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  
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My path in statistics

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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.
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
What are the dose finding methods in cancer drug development?

Historical Perspective of Approaches
Traditional Early Phase Drug Development in Oncology

- **Phase 1**: Find the maximum tolerated dose (MTD)
- **Phase 2**: Evaluate efficacy at the MTD
- Toxicty based dose finding
  - Chemotherapies/Cytotoxics
  - “More is better”
  - As dose increases, toxicity increases
  - As dose increases, efficacy increases
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
Traditional Phase I

- Combination drug trials for identifying MTD
  - 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)
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)
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.
Case studies:
Phase I studies missing the optimal dose
Two “Breakthrough” Immunotherapies
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.
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 sizes were 32 and 76, respectively.
  - Both gained breakthrough designation and worked with FDA to expedite development
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.
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
Revisiting dose finding objectives
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 single RP2D as part of a phase I trial? *

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*
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.”

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.
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
  - Wages et al. *Tailoring early-phase clinical trial design to address multiple research objectives*. Cancer Immunology, Immunotherapy (2020)
  - ........
Integrated dose finding design example

1. Dose escalation; Collect efficacy
2. Randomize to dose levels for efficacy outcomes; continue safety monitoring
3. Complete accrual for efficacy outcomes; continue safety monitoring
4. Estimate efficacy parameters among safe doses.

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!
Sequential dose finding approach

Part 1: Toxicity-based dose finding
→ Identify a set of doses with acceptable toxicity

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 phase 1

Similar to traditional single arm phase 2
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

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

Belumosudil arms:
- Arm 1: 200 mg daily
- Arm 2: 200 mg twice daily
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.**
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.”
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
Dose optimization in the post-market setting
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)
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 post market setting:
    - How can we arrive at an optimal dose?
    - What clinical trial designs should be considered and are feasible?
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/

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<th>Drug</th>
<th>Current Dosage</th>
<th>Recommended Dosage</th>
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<tbody>
<tr>
<td>Ibrutinib</td>
<td>420 mg</td>
<td>140 mg</td>
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<tr>
<td>Erlotinib</td>
<td>150 mg</td>
<td>25-100 mg</td>
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<td>Dasatinib</td>
<td>100 mg</td>
<td>50 mg</td>
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<td>Pembrolizumab</td>
<td>200 mg</td>
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<td>Abiraterone</td>
<td>1,000 mg fasting</td>
<td>250 mg with food</td>
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<td>Lapatinib</td>
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<td>Pazopanib</td>
<td>800 mg fasting</td>
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<td>Nivolumab</td>
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<tr>
<td>Atezolizumab</td>
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<tr>
<td>Pembrolizumab</td>
<td>Every 3-6 weeks</td>
<td>Every 8-12 weeks</td>
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Adapted from Serritella et al. (2020)
Other Opportunities for Trial Designers and Methodologists
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
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
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.

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Larkin et al., JCO, Feb 1, 2018. Checkmate 037 Nivo vs. ICC in Patients with advanced melanoma
Other areas for exploration and development:

**Pseudo-progression**

- Pseudo-progressions occur in some 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?
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?
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.
Key publications


- *Early Phase Trial Designs for Targeted Cancer Therapeutics (Ed. Chris Takimoto and Shivaani Kummar)*

- NCI’s Investigational Drug Steering Committee’s Trial Design Task Force
References

References


References


References


Yin J, Paoletti X, Sargent DJ, Mandrekar SJ. Repeated measures dose-finding design with time-trend detection in the presence of correlated toxicity data. *Clinical Trials*, v 14 (6), pp. 611 – 620