Dose optimization for anti-cancer agents in the era of immunotherapy and targeted agents.

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Dose Finding and Dose Optimization Paradigm Symposium
American Statistical Association Princeton-Trenton and New Jersey Chapters
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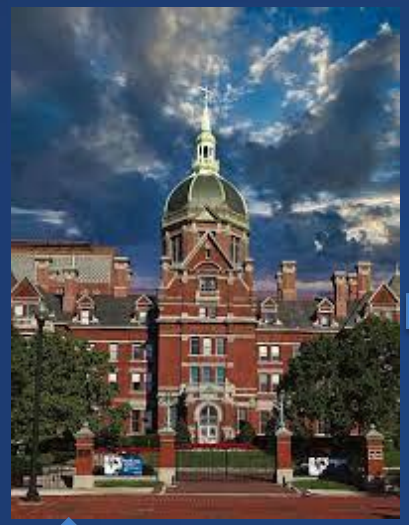
My path in statistics

Bowdoin College

Johns Hopkins School of Medicine
Sidney Kimmel Comprehensive Cancer Center



Medical University of South Carolina
Hollings Cancer Center

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KNOWLEDGE CONQUERS CANCER

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Two main points to make

1. Dose optimization needs to extend beyond safety/tolerability of treatments and incorporate efficacy of treatments, especially for targeted and immunologic anti-cancer agents

2. For many currently approved anti-cancer agents, dose optimization needs to be revisited.

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Overview of talk

- Historical perspective on dose finding in oncology
- Case studies: “Phase I” studies of immune checkpoint inhibitors
- Revisiting dose finding objectives
- Considerations for pre-market dose finding studies
- Post-market dose optimization
- Other Opportunities for Trial Designers and Methodologists

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What are the dose finding methods in cancer drug development?

Historical Perspective of Approaches

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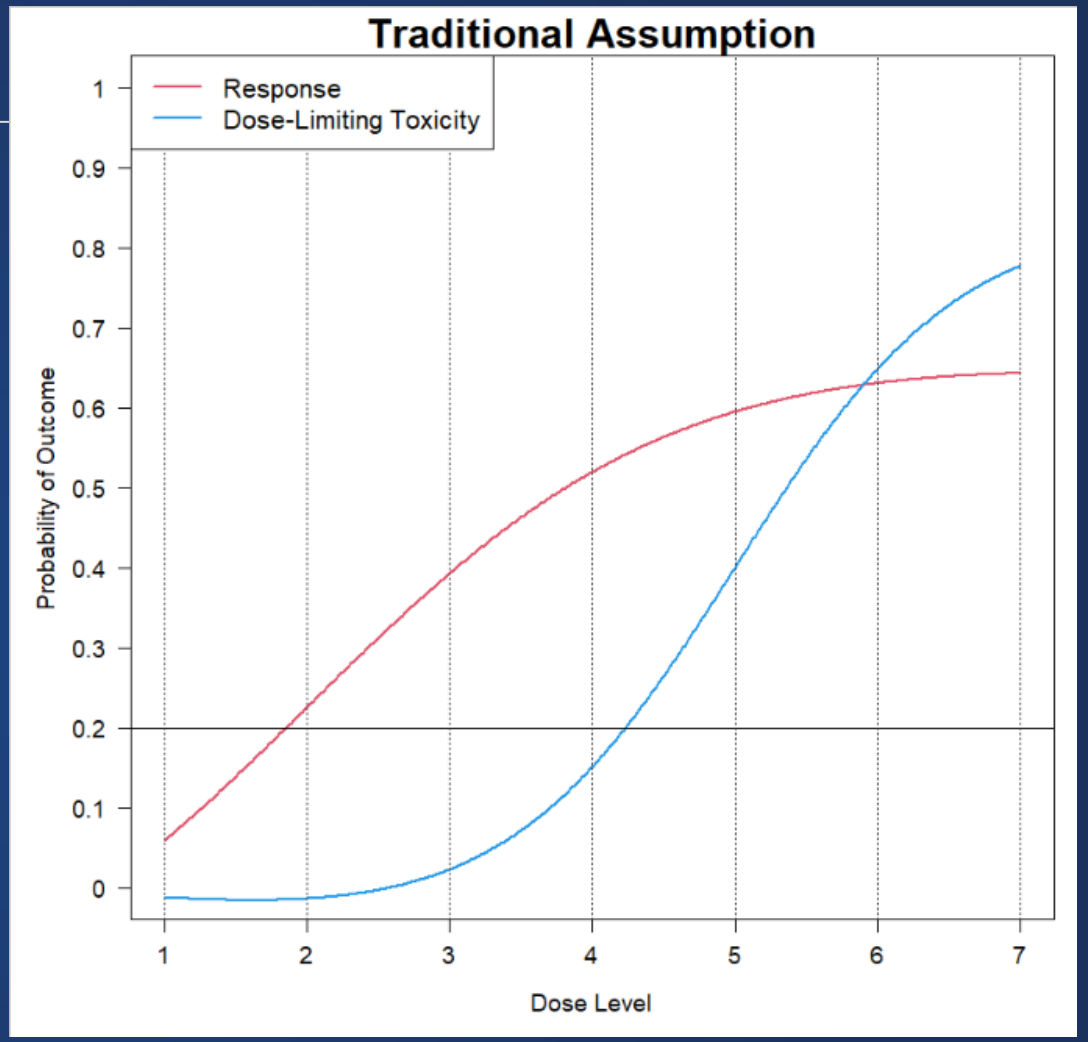
Traditional Early Phase Drug Development in Oncology

- Phase 1: Find the maximum tolerated dose (MTD)
- Phase 2: Evaluate efficacy at the MTD

- Toxicity based dose finding
  - Chemotherapies/Cytotoxics
  - “More is better”
  - As dose increases, toxicity increases
  - As dose increases, efficacy increases



