Phase I Trials for Immunotherapy

Howard L. Kaufman, MD

Massachusetts General Hospital

Boston, MA

Disclosures

- I am an employee of Immuneering Corporation
- I serve as a consultant to Replimune, Inc.

Important consideration in Phase I protocol development for immuno-oncology

- Phase I generally used to define drug safety, dosing and PK, but…
- Phase I can help define mechanism of action, be indication-finding, validate biomarker assays, provide early data for rapid approval, provide early information on potential combination approaches; so…
- It is important to define the role of Phase I studies in the larger development pathway for any given agent.

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Is Participation in Cancer Phase I Trials Really Therapeutic?

Jonathan Kimmelman, PhD
STREAM Research Group, Biomedical Ethics/Experimental Medicine, McGill University, 3647 Peel St, Montreal, Quebec, Canada H3A 1X1, Ph: 514 398-3306

Jonathan Kimmelman: jonathan.kimmelman@mcgill.ca

Immunotherapy Phase 1 Clinical Trials

- General consideration in developing Phase 1 clinical trials
  - Study definitions
  - Unique aspects for immunotherapy agents

- Designing phase 1 immunotherapy clinical trials
  - Key elements of the clinical protocol
  - Study and patient monitoring considerations

General Considerations

Phase 1 Immunotherapy Clinical Trials

What is a clinical trial?

- A properly ***planned*** and ***executed*** clinical trial is a powerful experimental technique for assessing the ***safety, mechanism of action*** and therapeutic ***effectiveness*** of an intervention, drug or combination regimen.

Types of Clinical Trials

- Natural History or Population (Cohort) studies
  - Untreated natural history
  - Treated with standard of care (SOC) therapy
- Prevention studies
  - Action studies (“do something”)
  - Agent studies (“take something”)
- Screening and Early Detection studies
  - Assesses methods for detecting cancer in asymptomatic individuals
- Diagnostic studies
  - Evaluates procedures (i.e., Imaging, blood tests) that more accurately diagnose cancer
- Biomarker studies
  - Tests prognostic and predictive markers from blood or tissue; bioshedding
- Quality-of-life and supportive care studies
  - Evaluates impact of intervention on quality of life, psychosocial impact on patients and caregivers
- **Intervention or Therapeutic studies**
  - Evaluates new approaches (drugs, radiation, surgery) or combinations on cancer outcomes
  - Typically occurs in 3-4 phases

What is an investigational product?

- A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial.
- This includes products already approved but being used or assembled (formulated or packaged) in a way different from the authorized form, or when being used in a different indication or to gather new information about an approved agent.

The traditional phases of clinical drug trials

Phase 1
- Safety/Tolerability
- Define MTD
- Pharmacokinetics
- Often First-in-Human

Small N = 8-10

Phase 2
- Determine activity
- Add to safety profile
- Optimize dose/schedule for Phase III

- Moderate N = 100-200

Phase 3
- Confirm clinical benefit
- Drug applied to various stages
- Drug used in combination

Large N = 1,000 – 3,000

Phase 4
- Post-marketing assessment
- May add information on eligibility, long-term safety and clinical impact, etc.

