Clinical Trial Design and Regulatory Issues

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Taking a Technology from Bench to Bedside
An Immunotherapeutic Product can be classified as:

(1) Active immunotherapy *Therapeutic vaccines*

(2) Adoptive cellular immunotherapy:
   
   a) *Transfer of immune cells [T and B cell therapies]*
   b) *Transfer of precursor cells [autologous or allogenic]*
   c) *Transfer of gene modified autologous or allogenic cells [Chimeric CAR/TCR engineered T cells]*

(3) Passive immunotherapy:
*Administration of antibody or receptor/ligand.*
Interferon alfa-2b [INTRON A]
- Was originally approved for a 6-months treatment plan for Hep C
- After a postmarketing study
- Results indicated that treatment for 12 months doubled the number of patients obtaining benefit
Biological product development overview

The development of immunotherapeutic products for cancer poses unique challenges to the drug development process

Product characterization:

**Early-phase product development**

A product should be sufficiently characterized at an early to discern changes of product overtime.

**Late-phase product development**

Define the product with regards to its critical quality attributes (CQA)
Criteria for Product Characterization During an early Phase:

1) **Identity:** Identity assays include cell surface markers, major histocompatibility complex (MHC) antigen markers, gene expression, genetic polymorphisms, secreted molecules, and peptide sequences.

2) **Purity:** Product purity includes assays for pyrogenicity/endotoxin and for contaminants such as *unintended cell populations* (e.g., distinguished by phenotypes), *residual proteins or peptides* used to stimulate or pulse cells, and *materials used during the manufacturing process*, such as cytokines, growth factors etc..

3) **Viability:** A minimum viability release criterion should be established for cellular immunotherapeutics. FDA’s guidances recommend that this specification be at least 70% for products administered by the intravenous route of administration.

4) **Potency:** Potency is defined as “the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product”
Biological product development overview

3-6 yrs

6-7 yrs

1-7 yrs

The development of immunotherapeutic products for cancer poses unique challenges to the drug development process.

**Product characterization:**

**Early-phase product development**

**Late-phase product development**

A product should be sufficiently characterized at an early phase to discern changes of product overtime. Define the product with regards to its critical quality attributes (CQA).

**Production scale-up:**

- Changes of manufacturing facilities
- Changes of equipment related to growth, processing, and storage
- Process changes.

1.2 million sq. ft

**CAR-T CELL**
Biological product development overview

3-6 yrs

6-7 yrs

1-7 yrs

Preclinical evaluation

General considerations for the preclinical assessment of immunotherapy products

The **overall goal is to provide data to support safety of the product**

**Safety concerns for these products can exist at multiple levels:**

A) **Product related:**
   a. Replication of a viral vector *in vivo*
   b. Autoimmunity due to a high homology between an immunogenic epitope and an endogenous target)

B) **Process itself**
   a. the introduction of adventitious agents
   b. cell transformation due to ex vivo manipulation),

C) **Biological function**
   a. polarization of the immune system
   b. overstimulation of the immune system due to immunc
Preclinical studies conducted to support immunotherapeutic product development

1) Identify potential target organs/tissues of toxicity and determine if these toxicities are reversible.

1) Identify an appropriate starting dose level and inform the dose-escalation scheme and the dosing regimen of a first-in-human trial.

1) Identify parameters for safety and activity monitoring in humans.

4) Adequate numbers of animals for statistical analysis.

4) Appropriate control groups.

5) A dosing regimen and route of administration similar to those planned for the clinical trials.

4) Adequate study duration to allow for comprehensive assessment of potential adverse findings.
Preclinical studies **CHALLENGES??**

Species-specific Differences in target and effector function

Often Impossible to obtain a relevant animal model

CAR T cells: Testing for their potency:

1) Challenging----- Do we correlate the potency with transduction efficiency (% of transduced cells)?