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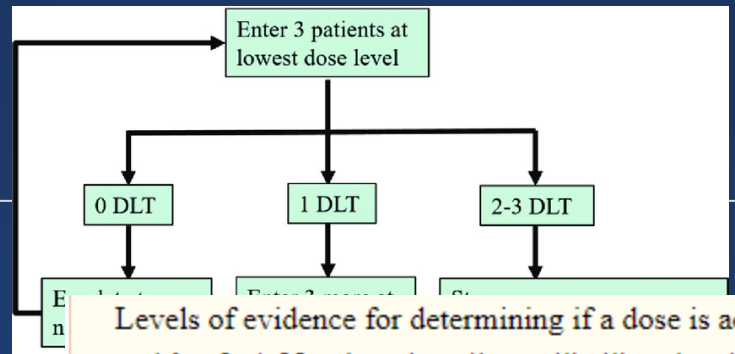
Traditional Phase I

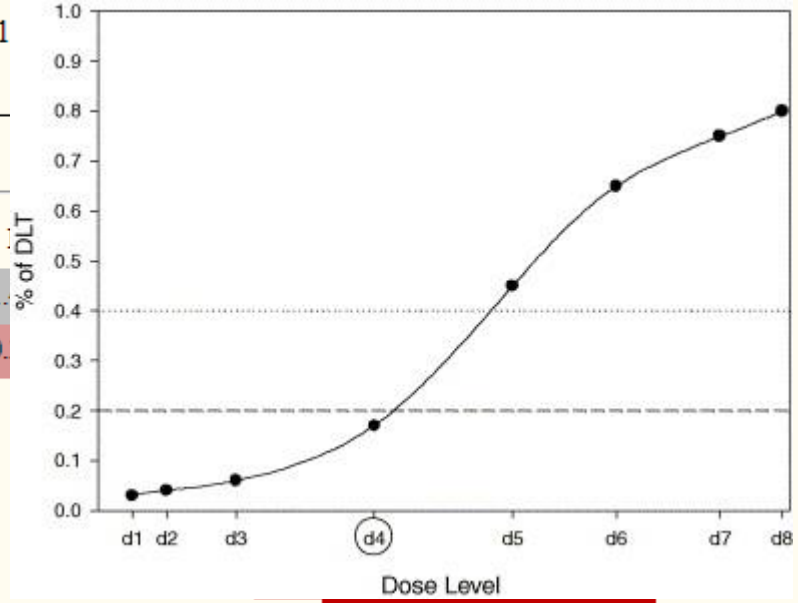
- A few designs
  - Algorithmic: “We like the 3+3” because we understand it”
  - Continual Reassessment Method (1990); Escalation with Overdose Control
  - Probability intervals (e.g. mTPI, BOIN)
  - Likelihood-based dose selection



Levels of evidence for determining if a dose is acceptable or toxic based on ($p_1 = 0.40$, $p_2 = 0.15$) and $k = 2, 4$. Numbers in cells are likelihood-ratios with colors indicating level of evidence. Dark/light green cells indicate evidence of acceptable dose; red/pink cells indicate evidence of toxic dose; gray cells indicate weak evidence. Dark green cells: $LR \geq 4$; light green cells: $2 \leq LR < 4$; gray cells: $1/2 < LR < 2$; pink cells: 1

Number of toxicities at dose j

0	1.
1	0.
2	
3	
4	
5	
6	<0.01 <0.01 0.01 0.01



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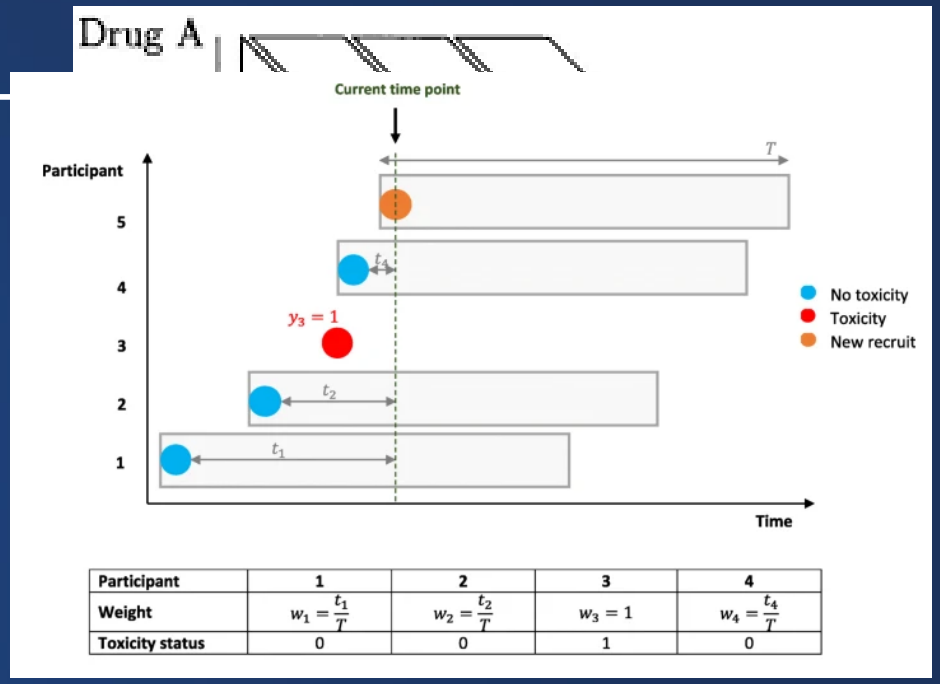
Traditional Phase I

- Combination drug trials for identifying MT
  - Model based
  - Partial orders (Wages)
- Delayed toxicity events
  - Time to event CRM (Cheung, Chappell)
  - Rapid escalation design
- Expansion cohorts
  - Add 6-12 additional patients at the MTD to confirm safety and better characterize safety profile at MTD
  - Recalibration of MTD (Iasonos)



Participant	1	2	3	4
Weight	$w_1 = \frac{t_1}{T}$	$w_2 = \frac{t_2}{T}$	$w_3 = 1$	$w_4 = \frac{t_4}{T}$
Toxicity status	0	0	1	0

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Defining Toxicity Outcomes

- Traditional binary endpoint for ‘dose limiting toxicity’ (DLT), defined in protocol.
- DLT: inconsistent across protocols—depends on expected toxicities associated with the agent under study
- More recent shift from binary DLT
  - Ordinal grades (Van Meter; Yuan)
  - Toxicity burden scores (O’Connell; Lee; Ezzalfani; Bekele & Thall; Yin)
- Relatedness and attribution (Iasonos & O’Quigley)
- Cycle 1 toxicities? Post-hoc evaluation of toxicities in later cycles (Lee; Paoletti)