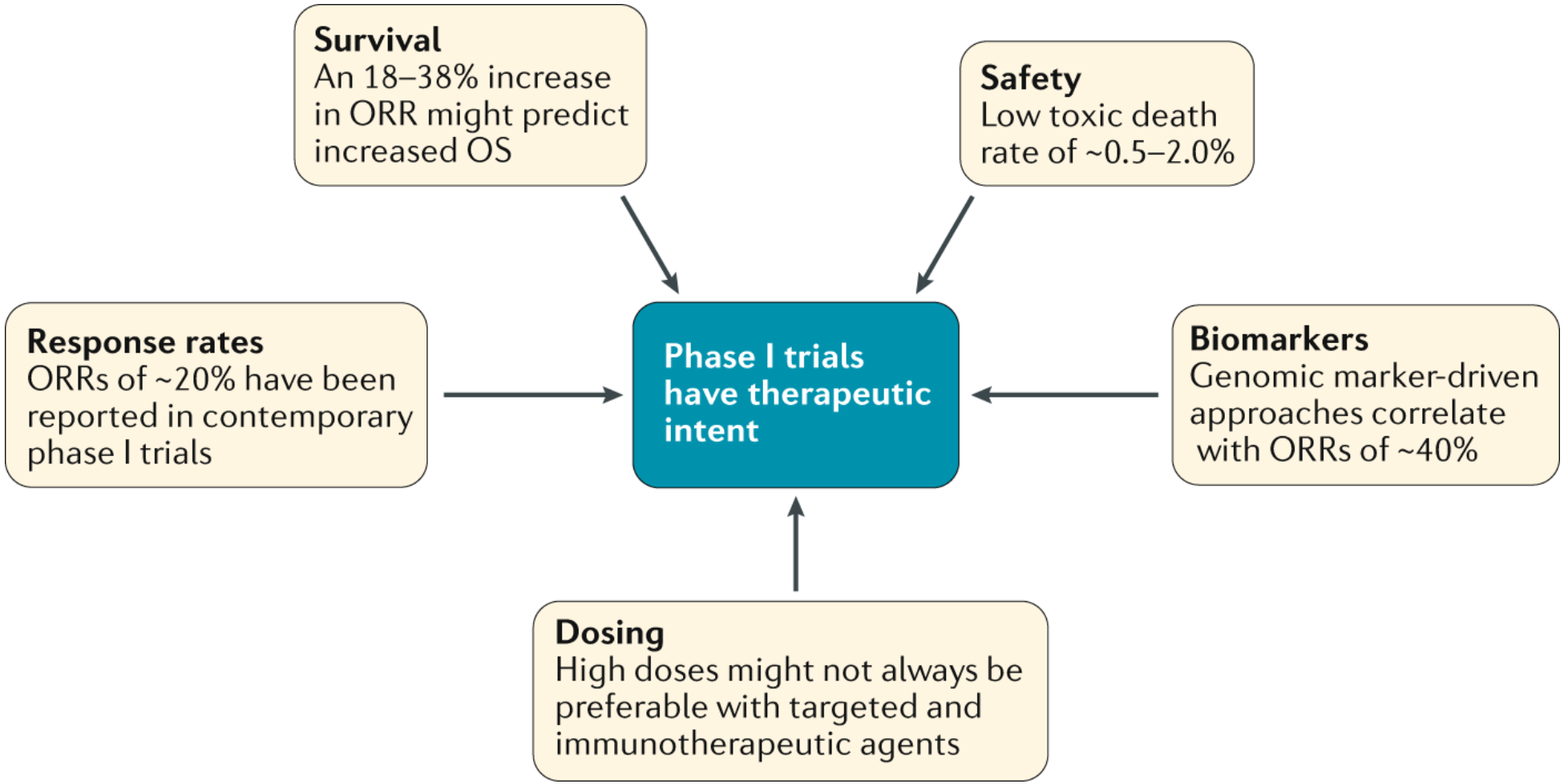
Variable N = 100 - 500

Phase 1 vs. Phase 0 Oncology Trials

	Phase 1	Phase 0
Primary Objective	Establish **toxicity** profile and MTD	Establish dose range that **modulates target**; for use in later phase 1 and 2 trials
Duration of Dosing	Repeat or multiple cycles until disease progression or unacceptable toxicity	Limited dosing (i.e. one cycle only)
Evaluation for therapeutic benefit	Tumor response usually reported	None
Tumor biopsies	Optional	Requited (usually pre- and post-dosing

