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Clinical Trial Design and Statistical Considerations in the Development of IO

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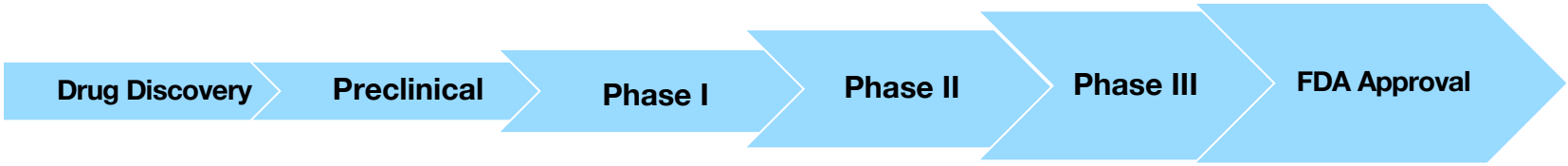
Clinical Trial Phases

Drug Discovery to FDA Approval can take 10-15 years



Evaluation of novel agents typically progresses through a three-phase system of clinical trials in humans

A new treatment that is successful in one phase will continue to be tested in subsequent phases

Clinical Trial Designs in Oncology

Phase I

- Determine drug safety
- Characterize toxicity profile
- Determine maximum tolerated dose (MTD)
- Determine dose for further study
- Pharmacokinetics

Phase II

- Assess initial signal of efficacy
- Disease Specific Tumor Response
  - ~30-60 patients

Phase III

- Gold standard
- Definitive studies
- Randomized Controlled
- Compared with standard of Care (superiority)
- Change clinical practice
- Large sample size

~500-100 patients

Designing any Phase Clinical Trial

- Have a clear purpose and research objective
- Why is the study important?
- Determine the specifics of the patient population
- When to treat (first line or later)
- Determine the number of patients
- Consider feasibility in terms of cost, ‘realistic’ assessment of accrual, study duration
- Will the study be a single center or multicenter trial?

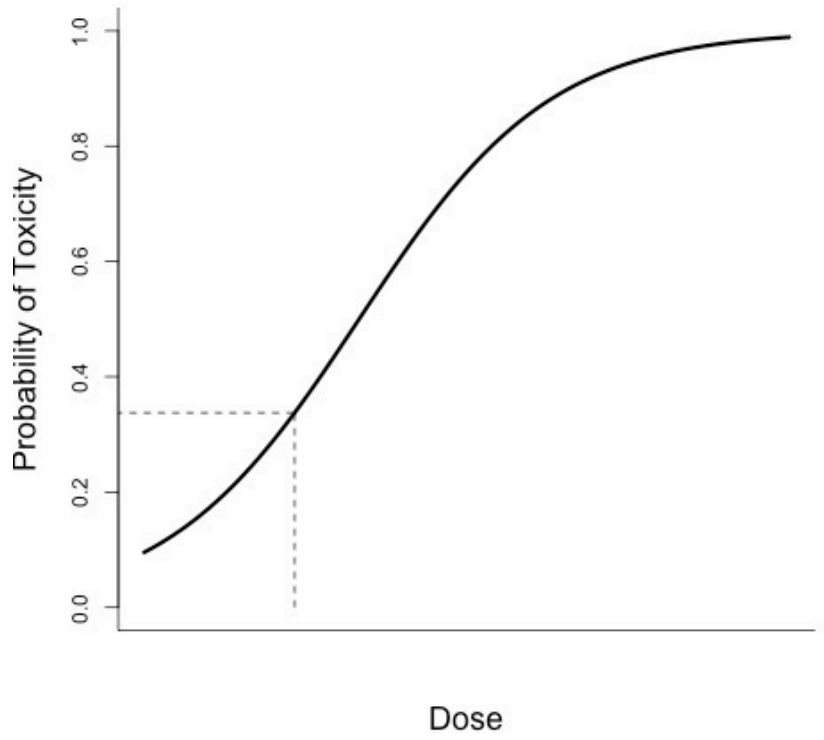
Primary Objectives of Phase I Trials

- Establish safety and tolerability of a novel agent(s)
- Identify Maximum Tolerated Dose (MTD)
- Evaluate Pharmacokinetics
- Determine the recommended phase II dose (RP2D) for further investigation

