Phase I Trials for Immunotherapy

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Disclosures

• I am an employee of Immuneering Corporation
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, conduct required ancillary tests (i.e., viral shedding), 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.
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 design and patient monitoring (endpoint) considerations
General Considerations
Phase 1 Immunotherapy Clinical Trials
What is a clinical trial?

Definition of 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/or predictive markers from blood or tissue

- **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 trials as valid therapeutic options for patients with cancer

<table>
<thead>
<tr>
<th>Series</th>
<th>Period covered</th>
<th>Trials included (n)</th>
<th>Patients (n)</th>
<th>Agents tested (n)</th>
<th>ORR</th>
<th>Grade 5 AEs at least possibly related to drug</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estey et al. (1986)</td>
<td>1974–1982</td>
<td>187</td>
<td>NR</td>
<td>54</td>
<td>4.2%</td>
<td>NR</td>
<td>12</td>
</tr>
<tr>
<td>Decoster et al. (1990)</td>
<td>1972–1987</td>
<td>211</td>
<td>6,639</td>
<td>87</td>
<td>4.5%</td>
<td>0.5%</td>
<td>12</td>
</tr>
<tr>
<td>Horstmann et al. (2005)</td>
<td>1991–2002</td>
<td>460</td>
<td>11,935</td>
<td>NR</td>
<td>10.6%</td>
<td>0.49%;</td>
<td>12</td>
</tr>
<tr>
<td>Roberts et al. (2004)</td>
<td>1991–2002</td>
<td>213</td>
<td>6,474</td>
<td>149</td>
<td>3.8%</td>
<td>0.54%</td>
<td>12</td>
</tr>
<tr>
<td>Schwaederle et al. (2016)</td>
<td>2011–2013</td>
<td>Biomarker-driven trials of targeted agents: 57</td>
<td>Biomarker-driven trials: 2,655</td>
<td>31.1% (42% in the case of genomic biomarkers)</td>
<td>1.9%</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-biomarker-driven trials of targeted agents: n = 177</td>
<td>Non-biomarker-driven trials: n = 10,548</td>
<td>5.1%</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-biomarker-driven trials of cytotoxic agents: n = 116</td>
<td>Non-biomarker-driven trials of cytotoxic agents: 4.7%</td>
<td>Non-biomarker-driven trials of cytotoxic agents: 2.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Unique aspects of immunotherapy trials

<table>
<thead>
<tr>
<th>Variables</th>
<th>Standard Cancer Drugs</th>
<th>Immunotherapy Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>Directly kills tumor cells</td>
<td>Indirectly kills tumor cells</td>
</tr>
<tr>
<td>Kinetics of response</td>
<td>Rapid</td>
<td>May be delayed</td>
</tr>
<tr>
<td>Dosing</td>
<td>Typically dose-response related</td>
<td>May not follow usual dose-response relationship</td>
</tr>
<tr>
<td>Eligibility</td>
<td>Excludes major medical conditions and CNS disease</td>
<td>May also exclude autoimmune disease but unclear on CNS disease</td>
</tr>
<tr>
<td>Duration of treatment / Endpoint evaluation</td>
<td>Typically until disease progression or unacceptable toxicity</td>
<td>Pseudoproggression and hyperprogression have been reported</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Usually early onset; on-target effects</td>
<td>May exhibit delayed onset; may include off-target effects</td>
</tr>
<tr>
<td>Regulatory considerations</td>
<td>Follows routine IRB approval</td>
<td>May require additional approvals (e.g. IBC)</td>
</tr>
</tbody>
</table>
Considerations in planning a phase 1 study

• Is the study scientifically and clinically important?
  • Strong scientific justification
  • Addressing an unmet medical need or condition

• Phase I vs. Phase I/II (or Ib/II)

• 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
  • Industry considerations
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
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 maximum tolerate dose (MTD)
  - 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)
- Explore/establish QOL and PRO measures
### Eligibility Issues Related to Immunotherapy

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| 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 pO2 ≥ 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

Enter 3

- 0 Toxic Response: Escalate to next dose
- 1 Toxic Response: Enter 3 at same dose
- 2-3 Toxic Response: Stop MTD=Previous

1 of 6 Toxic Responses

> 1 of 6 Toxic Responses

Stop MTD=Previous dose
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)
  - Dose de-escalation may be appropriate in some situations (i.e., approved agent for new indication or combination)

- 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
### Response Endpoint Assessment: RECIST or immune-related response criteria?

**TABLE 1. RECIST Criteria**

<table>
<thead>
<tr>
<th>Status</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to &lt;10 mm.</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>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).</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study</td>
</tr>
</tbody>
</table>

### Immune-Related Response Criteria

- **New, measurable lesions**
  - (≥ 5 × 5 mm): Incorporated into tumor burden
  - (<5 × 5 mm): Do not define progression (but preclude inCR)

- **Non-index lesions**
  - Contribute to defining inCR (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

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Other Study Endpoint Criteria for Immunotherapy Trials

Table 1 Features of criteria for immune-related responses

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

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.
Intratumoral RECIST (itRECIST) for local immunotherapy

- Consider injected and un-injected lesions
- 1 vs 2 dimensions (RECIST vs. WHO)
- Imaging of cutaneous lesions imperfect
- Photography helpful but time consuming
- “Pseudo-progression” may be common
- Complete regression may be hard to define
- Role for biopsy confirmation?
- irRECIST has not been validated
  - Modified RECIST
  - Allow treatment post progression
  - Use standard RECIST
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
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
# Special considerations in immunotherapy

## Phase 1 studies

<table>
<thead>
<tr>
<th>Phase 1-2 studies</th>
<th>Combination drug studies</th>
<th>Active biological agents</th>
<th>Biomarker integration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provides rapid advancement from phase 1 into phase 2</td>
<td>May be appropriate for various regimens (i.e., scientifically justified)</td>
<td>Oncolytic viruses must include bioshedding studies, transmission surveillance</td>
<td>Important to support MOA of agents/regimens</td>
</tr>
<tr>
<td>Does not allow review of data and amendment of clinical design or plan; may impact indications</td>
<td>Challenging to develop and requires close discussion with regulators; component analysis</td>
<td>Cell therapies require special logistical considerations and site expertise</td>
<td>May be mandatory or optional</td>
</tr>
<tr>
<td></td>
<td>Depends on whether one or both agents are experimental or SOC</td>
<td>May require long-term monitoring of patients (e.g. cell persistence, viral clearance)</td>
<td>Should be as standardized and validated as possible</td>
</tr>
<tr>
<td></td>
<td>Can keep standard agent at fixed dose and escalate experimental agent only</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Need to consider/anticipate any additive toxicity that may occur</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.”