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Clinical Trial Design and Statistical Considerations in the Development of IO

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Clinical Trial Phases

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

- » Phase I
- » Phase II
- » Phase III

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
  - ~25-50 patients

Phase III

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

Introduction

» Cytotoxic drugs work to kill cells while still in the body

» If there is no more treatment in the body, and cancer cells remain, progression and recurrence are likely to occur

» Immunotherapy works differently and may continue to work after treatment

Immune Targeted Agents

- Attack tumors by modulating immune cells
  - NOT tumor cells
- Require functioning immune system
- Do not demonstrate the conventional correlative relationship between toxicity and efficacy
- Baseline immune competency is critical as well as immune monitoring on treatment

Primary objectives of phase I trials have traditionally been

» To establish the safety and tolerability of a novel agent

» Determine the **recommended phase II dose** (RP2D) for further investigation

Evaluation of Dose Limiting Toxicity (DLT)

» Determination of maximum tolerated dose (MTD)

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

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

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

» 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

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

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

Lessons Learned from Early IO Trials

» One dose maybe enough to activate the immune system (response/survival benefit)

» Unique and previously unobserved, immune-related adverse events

» Divergent cycle lengths

» Unanticipated concerns regarding optimal dosing

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 efficacy and dose may not hold in this area of drug development.

Evaluation of IO in a phase I trial may pertain to the evaluation of:

- » Single agent dose
- » Dose of combination agents
- » Administered concurrently or sequentially
- » Schedule of administration
- » Combination of dose and schedule

Phase I – IO Studies

» More drug may not be better

» Objective of IO phase I trials may need to be modified to assess the minimum effective dose (MED) or minimum immunologically active dose rather than defining the MTD

» Determination of a dose that achieves a pre-specified pharmacodynamic (PD) or pharmacokinetic (PK) parameter

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.

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.

Dose Limiting Toxicities in IO Studies

Must Reconsider:

- Definition of DLT
- Limiting evaluation to first cycle of therapy
- Majority of adverse events are immune related
- Defining a DLT as an event that occurs within the first cycle may not be sufficient
- Must specify longer DLT window

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)

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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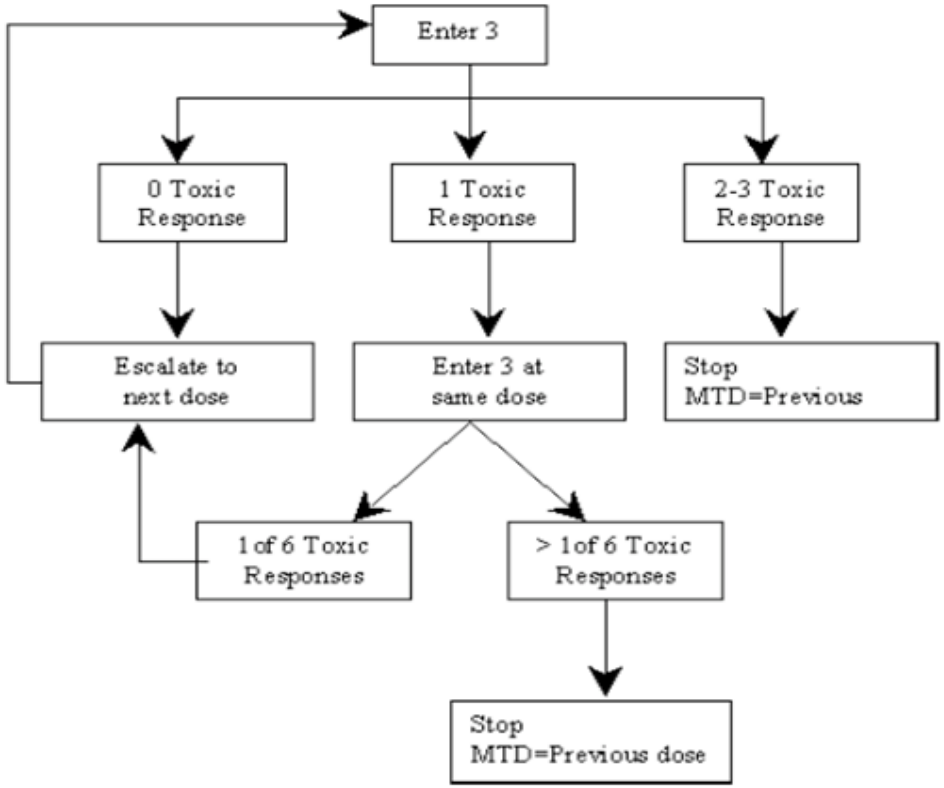
3 + 3 Phase I Study Design Schematic



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

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?

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

» 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

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.

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

» Most effective and safest doses in the combination setting are rarely the same as those of the respective agents used in monotherapy

Phase I Studies – Expansion Cohorts

- Phase I trials frequently include expansion cohorts after the dose escalation phase to:
  - further characterize toxicity
  - gain preliminary evidence of efficacy
  - determine the recommended phase II dose (RP2D)

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

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

Parameter of Interest vs Endpoint

Parameter of Interest **(Output of analysis; summary)**	**Endpoint** **(Data captured for each patient)**
Maximum tolerated dose (MTD)	Occurrence of dose-limiting toxicity *[with further definition of those specific toxicities]*
Objective response rate: proportion of patients with CR or PR	Best overall response (CR, PR, SD, PD) by RECIST criteria
6 month overall survival rate	Overall survival, defined as time from enrollment to death (or last known alive)
Hazard ratio for overall survival	Overall survival, defined as time from enrollment to death (or last known alive)
Mean change in quality of life	Difference in quality of life scores from baseline to a follow-up timepoint *[with further specification of the QL score and the timepoint]*

Early Phase IO Trials

» 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

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Questions