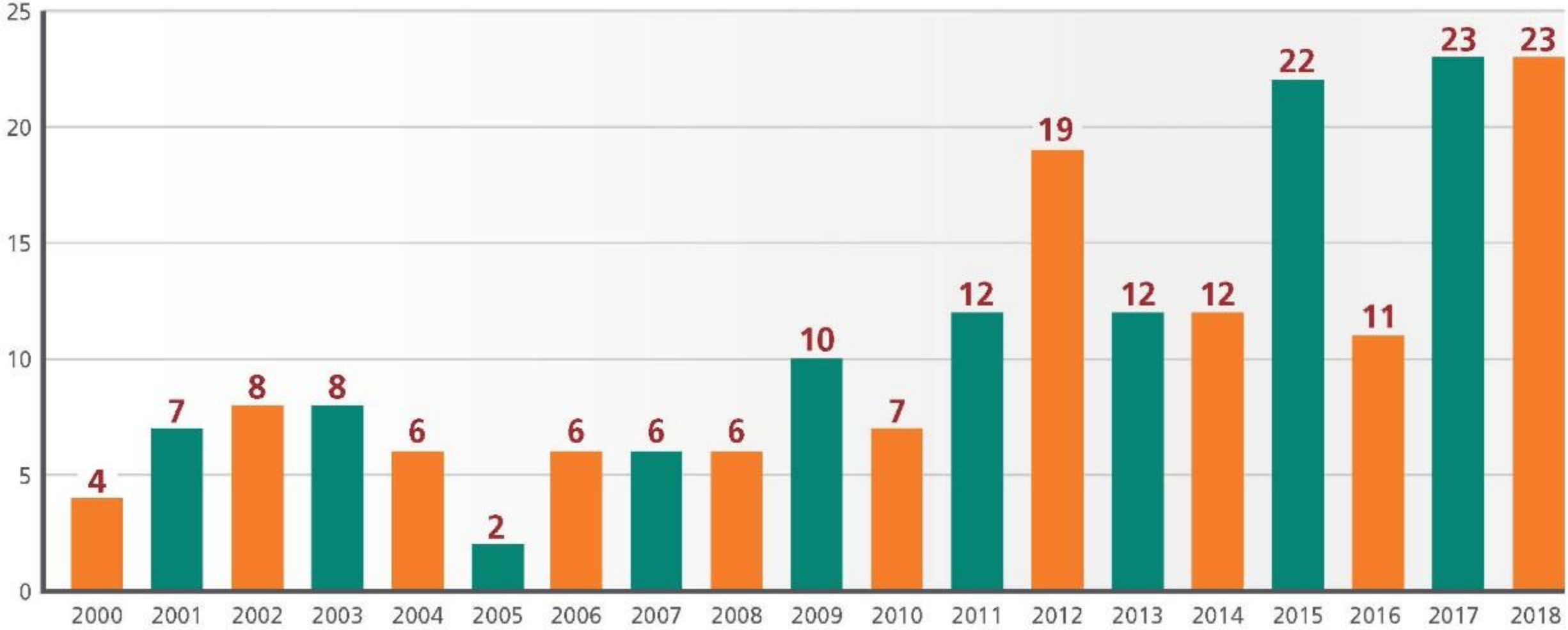
Adapted from FDA guidance document

Phase I studies may produce more than just safety data



Adashek et al. Nature Rev Clin Oncol 2019

ONCOLOGY DRUG APPROVALS BY YEAR



Phase 1 trials as valid therapeutic options for patients with cancer

Series	Period covered	Trials included (*n*)	Patients (*n*)	Agents tested (*n*)	ORR	Grade 5 AEs at least possibly related to drug	Ref.
Estey et al. (1986)	1974–1982	187	NR	54	4.2%	NR	13
Decoster et al. (1990)	1972–1987	211	6,639	87	4.5%	0.5%	14
Horstmann et al. (2005)	1991–2002	460	11,935	NR	10.6%	0.49%;	15
Roberts et al. (2004)	1991–2002	213	6,474	149	3.8%	0.54%	16
Schwaederle et al. (2016)	2011–2013	Biomarker-driven trials of targeted agents: 57	Biomarker-driven trials: 2,655	NR	31.1% (42% in the case of genomic biomarkers)	1.9%	17
		Non-biomarker-driven trials of targeted agents: *n* = 177	Non-biomarker-driven trials: *n* = 10,548		5.1%	NR	
		Non-biomarker-driven trials of cytotoxic agents: *n* = 116			Non-biomarker-driven trials of cytotoxic agents: 4.7%	Non-biomarker-driven trials of cytotoxic agents: 2.2%	
Waligora et al. (2018)	2004–2015	170	4,604	NR	10.29%	2.09%	18
Chakiba et al. (2018)	2014–2015	224	NR	224	19.8%	NR	19

Adashek et al. Nature Rev Clin Oncol 2019
Hamid et al. NEJM 2013

Unique aspects of immunotherapy trials

Variables	Standard Cancer Drugs	Immunotherapy Drugs
Mechanism of Action	Directly kills tumor cells	Indirectly kills tumor cells
Kinetics of response	Rapid	May be delayed
Dosing	Typically dose-response related	May not follow usual dose-response relationship
Eligibility	Excludes major medical conditions and CNS disease	May also exclude autoimmune disease but unclear on CNS disease
Duration of treatment / Endpoint evaluation	Typically until disease progression or unacceptable toxicity	Pseudoprogression and hyperprogression have been reported
Adverse events	Usually early onset; on-target effects	May exhibit delayed onset; may include off-target effects
Regulatory considerations	Follows routine IRB approval	May require additional approvals (e.g. IBC)

Considerations in planning a phase 1 study

- Is the study scientifically and clinically important?
  - Strong scientific justification
  - Addressing an unmet medical need or condition
- Do you have the resources to conduct the trial?
  - GMP manufacturing of investigational product
  - Clinical investigation support (research nurse, data management, statistics)
  - Institutional infrastructure (IRB, IBC, etc.); support for biospecimen collection/processing
- Do you have the time to devote to conducting a clinical trial?
- Do you have an adequate patient population?
  - Consider competing studies and local standards of care and referral patterns
- Is there financial support for the study?
  - Industry sponsorship
  - NCI support
  - Institutional support

The Principal Investigator (PI)

- Physician leader of the research team
- Understands the science of the protocol and has clinical expertise to manage patients and adverse events
- Accountable for maintaining the scientific integrity of the protocol and regulatory and reporting compliance
- Responsible for all aspects of the trial and for following GCP (Good Clinical Practices) guidelines
- May consider including expert in tumor immunology for IO studies

Logistical Requirements

- Locked drug storage
  - Refrigeration vs. freezer
  - Biohazard hood preparation
- Maintain/access to medical records
- Maintain/access regulatory binder
- Dedicated space for research work (dedicated Phase 1 space)
- Monitor work area (conference room)
- Specimen and study material storage

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Phase 1 Clinical Trials Design

The major method of clinical research: The clinical protocol

- Establishes the key question(s) to be investigated
- Provides guidance for all aspects of human subject management
- Prospectively defines the study objectives and endpoints
- Roadmap for investigators on how to treat and manage patients
- Lists potential safety concerns and describes how patients will be monitored and safety information reported to authorities
- Adherence to written clinical protocol is mandatory
  - Ensures consistency across patients and study sites
  - Allows ethical review and approval of research with experimental agents
  - Provides quality data for regulatory review