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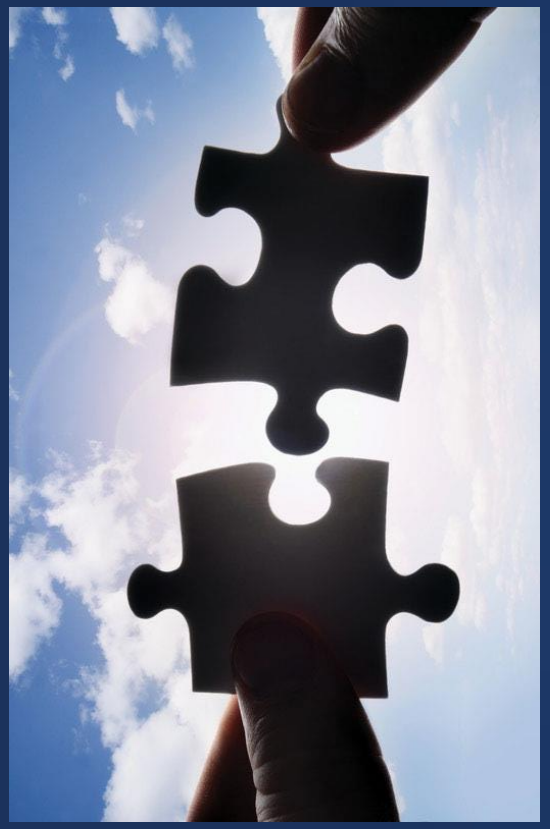
Phase I/II designs



- Historically, two separate phases within one protocol, answered sequentially.
  - Phase I question: **What is the correct dose**?
  - Phase II question: **Is there sufficient efficacy at the selected dose to warrant further study**?
- Benefit of phase I/II designs has been the avoidance of two submission & approval processes.

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Case studies:
Phase I studies missing the optimal dose

Two “Breakthrough” Immunotherapies

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A New Era: “Breakthrough Designation"

- In July 2012, the United States Food and Drug Administration Safety and Innovation Act (FDASIA) was signed.
- A new designation for an experimental treatment was created:
  Breakthrough Therapy Designation

- A breakthrough therapy is a drug…
  - which is intended alone or in combination to treat a serious or life-threatening disease or condition, and
  - for which preliminary clinical evidence indicates the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.

- If designated, FDA will expedite the development and review of such drug.

- This may mean that the Phase I trial will evolve with the FDA’s involvement

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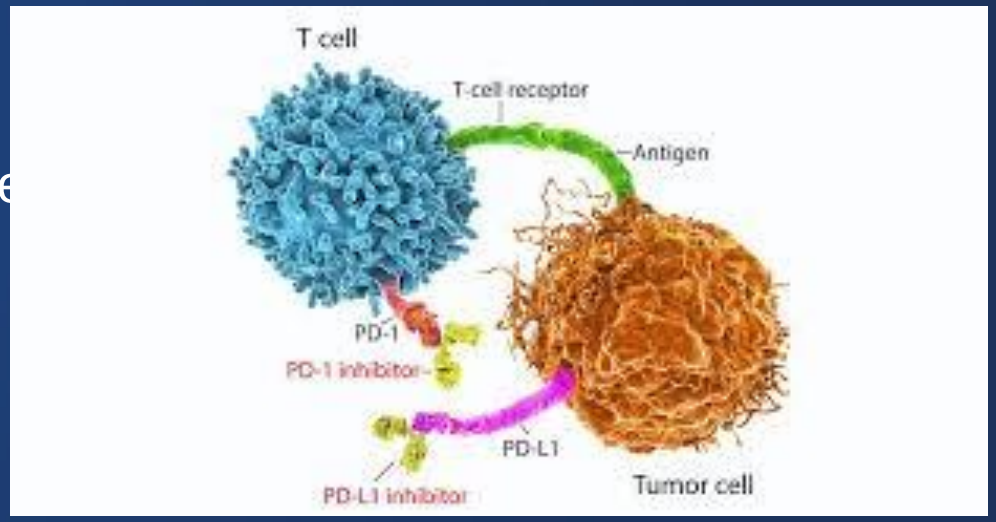
Immunotherapy Breakthroughs

- **Nivolumab (*Opdivo*) and Pembrolizumab (*Keytruda*):** block a protein called programmed cell death 1 (PD-1).
- PD-1 blockers free the immune system around the cancer by helping T-cells to attack cancer.

- Pembrolizumab and Nivolumab phase I trials
  - In version 1 of these protocols, proposed sample size were 32 and 76, respectively.
  - Both gained breakthrough designation and worked with FDA to expedite development



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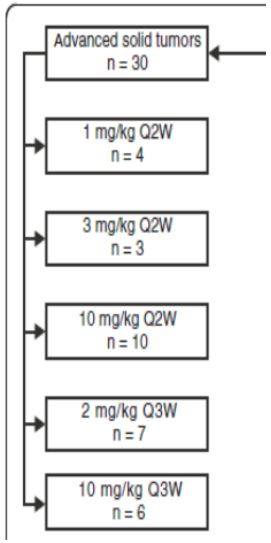
How did these trials evolve after breakthrough designation?

KEYNOTE-001, for pembrolizumab (KEYTRUDA).

Standard 3+3 algorithmic design before breakthrough designation….



Pembro trial, version 1

Example: Nivolumab (OPDIVO)

- **Protocol, version 1: 23 July 2008**
  - 3 dose levels. 1, 3, 10 mg/kg. 3+3 design (N = 12)
  - Four dose expansion cohorts with up to 16 patients per cohorts
  - Maximum N=76

- **Protocol, version 5: 23 Jan 2012**
  - Doses 0.1 mg/kg and 0.3 mg/kg added as part of Amendment 4.
  - Up to 14 expansion cohorts, enrollment to 7 expansion cohorts already completed.

- At the trial's end, 296 patients had been enrolled in five cancer subtypes.