………...NOT NECESSARILY as cells expand anyway post infusion
Following infusion of CART-19 T cells in patients, the *T cells expanded approximately 1000-fold* or more, with concomitant significant increase in proinflammatory cytokine levels, and associated adverse effects.
Biological product development overview

- 3-6 yrs
- 6-7 yrs
- 1-7 yrs

A phase I clinical trial of adoptive transfer of folate receptor-alpha redirected autologous cells for recurrent ovarian cancer

Lana E Kandalaft, Daniel J Powell Jr and George Coukos
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**Expression of Alpha-Folate Receptor by IHC**

**Choroid Plexus**

**Proximal Kidney Tubules**

**Breast Nodules**

**Lung Airways**

Kathleen Montone
INNOVATIVE CLINICAL TRIAL DESIGNS

Cohort 1
-5 -4 -3 0 1 2 3 4 5 28 40 58
Chemotherapy CAR T-Cells PBL
Labs/Assessments
Daily Twice weekly Weekly EOS1 EOS2
Tumor bx Long-term F/U 15 yrs

Cohort 2-5
-5 -4 -3 0 1 2 3 4 5 28 40 58
Chemotherapy CAR T-Cells PBL PBL*
Tumor bx Long-term F/U 15 yrs

SCREENING Enrollment Apheresis

Without infusion of bulk untransduced PBL on Day 2.

With infusion of bulk untransduced PBL on Day 2.
CONSIDERATION FOR EARLY CLINICAL TRIALS

COMBINATION

How specific combinations of IO compounds may be tested clinically and which combinations make most sense???
POINTS ABOUT COMBINATIONS

1) IO combinations will be more effective than IO monotherapy,
   - Requires recognition of the unique kinetics of IO agents
   - Early recognition of toxicity

2) Elucidate the mechanisms of immunologic synergy, and provide controlled demonstration of additive or synergistic benefit.

Are phase II and III IO monotherapy clinical trials worth and appropriate to perform?

Fortunately, FDA have demonstrated a willingness to explore novel-novel combinations in early-stage clinical trials
**PATIENT POPULATION**

Conventional model for **clinical development of a chemotherapeutic agent is in patients with advanced/metastatic diseases**.

However, the time interval from administration of study agent to subsequent disease progression in patients with metastatic cancer may be short.

This time may be **insufficient** for development of an **anti-tumor immune response** needed for activity/effectiveness of a cancer vaccine.

*In contrast, testing cancer vaccines in patients with minimal burden of disease may provide adequate time for the cancer vaccine to elicit a detectable immune response.*
An example of a Patient who may have achieved benefit from whole tumor vaccine
PHASE I DESIGN CONSIDERATIONS

CYTOTOXIC AGENTS

The primary objectives of most phase I studies
….. most appropriate dose and schedule of administration.

END POINTS

• maximum tolerated dose (MTD)
• dose-limiting toxicities (DLTs).

Designs commonly used are 3+3, accelerated titration designs, and various Bayesian designs
PHASE I DESIGN CONSIDERATIONS

IMMUNO ONCOLOGY AGENTS

MTD may never be reached, because some of these agents have more favorable toxicity profile (Vaccines)

An alternative endpoint to MTD is the dose required to maximize the inhibition of the relevant target (optimal biological dose)

Accelerated titration designs or a continual reassessment approach maybe more suitable Phase I design for an experimental cancer vaccine

DLTs may be difficult to identify: outcomes such as immune response should be used to identify the optimal dose

In some cases, a serial enrolment in up to 3 arms may provide the greatest opportunity to evaluate potential AEs with individual agent

(Agent 1, Agent 2, Agent 1+2)
The challenge with immunotherapies is that an immediate antitumor response within the typical assessment period of 6–8 weeks using standard RECIST may not be evident.

4 potential clinically beneficial response

- **Immediate response in reference lesions, with no delay and no new lesions emerging**, with no delay and no new lesions emerging.
- **Development of new lesions while on therapy, followed by a reduction and an eventual RECIST response**.
- **Initial increase in existing tumor volume, which may be followed with a gradual decline over time as the immune system is activated**.
- **Disease stabilization, with or without a subsequent slow decline in tumor volume**. 

![Graphs illustrating response types](image)
The first 2 pathways are characteristic of chemotherapy response kinetics and can be identified using standard RECIST.

In contrast, the latter 2 outcomes cannot be captured by RECIST and patients would be classified as having RECIST progressions and come off-study.

Using irRC, total disease burden is measured on a continuous scale and percent change between measurement times is used to quantify disease response.
In oncology practice, patients are normally taken off current treatment when they have disease progression/recurrence.