Clinical Protocol Elements

- Title
- Summary
- Introduction or Background
- Study Objectives
- Patient Population (Eligibility and Exclusion Criteria)
- Study Design
- Study Endpoints and Methods of Assessment
- Drugs
- Drug and Study Stopping Rules
- Adverse Events Definition and Reporting
- Statistical Analysis
- Ethics and Regulatory Requirements
- Data Handling and Integrity
- Informed Consent
- Appendix

The protocol title

- Very important
- Spend time developing the title
- Should describe the main elements of the clinical study
  - Single center vs. multi-institutional (global)
  - What drugs/agents/regimen being tested (include placebo, if applicable)
  - What patients and diseases are being treated
  - Study phase (or outcomes being tested)
  - Study design (randomized vs. single arm, active control vs. placebo, etc.)
- Other elements on the title page are also important
  - Who is conducting the study (sponsor, PI, study sites)
  - Contact information for key study personnel
  - Relevant study numbers (IND, etc.)

Study Summary

- Helpful for rapid review of the clinical protocol
- Should be brief
- Should include several key elements
  - Objectives
  - Sample size
  - Study duration
  - Key eligibility and exclusion
  - Drugs to be used
  - Study design
  - Statistical analysis plan
- Should be aligned with protocol texts

Study Objectives

- Primary endpoint
  - Provides prospective definition of the major study outcome
  - Ideally should be limited to one or only a few endpoints
- Secondary objectives
  - Allows collection of important data to answer additional questions
  - Endpoints usually strictly defined; likely outcome statistically pre-determined
  - Likely to influence further drug development
  - Should not detract from the primary objective
- Exploratory objectives
  - Allows additional data collection
  - Typically is not as rigorous in definition or conduct
  - May or may not influence further drug development
  - Often used when expected outcome is unknown

Major Goals of Phase 1 clinical studies

Toxicity Profile

- Define dose-limiting toxicity (DLT)
- Define the maximum tolerated dose (MTD)
- Begin definition the adverse events and safety profile of the agent(s)

Pharmacokinetic Profile

- Drug absorption
- Drug distribution
- Metabolic pattern
- Drug excretion

*Clinical activity may be observed, but is not the primary objective of Phase 1 studies

Major Goals of Phase 1 IO clinical studies

Toxicity Profile

- Define dose-limiting toxicity (DLT)
- Define the ***optimal*** tolerated dose (OTD)
- Begin definition the adverse events and safety profile of the agent(s)
- ***May require longer follow-up for delayed events to be seen***

Pharmacokinetic Profile

- Drug absorption
- Drug distribution
- Metabolic pattern
- Drug excretion
- ***IO may require evidence of immune response, cytokine release, T cell persistence, etc.***
- ***For biologic agents, agent shedding and transmission***

*Clinical activity may be observed, but is not the primary objective of Phase 1 studies

Other Objectives in Phase I Clinical Trials

- Evaluate new treatment schedule
- Evaluate new drug combination strategies
- Evaluate new multi—modality regimens
- Define initial clinical response patterns
- Explore potential indications for new drugs
- Explore biomarker associations with prognosis and confirming the proposed mechanism of action (MOA)

Introduction or Study Background

- Provides information on why the study is being performed
- Includes background on the disease under study and unmet medical need being addressed
- Contains pre-clinical data and any existing clinical data documenting agent safety and efficacy
- Should include alternative options and justification for study and study design
- Must contain relevant and accurate references
- Written at a level where non-oncology physicians can understand

Patient Population: Eligibility Criteria

- For phase 1 this is usually small (10-30; <100)
- Must consider whether to include all cancer patients or limit to specific cancer(s)
- Must define prior therapy status of subjects
  - Typically exhausted all standard therapy (may differ if combination being considered)
  - Should define refractory (e.g., confirmed PD; duration, etc.)
- Must define adequate organ function for participation
  - Hematologic, hepatic, renal function
  - May also consider other organ system function, e.g. CNS function, etc.
- Must define adequate performance status for participation

Patient Population: Exclusion Criteria

- Define patients that are not eligible based on safety concerns or situations where patients are unlikely to respond
- CNS disease
- Autoimmune disorders
- Prior exposure to hepatitis B and C
- Prior exposure to HIV
- Chronic immunosuppression; corticosteroid use; transplant recipients
- Prior vaccinations
- Co-morbid medical conditions and psychological issues
- Special populations (children, pregnant women, prisoners, etc.)