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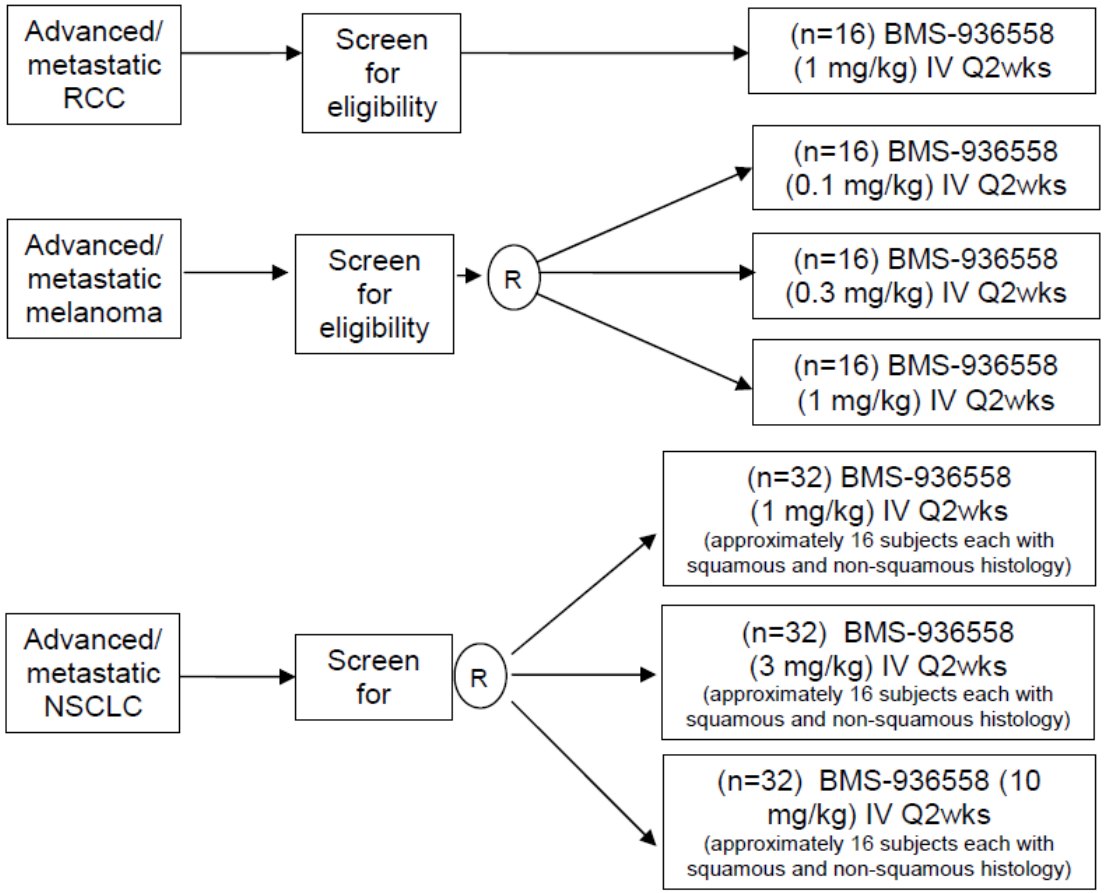
Expansion Cohorts in Nivolumab (OPDIVO) Phase I

Table 4: Expansion Cohorts Completed Prior to Amendment 4

- Melanoma 1 mg/kg
- Melanoma 3 mg/kg
- Melanoma 10 mg/kg
- Renal Cell Carcinoma 10 mg/kg
- Non-small Cell Lung Cancer 10 mg/kg
- Colorectal Cancer 10 mg/kg
- Prostate Cancer 10 mg/kg

Figure 3: Expansion Cohorts Added Under Protocol Amendment 4



Revisiting dose finding objectives

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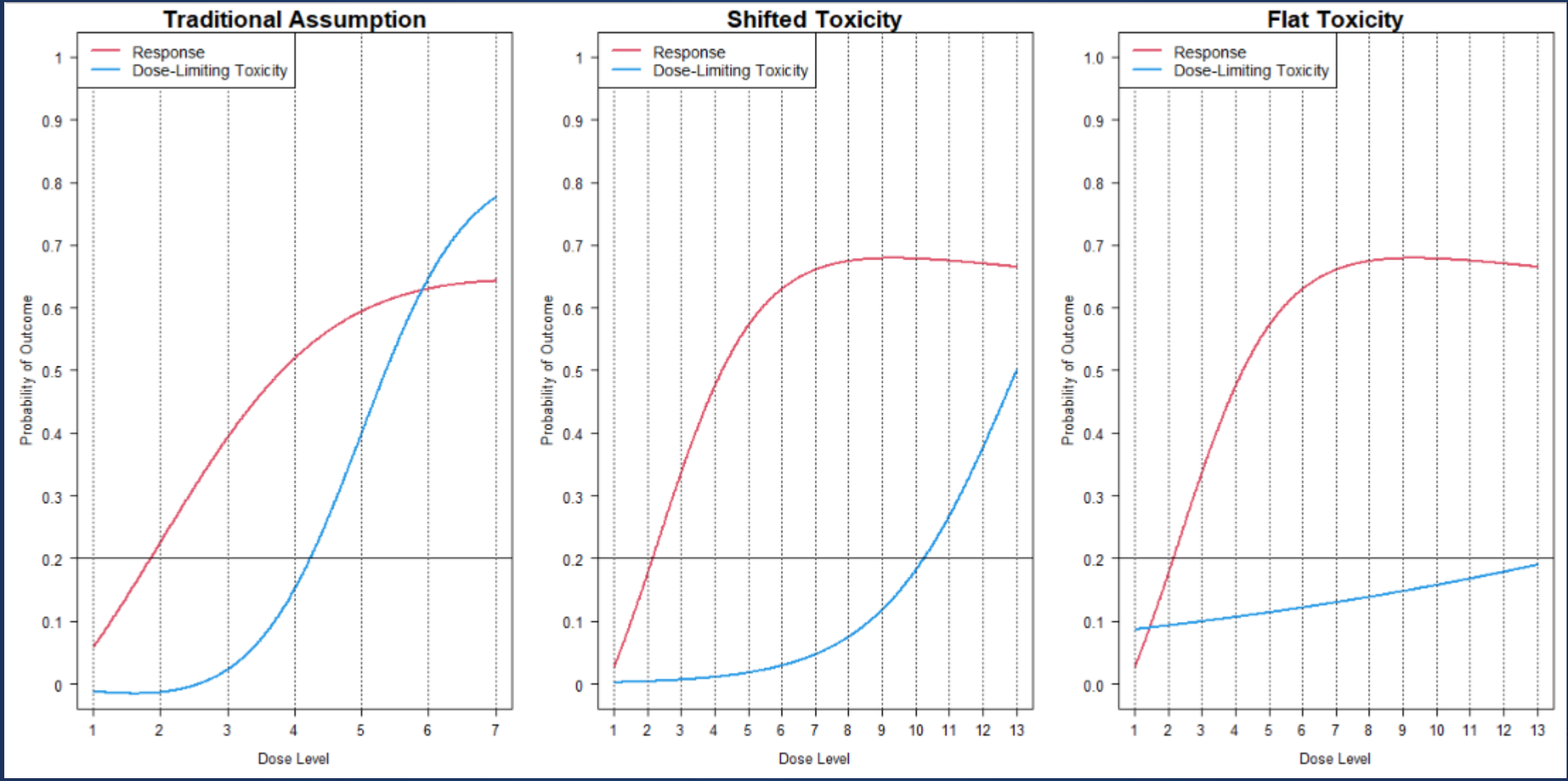
What we learned: Our assumption was incorrect