Because immunotherapeutic products may need time to elicit or amplify an immune response that could manifest as biological activity (i.e., a tumor-specific immune response), a delayed effect can be expected in the subjects who received the vaccine.
Patient on A Personalized Vaccine Study ......... Delayed Response

- DC + autologous oxidized tumor lysate
- Unpulsed DCs
- PBMCs only

Number of IFN-γ spots per 2 x 10^5 PBMCs

Kandalaft et al, In Prep
Randomized Designs

Given the delayed antitumor effects that have been observed with investigational immunotherapies, randomized designs in the phase II setting are recommended.

• The objectives of randomized phase II trials are typically:
  • to establish that the agent can be safety administered in a cohort of patients who would be potential drug candidates in a larger phase III trial
  • to determine if the investigational drug can generate a large enough treatment effect relative to the control group to warrant moving into phase III.
Randomized Designs

Although several types of randomized Phase II designs are possible, the randomized discontinuation design maybe appropriate for cancer vaccines: only patients with unimpaired immune system will receive the vaccine.
For ethical reasons, pts experiencing disease progression are often offered cross-over to the experimental agent or will go on to receive subsequent therapies: this will confound the OS endpoint.

Other confounding factor is the survival post-progression (SPP): the longer the SPP, the harder to detect an OS benefit.

With current standard of care (modern drugs, multiples lines of ttt, better supportive care), demonstrating OS benefit becomes harder.
PROPOSITIONS

One way to avoid the risk of a false-negative would be to use immune response progression-free survival (irPFS) as the primary endpoint.

With irPFS as a primary endpoint, patients responding to the immunotherapy based on the immune response criteria (but not by RECIST) would continue on study and not be switched to alternative treatments because of a perceived progression by conventional RECIST.

Adaptive designs may be useful for example, hybrid phase II/III adaptive trial, that involves changing the primary endpoint after completion of the Phase II portion \(\rightarrow\) change irPFS for OS in the Phase III portion, and expand sample size to fulfill the power requirements.
CLINICAL ENDPOINTS

MUST CONSIDER CHANGE IN ENDPOINTS

Clinical Response may need time to develop

Ir Progression Free Survival and Overall Survival are recommended

Disease Progression does not always mean progression

………………………………MUST define withdrawal criteria

Improvement in how a patient feels, as measured by patient-reported outcome instruments (PRO’s), if properly validated, could constitute a clinical benefit supporting licensure;
Measuring immune response

ELISpot assay
• The most common test
• It measures the quantity of specific cytokines produced by individual T cells after stimulation with particular Ags in vitro
• Used mostly in vaccine trials when the individual vaccine Ag is known
• Problem: there are many components in this process and variability at each step has contributed to the failure of this approach

Emerging alternatives
• Multicolor flow cytometry to directly assay for the presence of intracellular cytokines in individual cells
• The most reliable predictor of objective clinical response to IO compounds is the frequency of CD8+ tumor infiltrating lymphocytes in histologic specimens which can be approximated by flow cytometry evaluation of peripheral T cells restimulated with appropriate tumor-derived Ags in vitro
• Analysis of the immune infiltrate within the tumor
Harmonization of immune monitoring

We can learn so much from Proper Real Time Immune Monitoring.
WELL COORDINATED TEAM EFFORT AND CAREFUL REAL TIME MONITORING

At first, nothing happened. But after 10 days, hell broke loose in his hospital room. He began shaking with chills. His temperature shot up.

…..doctors moved him into intensive care and warned that he might die

Well coordinated careful efforts of the team With Real Time Monitoring
…..identified the elevated cytokines (IL-6 spike)

Patient got IL-6 Antibody (tocilizumab)
…… and is now alive
FOR IMMUNOTHERAPEUTICS THE CHALLENGES SEEM TO INCREASE...
Process Flow - Bench to Bedside

UNIL/LICR

Translational Research

Process Development - Optimization

GMP Facility

Quality Assurance

Process Development - Clinical Scale-Up

GMP Manufacturing

Quality Control

Tumor Processing Facility

Phase 1 Immunotherapy Unit

Leukapheresis

Infusion

Immune-monitoring
Thank you !!!

RECRUITING