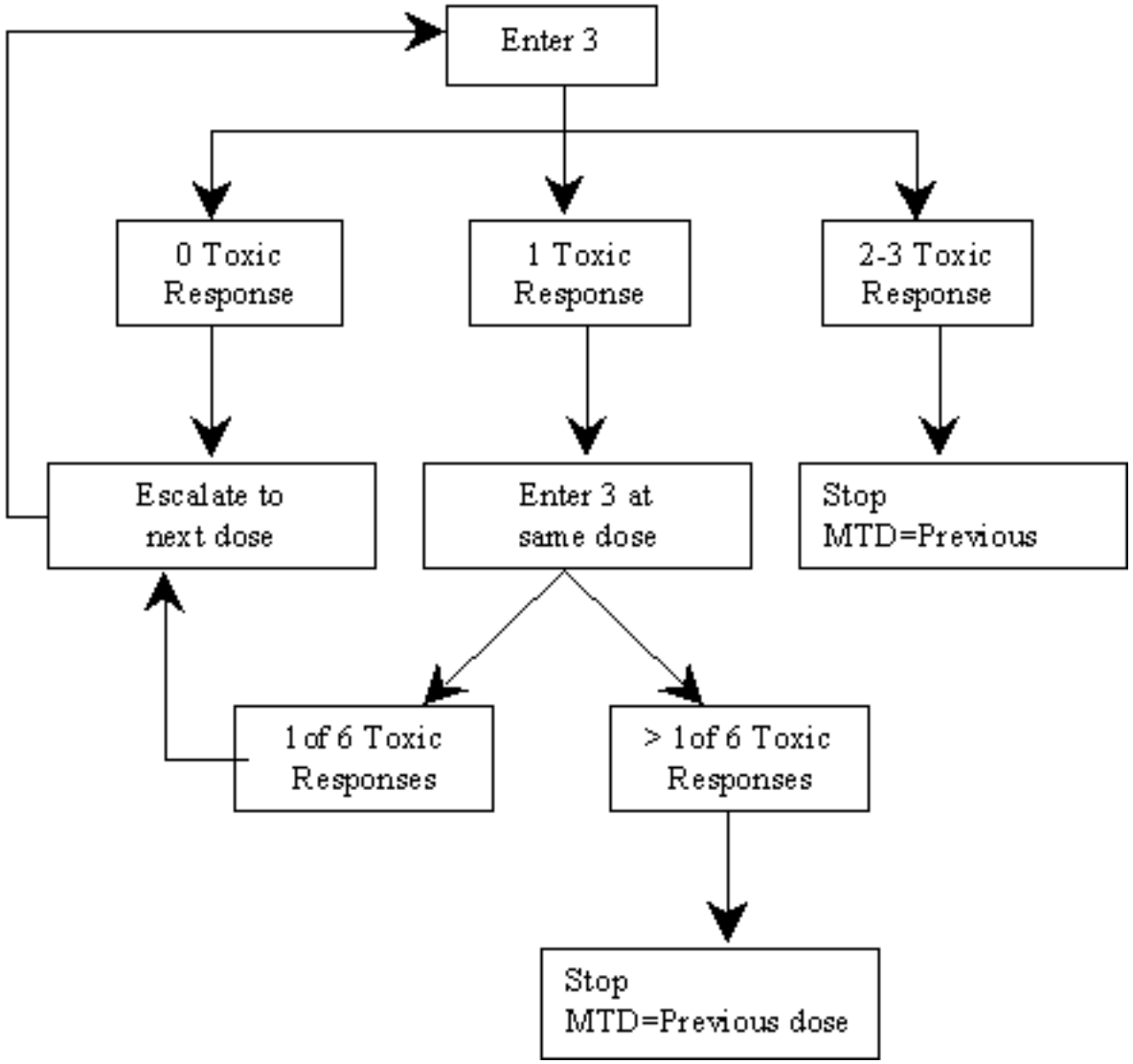
Eligibility Issues Related to Immunotherapy

Inclusion Criteria	Considerations
CNS Disease	• Since IO may have activity in the CNS, consider including such patients • Since IO takes longer for anti-tumor activity may exclude these patients
Prior Therapy	• No life-threatening events on prior immunotherapy within drug class • Fully recovered from any prior immune-related adverse events
Autoimmune Disorders	• IO may exacerbate underlying autoimmunity • Autoimmunity may identify patients more likely to respond
Immunosuppression	• Patients on chronic immunosuppression or populations who are suppressed (e.g. transplant recipients) should have clear criteria for eligibility/exclusion
Endocrine Function	• Baseline thyroid function studies recommended
Cardiac Function	• Baseline troponin recommended but follow-up and management not defined
Pulmonary Function	• Generally excludes ILD, prior pneumonitis or radiation-induced injury • Baseline p02 ≥ 92% on room air

Common **study designs** for phase 1 trials

- Algorhythm-based designs, such as standard 3+3 are most common
- Typically open-label, single arm, non-randomized
- Start at low dose and escalate in cohorts of 3 subjects
- Add additional 3 subjects, if one DLT is observed
- Pre-defined MTD at highest dose; or next lower dose where 2 DLTs occur
- Allows rapid dose finding
- May require adaptation if combination regimen is being assessed