Revisiting the Objectives

- In traditional cancer treatment, the dogma has always been to administer all drugs at the maximum tolerated dose (MTD)
- The same approach would not be expected to apply to molecularly targeted agents and immunotherapies
- We need to redefine the criteria used for the recommended phase II dose (RP2D)
- **Is it critical to define a <u>single</u> RP2D as part of a phase I trial? ***

* Ratain, Nature Reviews Clinical Oncology, 2014.

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Dose response: Is it a phase I question?

- **Dose efficacy relationship should be an integral part of drug development**
- The highest “safe” dose is not necessarily optimal
- Previous examples of cancer treatments lacking an increasing dose response relationship: lower doses are as efficacious as higher doses
  - Temsirolimus in kidney cancer (Atkins et al., JCO, 2004)
  - Anastrozole in breast cancer (Jonat et al., Eur J Cancer, 1996)

- Some proposals for change:
  - *Phase I should identify a range of doses for phase II instead of one dose based on safety*
  - *Phase II trials should include two or more doses*
  - *Phase I and II should be merged using a coherent approach for optimal dosing*
  - *Phase I, II, and III should be blended for a more continuous drug development process*

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Statistical Challenges

- Pembrolizumab and Nivolumab trials?
  - They morphed into dose ranging studies
  - Randomized components comparing different doses of the same agent, at doses shown to be safe from early part of the trial
  - Results showed:
    - There was a relatively flat dose response curve
    - There was a relatively flat dose efficacy curve

- How COULD we have designed these trials to find the best doses?
  - Need designs for a variety of dose-efficacy curves
  - Need to allow for flat, shallow and steep toxicity curves

- Was there information available at the time to suggest that a 3+3 design would fail at finding an optimal dose?

FDA's recent perspective

"**It's not unusual for doses and schedules of oncology drugs to be inadequately characterized before sponsors initiate registration trials**… The default decision to select the highest dose that has been evaluated reflects both the desire to make oncology drugs rapidly available to patients who have limited options and the belief that higher drug doses will have better therapeutic activity. Often, small cohorts of patients are assigned to receive escalating doses and are assessed for severe or life-threatening dose-limiting toxic effects for one treatment cycle to identify the maximum tolerated dose. **We believe this practice should be reexamined for targeted drugs and biologic therapies.**"

Shah, Rahman, Theoret, Pazdur. "The Drug-Dosing Conundrum in Oncology—When Less is More," NEJM, Oct 14, 2021.

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Project Optimus and FDA-ASCO joint workshop

- **FDA's Project Optimus:**

"The goal of Project Optimus is to educate, innovate, and collaborate with companies, academia, professional societies, international regulatory authorities, and patients to move forward with a dose-finding and dose optimization paradigm across oncology that emphasizes selection of a dose or doses that maximizes not only the efficacy of a drug but the safety and tolerability as well."

- **"Getting the Dose Right: Optimizing Dose Selection Strategies in Oncology – An FDA-ASCO Virtual Workshop" (May 3-5, 2022)**
  - Provide a forum for open discussion among academia, industry, regulatory agencies, and patient groups about anticancer agent dose optimization.
  - Discuss how to apply nonclinical, clinical pharmacology, clinical, and statistical evaluations to optimize the dose of anticancer agents.
  - Discuss benefits and challenges related to pre- and post-marketing dose optimization trials.
  - Discuss clinician and patient factors that impact participation in pre- and post-marketing dose optimization trials.

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Integrated toxicity and efficacy based designs

- Simultaneous or semi-sequential model-based approaches have been introduced by numerous authors 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).
  - …….

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 (e.g., 3+3) 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

→ 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.
- Often designed to 'pick the winner"

  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
- Pick the winner inferences (two arm setting):
  - If neither arm meets threshold for sufficient efficacy, abandon both arms for further study
  - If at least one arm meets the threshold for efficacy, pick the winner (e.g., higher response rate)
  - If there is a tie, pick the simpler arm

Rubinstein, Crowley, Ivy, LeBlanc, Sargent. Randomized Phase II Designs, Clinical Cancer Research, 2009

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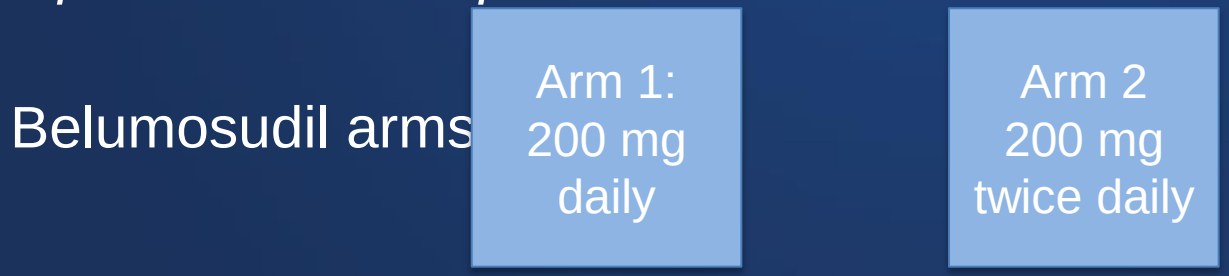
Randomized phase II selection design

Design approach:

- Design each arm as a single arm study
- Select the arm with the higher response rate as the winner.
- Include other endpoints (safety, PROS, etc.) to assess tolerability to patients

Example: Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar Study (Cutler et al, 2021, Blood).

