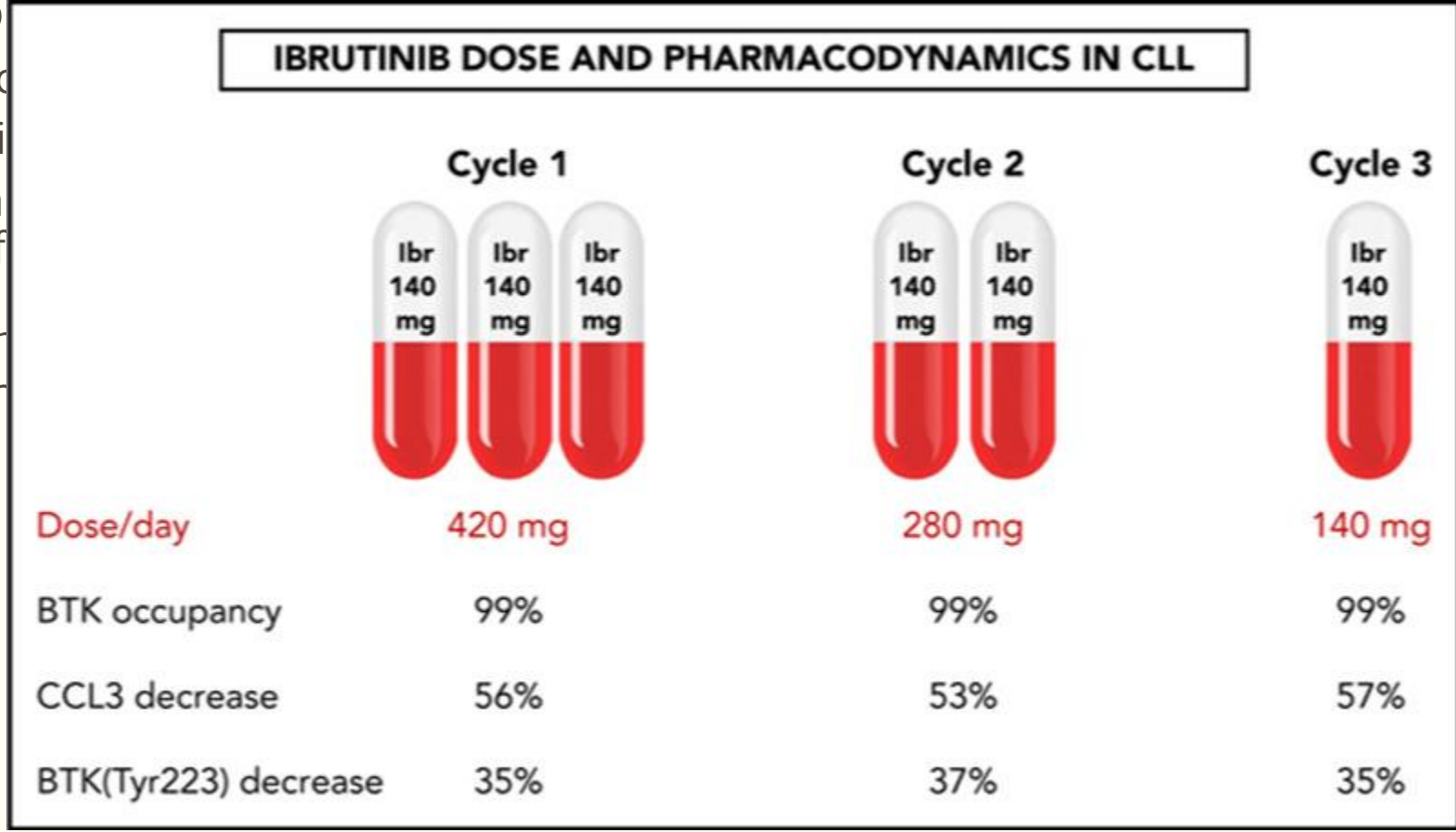
- Active dose may not be consistent across all populations, ages, tumor types, mutations, and cancer stages.
- More complexity in testing and changes of infrastructure may lead to increased costs, including upfront costs.
 - May make things more challenging for small drug development companies.
- Larger number of patients may be needed in early phase trials.
 - Smaller sample sizes in dose comparisons may make it challenging to show non-inferiority.
- May slow down time to drug development and approval.
- May reduce interest in development of novel agents.
- Not all medications have identifiable biomarkers to track efficacy

Examples of dose optimization cases

- Cetuximab
 - No MTD
 - Trial used PK data to show when clearance levels approached a plateau, implying maximal target engagement.
 - Based on this data, recommended dose 200mg/m² was selected for phase II trial.
 - FDA approved dose – 400mg/m² loading dose, followed by 250mg/m² maintenance
- Pembrolizumab
 - No MTD
 - Using IL2 as a biomarker, looked through doses from 0.005 to 10mg/kg.
 - Exposure response based on tumor regression was performed on doses from 2mg/kg through 10mg/kg with similar responses.
 - 2mg/kg q3weeks was selected
 - Continuing to expand on dosing with expanded intervals, dose banding

Examples of dose optimization cases

- Ibrutinib
 - Bruton's tyrosine kinase (BTK) inhibitor
 - Median overall survival (OS) of 35.5 months
 - Complete response (CR) rate of 48%
- Recommended starting dose is 420 mg once daily
- Recommended maximum daily dose is 420 mg



secondary

The “perfect” dose

- PK/PD function can vary as much in an individual as between patients
- Phenotype
 - Weight/Body surface area
 - Age/Sex/Ethnicity
 - Organ function
 - Microbiome
- Genotype
 - Variation in metabolizing enzymes, transporters, receptors, binding protein
- Lifestyle
 - Compliance
 - Exercise
 - Smoking/alcohol/drug use
 - Drug-drug interactions
- Disease
 - Resistance mutations/ tumor heterogeneity
 - Downstream effects

How we can improve patient care together

- Ongoing goals of care discussions
- Frailty testing
- Geriatric assessment
- Assessing for drug interactions
- Free communications between providers
- Encourage patients to participate in clinical trials



Oncologist's Prayer

*Dear Lord, let there be a cure for cancer...
And may it be so complicated that only I can understand it.*





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