Standard 3+3 Dose Escalation Design



Dose escalation design issues

- Starting dose
  - 1/10th the lethal dose in the most sensitive animal model (dose where 10% of animal die)
  - Unlikely to cause significant toxicity
  - Pediatric doses often begin at 80% of the adult MTD
- Escalation criteria
  - Use modified Fibonacci scheme
  - Logrhythm dose escalation (e.g. for oncolytic viruses)
- Delay and Stopping rules
  - May wait for follow-up period to assess toxicity prior to dose escalation
  - Pre-define AE criteria for treatment discontinuation and study discontinuation

Classic Modified Fibonacci Dose Escalation Scheme

% Increase Above Preceding Dose:

Level 1: Starting dose

Level 2: 100% increase from Level 1

Level 3: 67% increase from Level 2

Level 4: 50% increase from Level 3

Level 5: 40% increase from Level 4

Levels 6+: 33% increase from Level 5+

Alternate Phase 1 Study Designs

- Accelerated designs
  - 1 subject enrolled per dose level until one drug-related grade 2 AE occurs
  - Then resume standard 3+3 design
- Up/Down designs
  - Observe one or two patients
  - If no toxicity, escalate up; If toxicity, de-escalate down
- Intra-patient dose escalation
  - Once a dose level is determined to be safe (no DLTs), the subject can escalate to the next dose level
  - May be useful when prior exposure mitigates toxicity (e.g. seroconversion in oncolytic virus studies)

Common Phase 1 Study Endpoints

- Safety and Tolerability
  - Dose Limiting Toxicity
  - ≥ Grade 3 non-hematologic AEs
  - Grade 4 hematologic AEs (neutropenia > 5 days)
  - May also include criteria for immune-related AEs
- Define the maximum tolerated dose (MTD)
  - Highest dose level at which ≤1/6 patients develop a DLT
- Pharmacokinetics
  - Drug biodistribution, metabolism and excretion
  - Immune products may also determine immune response, cytokine release, etc.
  - Biologic products may also evaluate agent clearance and transmission

Study Endpoints

- For most phase I studies, this includes safety profile, defining the MTD and pharmacokinetic analyses
- May also include exploration of clinical activity and confirmation of mechanism of action (e.g., biomarker analyses)
- If clinical endpoints being collected, need to define the method
  - Objective response rate (most common for phase 1)
  - Progression-free survival
  - Time-to-progression
  - Overall survival
  - Landmark survival

"exploratory"

RECIST or immune-related response criteria?

TABLE 1. RECIST Criteria[1]

Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (Note: The appearance of 1 or more new lesions is also considered progression).
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Immune-Related Response Criteria

New, measurable lesions (≥ 5 × 5 mm)	Incorporated into tumor burden
New, nonmeasurable lesions (<5 × 5 mm)	Do not define progression (but preclude irCR)
Non-index lesions	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in 2 consecutive observations not less than 4 weeks apart
PR	≥ 50% decrease in tumor burden compared with baseline in 2 observations at least 4 weeks apart
SD	Neither a 50% decrease in tumor burden compared with baseline nor a 25% increase compared with nadir can be established
PD	At least 25% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart

irCR = immune-related response criteria; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

Hoos A, et al. *J Natl Cancer Inst*. 2010;102:1388-1397[7]; Wolchok JD, et al. *Clin Cancer Res*. 2009;15:7412-7420.[8]

Other Study Endpoint Criteria for Immunotherapy Trials

Table 1 Features of criteria for immune-related responses

Features	irRC	irRECIST	iRECIST	imRECIST
Source	Wolchok 2009	Nishino 2013	Seymour 2017	Hodi 2018
Model based on	WHO criteria	irRC & RECIST 1.1	RECIST 1.1	irRC & RECIST 1.1
Dimension	Two	One	Same as irRECIST	Same as irRECIST
Progressive disease definition	25% increase from the nadir	20% increase from the nadir	20% increase from the nadir; results in unconfirmed progressive disease; confirmation is necessary for confirmed progressive disease	Same as irRECIST
New lesion	The presence of new lesion(s) does not define progression; the measurements of the new lesion(s) are included in the sum of the measurements	Same as irRC	The presence of new lesion(s) does not define progression; the measurements of the new lesion(s) are not incorporated in tumor burden	Same as irRC
Confirmation	4 weeks	4 weeks	4 weeks; no longer than 8 weeks	4 weeks
Development cohort	Melanoma treated with ipilimumab	Advanced melanoma treated with ipilimumab	Consensus base	Advanced NSCLC and mUC treated with atezolizumab
Outcomes of development cohort	OS	irRC response	Not applicable	OS

irRC, immune-related response criteria; irRECIST, immune-related response evaluation criteria in solid tumors, iRECIST, immune response evaluation criteria in solid tumors; imRECIST, immune-modified response evaluation criteria in solid tumors; WHO, World Health Organization; NSCLC, non-small cell lung cancer; mUC, metastatic urothelial carcinoma; OS, overall survival.

Kataoka and Hirano Ann Transl Med 2018

Which criteria should be used?