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



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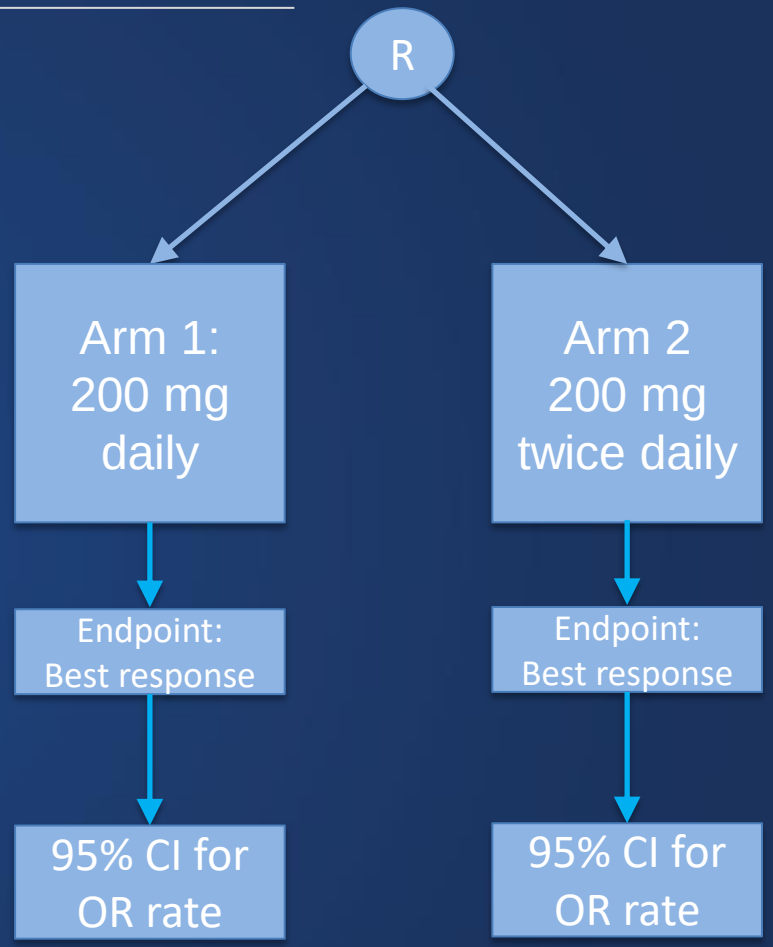
Study design

- Primary outcome: objective response (OR) (partial or complete response)
- 1:1 randomization: 200 mg daily vs. 200 mg twice daily
- Expected OR rate: 55%
- With 66 patients in an arm, each arm has 90% power to exclude 30% OR rate as lower bound.



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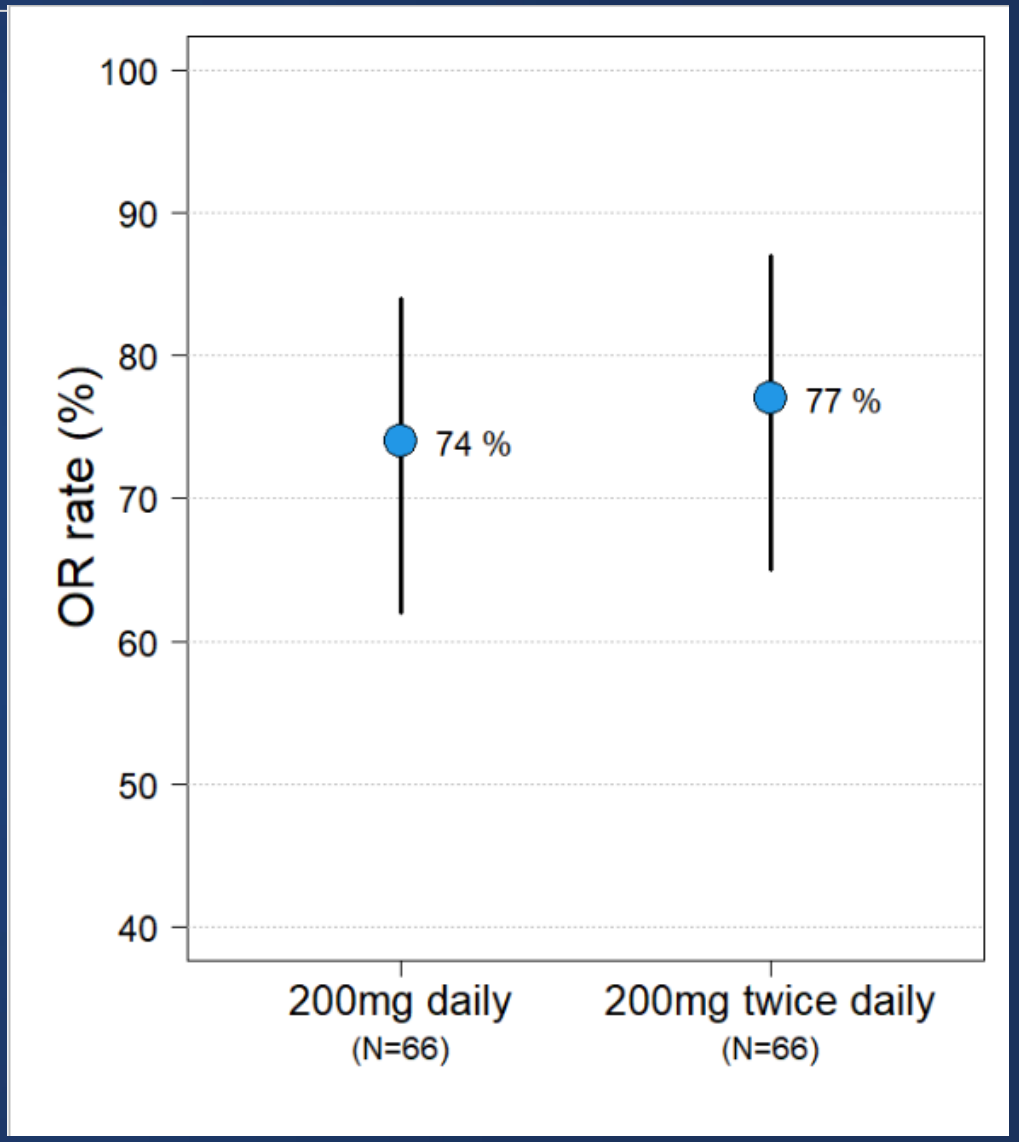
Results

- 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



Confidence in correct dose?

