Overview of Phase 1 Oncology Trials of Biologic Therapeutics

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Assumptions and Ground Rules

- The goal is regulatory approval of the product in an efficient, clinically meaningful, and responsible manner
- Science, rather than tradition, dogma or “checking the box” will drive study design
- “Less may be More” i.e. the MTD is generally not applicable for many biologics
- Preclinical program was well planned and well conducted

Goals for Phase 1

- Describe preliminary safety profile
  - Multiple tumor types vs. indicated population
  - Experience to allow for any needed dose modification rules for Phase 2 and beyond
- Determine dose and schedule
  - Route (intradermal, intratumoral, IV, hepatic artery, intrapleural, intracranial, etc)
  - Dose escalation schema
  - Prospectively defined basis for selection of recommended dose
- Demonstrate proof of concept
  - Special assays
  - Biomarkers
  - Surrogate endpoints that measure mechanism related outcomes

What can go wrong?

- Just about anything!
- Keep the focus on Patient Safety
- Phase 1 is designed to prevent or address problems in an optimal manner
- ICU resident analogy: We know the disasters are coming; the question is how prepared are we to deal with them

What do we need to start?

- GMP manufactured product (challenges here are not to be underestimated)
- Preclinical efficacy data (if relevant model)
- Preclinical toxicology data in most relevant and most sensitive species and of proper duration to support duration of treatment in Phase 1 design
- Proper expertise and administrative structure
- Regulatory permission [FDA, RAC (for gene therapies, EMEA, etc]
  - Pre IND meetings are often critical
- Target Product Profile (FDA Guidance)

The Vision: Target Product Profile

- Indication and usage
- Dosage forms and strengths
- Contraindications
- Warnings and Precautions
- Adverse reactions
- Drug interactions
- Special populations (e.g. pts who are pregnant or lactating, geriatric, pediatric, renal or hepatically impaired)
- Overdosage
- Product Description
- Clinical Pharmacology (e.g. MOA, PK, PD)
- Non-clinical toxicology
- Clinical studies (measures of efficacy – endpoints)
- How supplied
- Patient counseling information

Dose

- Defined by preclinical pharmacology and toxicology studies
- Starting Dose: Adequate margin of safety
  - FDA guidance on safe starting dose helpful for therapeutic proteins and antibodies; may or may not apply to vaccine, cell and gene therapy
  - EMEA guidance on high risk agents
- Maximum dose
  - Supported by anticipated range for efficacy and toxicology data
  - MFD (maximum feasible dose)

Dose Escalation and Duration of Txt

- Dose escalation
  - Stagger enrollment to achieve observation period between patients and cohorts
  - Length of observation period dependent on MOA and construct of the product
- Duration of treatment matches duration in toxicology studies
  - Single dose vs. repeat dosing
- Take into account mechanism of action
  - Don’t depend completely on toxicology studies (e.g. Tegenero experience)

Endpoints in Phase 1

- Primary
  - Safety and Tolerability
  - Recommended dose
- Secondary
  - PK
  - PD
  - Surrogate endpoints (biomarker, imaging study, immune response assay, tumor response, and others related to mechanism of action of the product)

Therapeutic Areas – Key Issues

- Therapeutic Proteins
- Monoclonal Antibodies
- Therapeutic Vaccines
- Cellular and Tissue Therapies
- Gene Therapies
- Combinations
- Novel Products

Therapeutic Proteins and MoAbs

- Regulated in CDER
- Estimation of safe starting dose (FDA Guidance)
- Dose escalation somewhat empiric
- PK/PD
- Immunogenicity
- Biomarkers for targeted therapies
- Assays may be critical to aid in dose selection

Therapeutic Proteins

- Usually there are relevant animal models from which to estimate safe starting dose
- Healthy volunteer vs. patients
  - Risk benefit analysis

Antibodies

- Construct (e.g. chimeric, humanized, fully human, engineered to enhance specific functions)
  - May limit relevance of animal studies
  - Syngeneic models sometimes needed
- Tissue cross reactivity panel
  - Critical for safety profile estimation
  - Impact on clinical monitoring during clinical trial
- Selection of patients for targeted therapy (enrichment) vs. all comers with assessment of target presence or absence in all
  - Phase 1 may be the best time to look at all comers

Therapeutic Vaccines (I)

- Components to improve immune response
  - One or more adjuvants
  - Immune modulators
  - Route of administration
- Autologous vs. allogeneic vs. neither
- Increase in heterogeneity of outcome for the endpoint measured may necessitate increase in sample size
  - Placebo control may help address variability issue and aid in improved interpretability of the data
- Assays for outcome measures

Therapeutic Vaccines (II)

- Dose escalation methodology
  - Tend to have fewer dose levels compared to proteins and antibodies
  - Usually half log increments
- PK may not be possible or relevant parameter for some products
- Basis for decisions
  - Prospectively define how the recommended dose(s) will be selected

Cellular and Tissue Therapies

- Among the most challenging products to characterize
- Many issues similar to those with therapeutic vaccines
- Derivation of product
  - Issues around manufacture
- Dose escalation methodology
  - Typically half log increments

Gene Therapies Definition

"All products that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered organisms." [applies to in vivo or ex vivo settings]

-FDA Guidance Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events, Nov 2006

Gene Transfer System Selection

- Impact on clinical study design
- Elements
  - vector and vector formulation
  - route and method of delivery
- Identification of recommended dose
  - Proof of concept
  - Assays for duration of transfer or gene product expression or downstream effect
- Safety
  - Two Guidance documents (Gene Therapy-Delayed AEs and Testing for Replication Competent Retrovirus (RCR))

Gene Therapies - LTFU

- MFD may not be clinically relevant dose limiting predictability of animal models
- Factors that increase risk of AEs
  - Persistence
  - Integration
  - Prolonged expression
  - Alteration of host genome
- LTFU plan must be included with protocol submission to IND
  - 15 years
  - Intensity of FU depends on product and results of clinical and laboratory evaluations.

GT – LTFU Algorithm

- Ex vivo product?
- Persistence?
- Integration?
- Potential for latency or reactivation?
- Answers form the basis for LTFU plan by segregating low vs. higher risk products
  - Determines whether LTFU is needed

Combination Therapy

- Co-administration or sequential administration
- Achieve additive or synergistic efficacy based on MOA
- May or may not require additional toxicology testing of the combination prior to clinical trial
  - Overlapping toxicology findings or AE profiles of the individual agents may necessitate combo tox
- If both products are unapproved, need separate phase 1 trials of each as monotherapy
  - Complex dose escalation issues with combo
  - Show contribution of both

Combination Product

- Biologic-Device
- Biologic-Drug
- Biologic-Drug-Device
- Regulatory definition which links the given combination
  - Discuss with FDA early
    - Inter-center collaboration may be needed

Novel Biologic Products

- Call FDA early to get guidance on preclinical program planning and possibly on CMC issues.

Phase 1 Outcome

- Recommended dose(s)
  - May still need to do additional dose finding in Phase 2
- Proof of Concept
  - Helpful for “go” vs. “no-go” decision making
  - May be based on a surrogate
- Safety Profile (rough estimate only)
- Refinement of target patient population or indication
  - May still need additional Phase 1 data prior to initiating Phase 2
- Paves the way to Phase 2 and Beyond

Useful Reference

"A Clinical Development Paradigm for Cancer Vaccines and Related Biologics"

Cancer Vaccine Clinical Trial Working Group

J. Immunotherapy 30(1), Jan 2007, pp1-15

END