Considerations:

- Depends on anticipated mechanism of action
- Has important implications for further development
- May collect both standard and immune-related RECIST
- May use standard RECIST but allow treatment beyond progression
- Helpful to think about how phase 2 and 3 trials might proceed (e.g., what data will be needed to power these studies?)

Caveats:

- irRC allows for pseudo-progression
- irRC may overestimate true ORR
- irRC has NOT been validated
- Unclear if standard and irRC results in significant differences

A word about imaging

- Response endpoints usually depend on imaging
- Must consider the type of imaging and timepoints for evaluation
- Using SOC timepoints and imaging modalities simple and common
  - Whole body CT scans (chest, abdomen, pelvis and other sites of disease)
  - MRI brain
  - PET may be helpful but usually not used (except as exploratory study)
  - Earlier and/or more frequent imaging allows more opportunity to see a response
- Some tumors may be challenging to monitor
  - Can use biopsy for confirmation (e.g., melanoma, CSCC)
  - Consider biomarker analyses, if validated
- Important point to discuss with regulatory authorities

Drugs

- Section that describes the experimental agents in detail
- Includes information of drug storage, preparation, administration and destruction
- Can promote any additional information (e.g., cell therapy, oncolytic viruses)
- Consider adding detailed information to the appendix

Drug and Study Stopping Rules

- Provides details on when to hold or stop treatment in an individual subject
  - Disease progression (should be confirmed); problematic for agents known to induce pseudo-progression
  - Change in clinical performance status
  - Achieving complete response
  - Unacceptable toxicity (should be clearly defined)
- Provides details on when to stop the study
  - Serious adverse events, including death
  - Futility endpoint is met
  - Sponsor decision

Adverse Events

- Includes definition of adverse events to be reported in a study
- Includes how to report and when to report
- Need rules for immune-related adverse events (irAEs)
  - Generally follows standard clinical pathways
  - May adjust depending on how experimental drug(s) work
  - Clear rules needed for resuming experimental therapy
- Need rules for corticosteroid management of irAEs
  - Usually allowed for irAE management
  - Can include management guidance

Statistical Analysis

- Critical component of all clinical trials, including phase 1
- Sample size justification
  - Immunotherapy studies should consider inter-patient variability in immune response(s)
  - May need to adjust if combination being tested (monotherapy data vs. combination)
- Guidelines for reporting adverse events (e.g., descriptive, means/medians, etc.)
- Guidelines for secondary and exploratory analyses
  - Defining endpoints
  - Reporting definitions
  - Summary of how decisions will be made (go/no go)

Ethical and Regulatory Requirements

- Must ensure ethical and IRB approvals are obtained prior to starting
- May need to consider other committees
  - Institutional biosafety committee (IBC)
  - Radiation safety committee
  - Cancer center committee
- Opportunity to collect additional supportive data for regulatory review
  - Quality-of-life questionnaires
  - Patient-reported outcomes
  - Biomarker analyses

Appendix

- Place in the protocol for additional/clarifying information
- Can include guidelines for response assessment, adverse event management, biomarker collection and processing, etc.

Limitations of Phase 1 Clinical Trials

- May not have clinical benefit to participating patients
- Initial patients may be treated at sub-therapeutic doses
- Accrual may be slow (needs healthy but advanced cancer patients)
- Toxicity profile may be influenced by prior therapy
- Inter-patient variability
- Imperfect assessment of MTD
- Studies may end early limiting late or chronic effects of treatment from being documented

Phase 2 Primary Objectives

- Evaluation of clinical activity (not clinical benefit)
- Further safety assessment (at MTD)
- Uses homogeneous population
- Patients need to have measurable disease
- May limit number of prior treatments
- May be single arm or randomized

Basic Elements of Informed Consent

- Description of clinical investigation
  - Statement that the study involves research
  - Explanation of the purpose of the study
  - Description of study procedures and duration
- Risks and discomforts
- Potential benefits, if any
- Alternative procedures or treatments
- Confidentiality
- Compensation and Medical Treatment in Event of Injury
- Institutional contacts
- Voluntary participation

Other Elements of Informed Consent

- Unforeseeable risks may be possible
- Reasons why patients may be involuntarily terminated from study
- Any additional costs to subjects
- Consequences of subject decision to withdraw from study
- Statement that significant new findings will be provided to subjects
- Number of subjects to be enrolled

Informed Consent Elements Unique for Immunotherapy Agents

- Management of immune-related adverse events
  - Include implications of continuing or discontinuing study treatment
  - Potential for long-term toxicity
- Treatment beyond progression
  - May be beneficial and included in some protocols
  - FDA prefers re-consenting with any available data supporting continued treatment

Special considerations in immunotherapy Phase 1 studies

Phase 1-2 studies

Provides rapid advancement from phase 1 into phase 2

Does not allow review of data and amendment of clinical design or plan; may impact indications

Combination drug studies

May be appropriate for various regimens (i.e., scientifically justified)

Challenging to develop and requires close discussion with regulators; component analysis