- Statistically: Simon et al (1985) demonstrate that 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 using pick-the-winner approach.
  - Acceptable power
  - Large difference (15%) for this sample size
  - Larger sample sizes allow smaller difference with 90% power
  - Can be extended to more than 2 dose levels

- Practically: What defines correct dose?
  - Consider agent type
  - Efficacy vs. toxicity trade-off
  - Patient tolerability – not always grade 3+ adverse events!
  - 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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Dose optimization in the post-market setting

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Can we optimize doses of already approved drugs?

- Oncologists frequently start at doses lower than those approved (i.e., indicated) due to experience with the toxicity profile in the ‘real world’
- Frequent dose modifications in certain populations

  (e.g., older adults, poor performance status)

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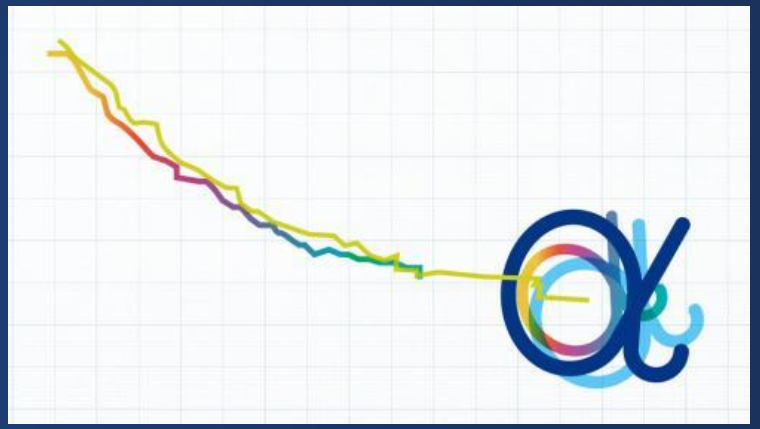
FDA's Project Significant

- Project Significant objectives:
  - Provides a platform to participate, discuss, and advance the science of oncology trial designs.
  - Promotes non-product specific scientific discussions on design and analysis of cancer clinical trials.
  - Fosters collaboration among regulators, professional organizations, industry, academicians, and patients to advance cancer therapies with improved design of cancer clinical trials.
- Collaboration of ASA BIOP Statistical Methods in Oncology Scientific Working Group, the FDA Oncology Center of Excellence, and LUNGevity Foundation, and hosted by ASA
- June 2021 session:
  - In the <u>post market</u> setting:
    - ➢ How can we arrive at an optimal dose?
    - ➢ What clinical trial designs should be considered and are feasible?



Project Significant: Statistics in Cancer Trials

Promoting collaboration in design and analysis of cancer clinical trials

https://www.fda.gov/about-fda/oncology-center-excellence/project-significant-statistics-cancer-trials

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The Optimal Cancer Care Alliance (OCCA)

- **“The Optimal Cancer Care Alliance (OCCA) believes it is a clinical, financial, and ethical imperative to replace current oncology overdosing with optimal dosing. The right amount of medication at the right time reduces toxic side effects, provides the best clinical outcomes and lowers costs.”**
- Led by academic medical oncologists.
- https://optimalcancercare.org/

Drug	Current Dosage	Recommended Dosage
Ibrutinib	420 mg	140 mg
Erlotinib	150 mg	25–100 mg
Dasatinib	100 mg	50 mg
Pembrolizumab	200 mg	2 mg/kg
Abiraterone	1,000 mg fasting	250 mg with food
Lapatinib	1,250 mg fasting	500 mg with food
Pazopanib	800 mg fasting	400–600 mg with food
Nivolumab	Every 2–4 weeks	Every 8–12 weeks
Atezolizumab	Every 2–4 weeks	Every 8–12 weeks
Pembrolizumab	Every 3–6 weeks	Every 8–12 weeks

Adapted from Serritella et al. (2020)

Other Opportunities for Trial Designers and Methodologists

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Common Themes in these examples?

- Flat dose-response relationship
- Low toxicity (relatively)
- Randomization to different dose levels—ended up as dose ranging studies
- Uncertainty about optimal dose, even after hundreds of patients
- Haphazard dose escalation based on MTD paradigm

- These examples highlight the need for uptake of appropriate dose-finding approaches
  - Need designs for a variety of dose-efficacy curves
  - Need to allow for flat, shallow and steep toxicity curves

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Other Areas for exploration and development:
Toxicities measurement

- Mechanisms of action of immunotherapies behave differently for efficacy and toxicity
- Unlike cytotoxics, tolerances differ
  - Patients can tolerate chemo less as time goes on
  - Anecdotal evidence that patients can tolerate (or may even need) higher doses of immunotherapies in later cycles
- Inclusion of toxicities at later time points will be important (Lee; Paoletti; etc)
- **Intra-patient** dose escalation may be more common
- **Symptom patterns** are different in immunotherapies vs. cytotoxic agents

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Areas for exploration and development:
Durability of response

- Some of the most striking data from pembrolizumab and nivolumab trials were durable responses among responders.
- Designs need to accommodate ‘conditional’ inference for duration of response.
- Survival curves (PFS and OS) are characterized by long flat tails.
  - Standard methods for comparisons may be invalid or lack power when proportional hazards are violated

Larkin et al., JCO, Feb 1, 2018. Checkmate 037
Nivo vs. ICC in Patients with advanced melanoma