Usually conducted in patients with advanced disease across all solid tumors

Phase I – Dose Finding Trials

» Cytotoxic Drugs:
assume dose-response
and dose-toxicity
relationships



Phase I - Evaluation of Dose Limiting Toxicity (DLT)

» DLT used to determine maximum tolerated dose (MTD)

» Definition of type and grade of toxicity considered to be dose limiting is determined at the trial design stage

» DLT specification is disease and drug specific

» Whether or not a patient experiences a DLT is the endpoint of interest

» Evaluation of DLTs are usually limited to the first cycle of therapy

Phase I - Evaluation of Dose Limiting Toxicity (DLT)

» Based on the principle that the maximum tolerated dose (MTD) for cytotoxic chemotherapy agents will provide the greatest therapeutic effect

» The RP2D of cytotoxic drugs has been selected based on a dose escalation schema and assumes there is a proportional increase between dose, efficacy and toxicity for any given drug

Goal of Early Phase IO trials

» To demonstrate therapy can produce immunologic effect with the potential to translate to clinical benefit.

» Immunologic endpoints provide a measure of biologic activity that can drive the trial design

Immunotherapy

» Checkpoint inhibitors and other IO agents have no direct effect on malignant cells.

» Instead, immune cells, such as T cells or natural killer cells, indirectly mediate the cytotoxic efficacy of this class of drugs.

» The traditional assumption of a linear relationship between dose and toxicity/efficacy may not hold in this area of drug development.

» Baseline immune competency is critical as well as immune monitoring on treatment

IO Dose Finding Trials

» Immune-related adverse events (irAEs) are toxicities associated with checkpoint inhibitors that are autoimmune or autoinflammatory in origin

» Differ in their severity, grade, and tolerability

» irAEs are expected to occur beyond the first cycle and they allow investigators to observe delayed toxicities

Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378:158–68.

Phase I IO trial may evaluate:

Simple case:

» Single agent /Single schedule

More Complicated cases:

» Dose of combination agents

» IO administered concurrently or sequentially

» 2 or more schedules of administration

» Combination of dose and schedule

» DLT definition (late adverse event)

Phase I IO Studies

- More drug may not be better
- One dose maybe enough to activate the immune system (response/survival benefit)
- Objective of IO phase I trials no longer the MTD
- Under/overdosing is less of a concern since the curve is flat
- Assess the minimum effective dose (MED) or minimum immunologically active dose rather than defining the MTD

Friedman CF, Panageas KS, Wolchok JD. Designing Immunotherapy Clinical Trials in Oncology Clinical Trials, Second Edition. Kelly WK, Halabi S, eds. New York, NY: Demos Medical Publishing; 2018.

Dose Limiting Toxicities in IO Studies

Must reconsider:

- Definition of DLT
- Majority of adverse events are immune related
- Defining a DLT as an event that occurs within the first cycle may not be sufficient
- Heterogeneity of patient population
- Toxicity ordering may not hold

Define Success of a Phase I Trial

- Simple Safety Objective – Success if DLT Rate <33%
- More Complex Objectives – Success if safety and efficacy achieved simultaneously; multiple agents / doses /schedules