Depends on whether one or both agents are experimental or SOC

Can keep standard agent at fixed dose and escalate experimental agent only

Need to consider/anticipate any additive toxicity that may occur

Active biological agents

Oncolytic viruses must include bioshedding studies, transmission surveillance

Cell therapies require special logistical considerations and site expertise

May require long-term monitoring of patients (e.g. cell persistence, viral clearance)

Biomarker integration

Important to support MOA of agents/regimens

May be mandatory or optional

Should be as standardized and validated as possible

Study Budget

Invoiceable Items

- Personnel
- Study Events
  - Screening activities
  - Physician visits
  - Blood work
  - Imaging
  - Drugs
  - Drug administration
  - Biomarker collection and processing
  - Clinical data collection
- Data Management
- Data Storage
- Data Analysis
- Safety
- Regulatory Management

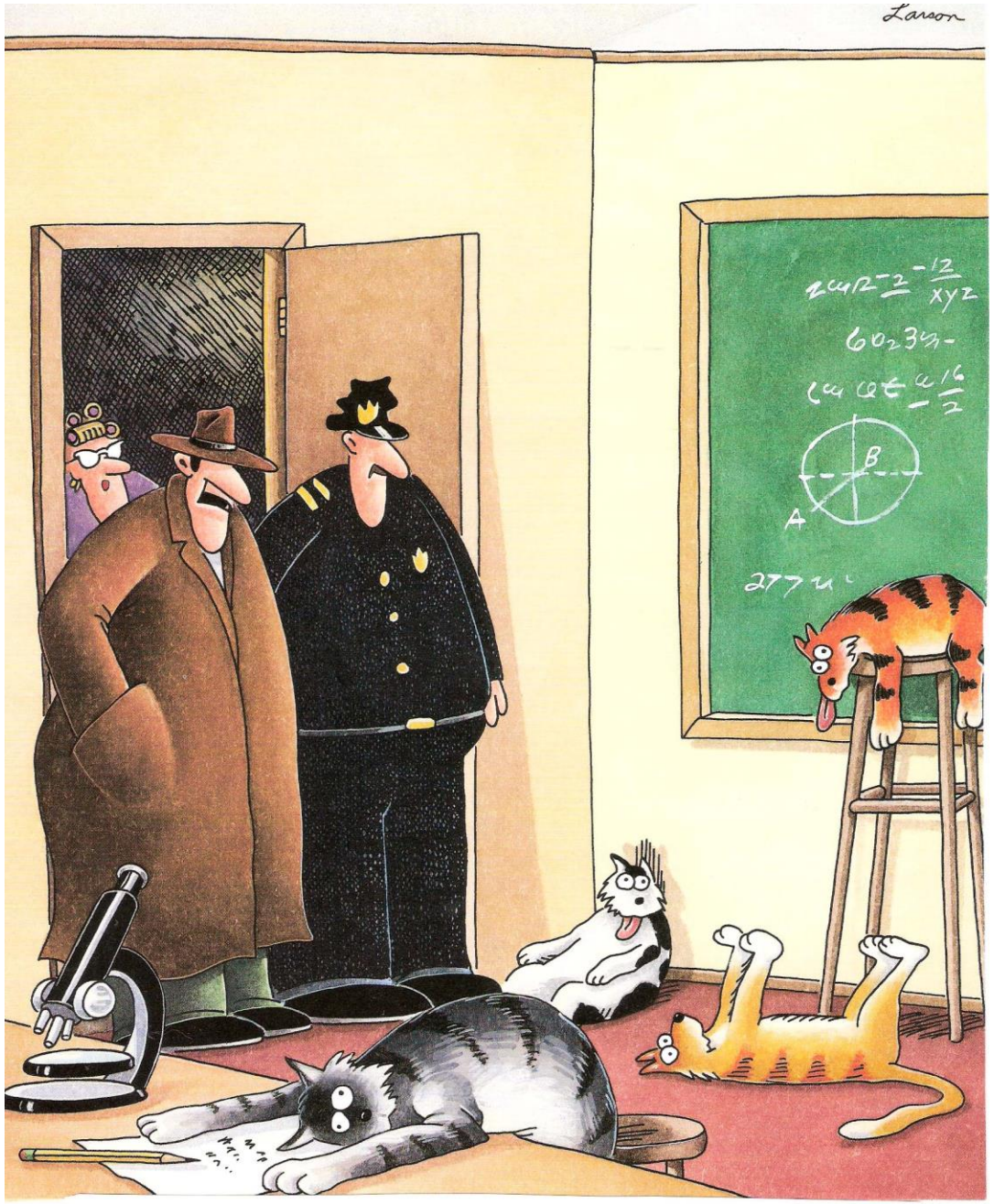
Funding Sources

- Industry
- NCI
- Institutional
- Professional Societies
- Private Foundations
- Healthcare Insurers

Websites

- FDA IND application
- FDA Guidance: *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*
- FDA Guidance: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Questions?



"Notice all the computations, theoretical scribblings, and lab equipment, Norm. … Yes, curiosity killed these cats."