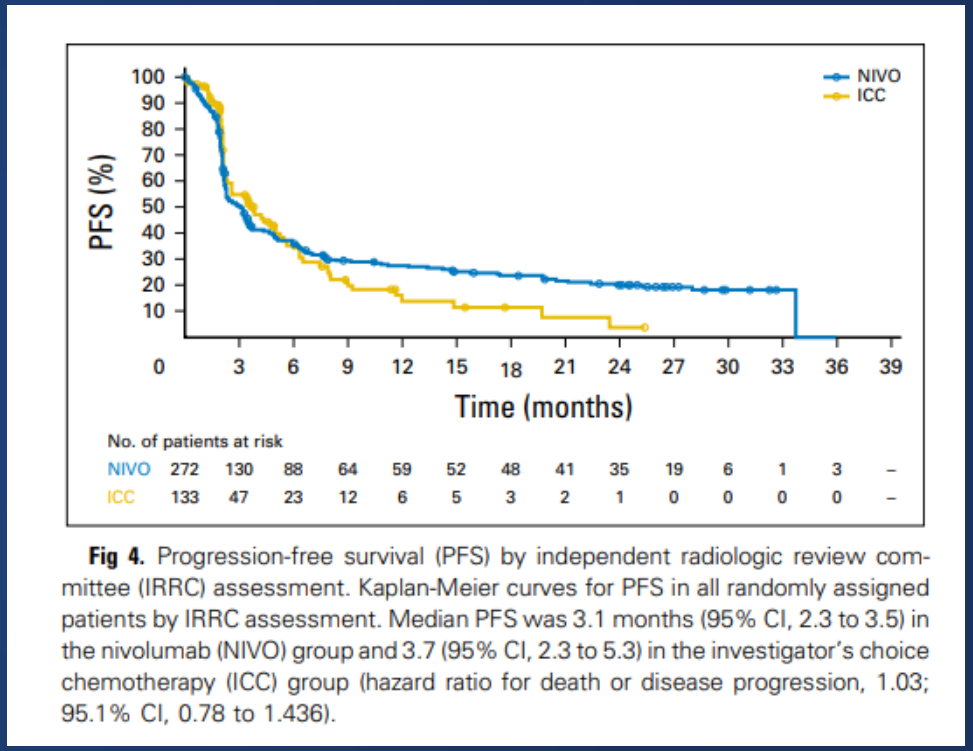

Fig 4. Progression-free survival (PFS) by independent radiologic review committee (IRRC) assessment. Kaplan-Meier curves for PFS in all randomly assigned patients by IRRC assessment. Median PFS was 3.1 months (95% CI, 2.3 to 3.5) in the nivolumab (NIVO) group and 3.7 (95% CI, 2.3 to 5.3) in the investigator's choice chemotherapy (ICC) group (hazard ratio for death or disease progression, 1.03; 95.1% CI, 0.78 to 1.436).

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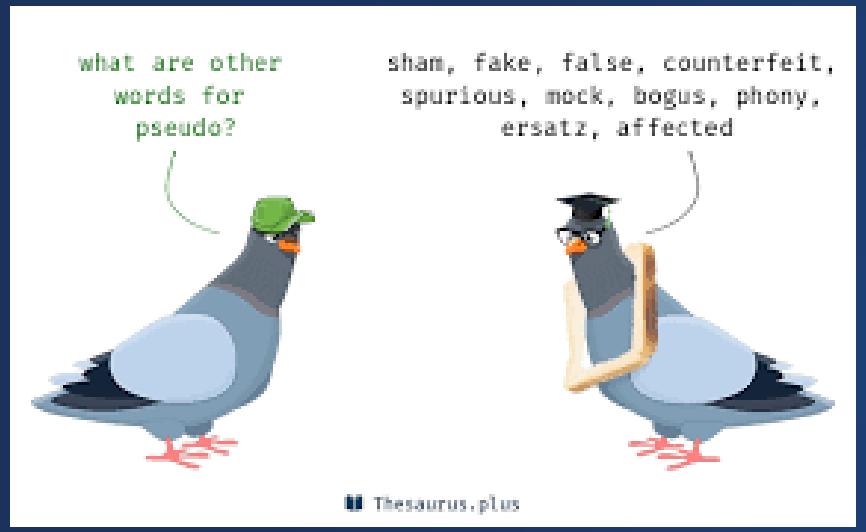
Other areas for exploration and development:

Pseudo-progression



- Pseudo-progressions occur in some in patients treated with immunotherapy and are indicative of patients who may be having greatest benefit.
- Rare, but important!
- What is a pseudo-progression? Increase in tumor size, measured by standard metrics, but is due to something else (e.g., increase in T-cell infiltration in the tumor).
- How to distinguish between true and pseudo-progressions?
- Or, is there **another efficacy** outcome to be considered?

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Areas for exploration and development:

Abandon traditional phase terminology

"Much of what is written about clinical trials tells us what to do. As a result, many investigators, sponsors, and regulators become proficient in standard practice, perhaps to the point that they view it as restrictive. Not as much of the literature explains why we do what is recommended. Knowing only what to do creates patterned thinking, whereas knowing why we do it allows appropriate creative exceptions and coping with atypical circumstances." – Piantadosi, Clinical Trials: A Methodologic Perspective, 3rd Edition (2017)

- Current phase I paradigm in oncology is illogical for targeted and immunotherapies.
- Current three phase paradigm is not flexible enough
- Piantadosi: "some widely used terminology regarding trials is unhelpful" but can be counteracted with alternative terminology to accurately reflect intent of trials.
- What does the label "phase I" tell us about a trial anymore?

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Two main points to make

1. Dose optimization needs to extend beyond safety/tolerability of treatments and incorporate efficacy of treatments, especially for targeted and immunologic anti-cancer agents

2. For many currently approved anti-cancer agents, dose optimization needs to be revisited.

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Key publications

- Shah, Rahman, Theoret, Pazdur. “The Drug-Dosing Conundrum in Oncology—When Less is More,” NEJM, Oct 14, 2021.

- *Early Phase Trial Designs for Targeted Cancer Therapeutics (Ed. Chris Takimoto and Shivaani Kummar)*
  - Chapter “Evolution of Phase I Trials, Past, Present and Future: A Biostatistical Perspective.” E Garrett-Mayer & N O’Connell.

- NCI’s Investigational Drug Steering Committee’s Trial Design Task Force
  - Seamless Designs: Current Practice and Implications for Early Phase Drug Development in Oncology (Hobbs et al.), JNCI, 2019.

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