Phase I Dose Escalation Designs

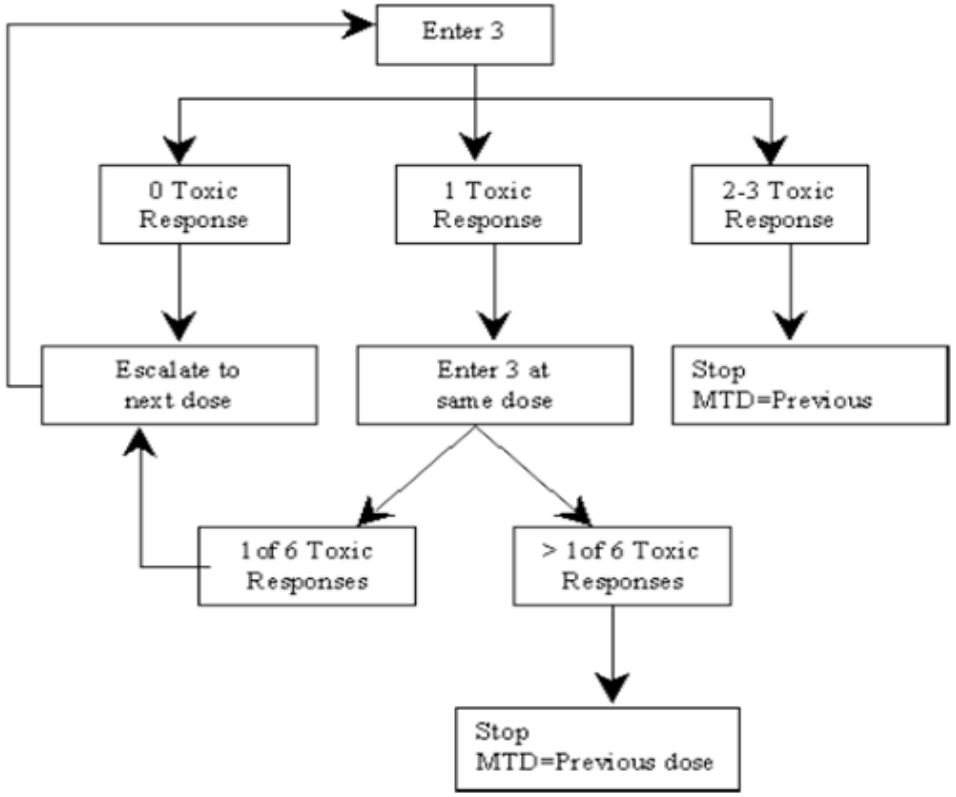
Rule based designs:

- Simple to understand and implement
- Specific rules based on observed events to assign patients to specific dose levels (e.g., 3+3 design)

Model based designs:

- Assume a statistical model of dose-toxicity relationship
- Patients assigned dose levels and determination of MTD is based on the assumed model
- Continual Reassessment Model (CRM)
- Bayesian logistic regression model (BLRM)
- Escalation with overdose control (EWOC)

3 + 3 Phase I Study Design Schematic



http://onbiostatistics.blogspot.com/2015/01/phase-i-dose-escalation-study-design-3.html

Model-based designs

» Model-based designs are more efficient and have a greater chance of treatment at the optimal dose for participants

» More likely to result in a more precise estimate of the MTD

» Requires close collaboration with statistician for input and conduct of the trial, results in model-based treatment assignments (can be viewed as black box approach)

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Model-based designs

- How are model-based designs more efficient?
- Borrow information from dose levels, schedules, disease groups
- More likely to get to the MTD vicinity faster and more accurately
- May result in shorter trial duration and expose less patients to unsafe agents

Friedman CF, Panageas KS, Wolchok JD. Designing Immunotherapy Clinical Trials in Oncology Clinical Trials, Second Edition. Kelly WK, Halabi S, eds. New York, NY: Demos Medical Publishing; 2018.

Model-based dose escalation

- Treat one patient at the best dose based on assumed initial dose toxicity distribution
- Evaluate outcome on that patient: toxicity or not
- Use this information to update the model
- Treat next patient at next dose specified by the model (escalate dose, de-escalate dose or stay at same dose)
- Continue until total target sample size reached (n~25)

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Phase I Studies of IO Combinations

» Development of combination regimens is motivated by synergistic effects leading to greater efficacy than either agent alone.

» The challenge is to increase overall efficacy without significantly increasing toxicity

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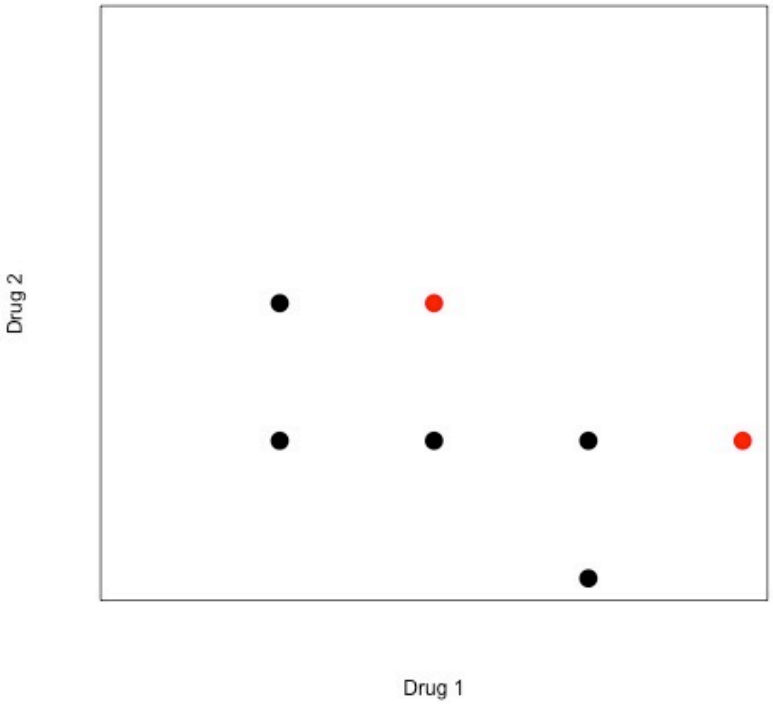
Phase I Studies of IO Combinations

- Are toxicity profiles overlapping?
- Are toxicity profiles additive?
- Is efficacy additive or synergistic?
- Most effective and safest doses of combinations are rarely the same as those of the respective agents used in monotherapy



Phase I Studies of IO Combinations

- A set of predetermined dose-level combinations are typically explored based on the MTD already known from monotherapy as well as preclinical data suggesting synergy
- Results in a toxicity boundary specified by the dose limiting toxicity of drug 1 and that of drug 2
- Multiple dose combinations can result in the same amount of toxicity
- How do you select? Requires evaluation along the boundary/Efficacy evaluation?

Phase I Studies of IO Combinations

If two drug IO combination is being studied

» Dose of one IO agent is escalated while the dose of the second agent is kept fixed until a tolerable combination is achieved

» Overlapping toxicities can limit escalation of the combination to active levels

» It is recommended that combinations be derived with non-overlapping toxicity profiles

Phase I Studies of IO Combinations

» Dose finding trials with combination treatments are complex

» Identification of the MTD of a combination regimen requires careful consideration

» To determine the optimal dose we need to treat sufficient numbers of patients at each dose level on the toxicity boundary

» With multiple drug combinations on the boundary with same toxicity, we may need to determine the combination by efficacy assessment

Phase I Studies – Expansion Cohorts

» Phase I trials frequently include expansion cohorts after the dose escalation phase to:

› further characterize toxicity profile

› gain preliminary evidence of efficacy

› determine the recommended phase II dose (RP2D)

› ~10-20 additional patients in the expansion cohort

Phase II Trials

» Single arm phase II trials are used in earlier drug development with the goal of establishing initial activity of a treatment

» Oftentimes are single institution studies and can suffer from confounding effects such as accrual of patients with better risk profiles

» Failed randomized phase III; lower measures of effectiveness

Mandrekar SJ, Sargent DJ. Randomized phase II trials: time for a new era in clinical trial design. *J Thorac Oncol*. 2010;5(7):932-934. doi:10.1097/JTO.0b013e3181e2eadf

Phase II Trials - Single Arm

» Determine whether the (null) hypothesis of insufficient treatment efficacy can be rejected

» If so, decide treatment is active in the patient population → advocate further testing

» If not, decide treatment is not sufficiently active → halt further testing or change dosing/schedule, combine with other active agents

» “Go/no go” decision

Phase II Trials - Single Arm Two Stage

- Common to have a two-stage design to stop early if therapy is not sufficiently active (futility)
- Interim look after n_1 patients evaluated and then a (potential) final look after N patients are evaluated for response
- Simon's two-stage design (Simon, 1989)
- Optimal design: minimizes the sample size under the null hypothesis (unpromising response rate)
- Minimax design: minimizes the maximum sample size

IO Phase II Trials

» Given the pace at which IO single agents and IO combinations are being studied, single arm phase II trials may not be ideal for evaluating multiple experimental treatments

» Randomized phase II trials can evaluate multiple potential treatments and ensure better patient comparability

Mandrekar SJ, Sargent DJ. Randomized phase II trials: time for a new era in clinical trial design. J Thorac Oncol. 2010;5(7):932-934. doi:10.1097/JTO.0b013e3181e2eadf

Randomized Phase II Trials

- Randomize to multiple parallel non-comparative treatment arms
- Randomized selection or pick the winner design where competing treatment with the best outcome is selected
- No intention to directly compare arms

Randomized screening designs

- Treatment compared against standard of care to obtain early evidence of increased efficacy

Mandrekar SJ, Sargent DJ. Randomized phase II trials: time for a new era in clinical trial design. J Thorac Oncol. 2010;5(7):932-934. doi:10.1097/JTO.0b013e3181e2eadf

Randomized Discontinuation Designs

» All patients treated in first phase

» Patients who respond and progress discontinue treatment

» Patients with stable disease are randomized to continue treatment or receive placebo

Mandrekar SJ, Sargent DJ. Randomized phase II trials: time for a new era in clinical trial design. J Thorac Oncol. 2010;5(7):932-934. doi:10.1097/JTO.0b013e3181e2eadf

Patient Eligibility Criteria – IO Trials

» Patient population defined through eligibility criteria

» Broad categories - localized disease, advanced disease, specify number of prior treatments

» Safety Evaluation - For certain patient groups treatment considered too toxic (e.g. IO combinations)

» Homogeneity group of patients to determine clinical benefit

Patient Eligibility Criteria – IO Trials

- Eligibility criteria for IO derived from cytotoxic chemotherapy trials
- May not be relevant for IO agents
- Expand to include lower performance status, patients with brain metastases or patients with abnormal blood counts
- Exclude those with autoimmune diseases
- Exclude patients on chronic immunosuppressants

IO Responses and Efficacy Assessment

» Response Evaluation Criteria in Solid Tumors (RECIST) are unified set of criteria first implemented to provide a uniform assessment of tumor response to therapy in a clinical trial

» May not be relevant for IO agents

Schwartz LH, Litière S, de Vries E, et al. RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer. 2016;62:132-137. doi:10.1016/j.ejca.2016.03.081

RECIST definitions for tumor response categories

Complete Response (CR):	Disappearance of all lesions
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions
Stable disease (SD):	Disease other than progressive disease, complete response, or partial response
Progressive Disease (PD):	A 20% increase in the sum of the longest diameters of target lesions, unequivocal progression of nontarget lesions, and/or the development of new lesions.

RECIST guidelines are not applicable to all types of cancer. Separate criteria are available for other cancers, such as lymphomas, brain tumors

Schwartz LH, Litière S, de Vries E, et al. RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer. 2016;62:132-137. doi:10.1016/j.ejca.2016.03.081

Immune Related RECIST (irRECIST)

- Atypical response patterns have been well documented initially in patients with advanced melanoma
- Pseudoprogression
- Reflect unique dynamics of Tcell expansion and infiltration
- Delayed effects in IO
- Led to concerns about the use of RECIST and other standardized response criteria and development of irRECIST

Wolchok et al 2009 DOI: 10.1158/1078-0432.CCR-09-1624

Immune Related RECIST (irRECIST)

- Created to capture additional response patterns observed from IO beyond that observed from RECIST and WHO
- irCR, complete disappearance of all lesions whether measurable or not, and no new lesions, confirmed by a consecutive assessment >4 wks from the date first documented
- irPR, decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment >4 wks
- irSD, not meeting criteria for irCR or irPR, in absence of irPD
- irPD, increase in tumor burden ≥25% relative to nadir, confirmation by a repeat, consecutive assessment >4 wks

Wolchok et al 2009 DOI: 10.1158/1078-0432.CCR-09-1624

Early Phase IO Trials Summary

» Oncology trial landscape is changing rapidly with immunotherapies

» Clinical investigators must be aware of unique properties of these agents when designing trials with IO agents

» Dose response relationships may not hold for IO agents

» Toxicity events may occur later and evaluation of tumor response may be observed later in the course of treatment

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Questions