

# Success Factors for Phase 3 Cancer Vaccines Trials

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# Outline

- OCTGT
- Prior to planning a Phase 3 study
- Planning a Phase 3 study
- Conducting a Phase 3 study

# Organization

- CBER (Center for Biologics Evaluation and Research): vaccines, blood and blood products, human tissue/tissue products for transplantation, cells, gene therapy
  - **Office of Cellular, Tissue, and Gene Therapy**
  - Office of Vaccines Research and Review
  - Office of Blood Research and Review
- CDER (Center for Drug Evaluation and Research): drugs, some biological products
- CDRH (Center for Devices and Radiological Health): devices for treatment, implants, diagnostic devices
- CVM
- CFSAN
- NCTR

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# OCTGT Regulation

- Cellular therapies
- Tumor vaccines
- Gene therapies
- Tissue and tissue based products
- Xenotransplantation products
- Combination products
- Devices used for cells/tissues
- Anti-idiotypic antibodies

# Prior to Planning the Study

- Product/manufacturing for Phase 3
- Information from early clinical studies

# Product for Phase 3

- Release testing requirements for Biologics
  - Microbiological- Sterility, Mycoplasma
  - Purity
  - Identity
  - Potency
- Release criteria based on data collected from early phase trials

# Manufacturing for Phase 3

- Coordination of vaccine manufacturing with administration schedule
- Central vs distributed manufacturing
- Scale
  - Scale up or Scale Out?
- cGMP compliance

# Manufacturing for Phase 3: Autologous Products

- Control of product variability
- Rate of manufacturing failures
- Facility “scale out” for individual lot production

# Early Studies

- Patient population
  - First line versus failed other treatment
  - Early stage versus later stage disease
  - Adjuvant
  - Neoadjuvant
  - Combination
  - Part of multimodal therapy
- Dosing and administration
- Effect of placebo

# Early Studies (cont'd)

- Parameters/assessment methods
  - Biomarkers (think ahead!)
    - Patient selection
    - Immunologic
  - Tumor response measures
- Accrual rate

# Early Studies (cont'd)

- Analysis:
  - Modelling for relationship of endpoints
  - Estimate of effect size (timing, magnitude)
  - Timing of events
  - Decision making criteria for initiating a Phase 3 study

# Planning the Study

- Your team
- Adequate information to support study design
- Key study design issues
- Working with FDA

# Your Team

- Communication between clinician, statistician, and product manufacturer during the study design phase is key
- Statistical design elements have a clinical interpretation
- Product must be able to be manufactured and delivered to the subjects per the protocol plan

# Adequate Information to Support Phase 3 Study Design

- Data (from prior studies) to support:
  - Patient population
  - Safety and efficacy parameters
  - Product administration and concomitant care
  - Statistical analysis plan
  - Etc.
- Experience (from prior studies) to support study logistics:
  - Accrual rate/number of sites/inclusion criteria
  - Logistics of coordination of product availability with administration schedule

# Key Study Design Issues

- Autologous vaccines:
  - When to randomize
  - Time to event?
- Effectiveness onset may be delayed
  - Time to event?
  - Efficacy parameters?
- Enrichment strategies?
- Studies need close collaboration with a statistician

# Working with FDA

- Meeting with FDA
- Special Protocol Assessment (SPA)
- Accelerated Approval
- Fast Track
- Endpoints

# Meeting With FDA

- Why meet?
  - Obtain FDA advice and direction
  - Clarify procedures
  - Clarify expectations
  - Resolve disputed issues
- When to meet?
  - Meet early before you're committed to a final action
  - Pre-IND
  - End of Phase 2/Pre-Phase 3 (Consider Special Protocol Assessment)
  - Pre-BLA
  - Disputes stalling product development

# End-of-Phase 2 Meeting

- Requested by IND sponsor: CMC, pharmacology-toxicology, proposed phase 3 studies
- Goal: ensure that the development plan is adequate to support licensure
- Prior to requesting SPA

# Special Protocol Assessment

- Request submitted by sponsor
- Goal is to reach formal agreement on protocol design
- 45 day review timeframe
- Commitment by FDA that depending on the results the study will support filing of a licensing
- Significant protocol amendments must be agreed to in writing by FDA and IND sponsor

# Accelerated Approval

- Serious or life-threatening diseases
- Benefit over available therapy
- Approval based on a surrogate that is reasonably likely to predict clinical benefit
- Postmarketing studies to verify and describe the benefit

# Fast Track Designation

- **Serious or Life-Threatening Condition**
  - Whether a condition is serious
  - Whether the drug is intended to treat a serious condition
- **Demonstrating the Potential to Address Unmet Medical Needs**
  - Evaluation of whether the drug development plan addresses unmet medical needs
  - Demonstration of the drug's potential

# Trial Endpoints: Guidance

- Overall Survival
- Endpoints Based on Tumor Assessments
  - Disease Free Survival
  - Objective Response Rate
  - Time to Progression and Progression Free Survival
- Time to Treatment Failure
- Endpoints Involving Symptom Assessment
- Biomarkers
- Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics  
<http://www.fda.gov/cder/guidance/6592dft.htm>

# Endpoints Based on Tumor Assessments: Challenges

- Standardization of Assessments
- Timing of Assessments
- Interpretation of Response Rate

# Endpoints based on Tumor Assessments: Standardization

- Standardize imaging
- Standardize measurement technique
- Need for masked assessment
- Which lesion(s)
- Difficulties in imaging bone

# Endpoints based on Tumor Assessments: Timing

- Determined at fixed intervals
- Assessments may be made earlier depending on clinical status of the patient
- For time to event analysis need to decide how to handle in analysis plan

# Endpoints based on Tumor Assessment: Interpretation of Response Rate

- Number of CRs vs. PRs
- Duration of responses
- Location of responses (e.g., liver vs. skin)
- Association with symptom improvement
- Extent or bulk of metastatic disease

# Conducting a Phase 3 Study: Monitoring Accrual

- Accrual length and duration
- Monitoring accrual rate
- Solutions for slow accrual (?):
  - Add sites
  - Modify entry criteria or other study design elements
- Better to plan ahead!!

# Submission of Portions of an Application: Criteria

- Clinical trials that would form the basis for the agency's determination of the safety and effectiveness near completion or complete
- Product continues to meet criteria for fast track designation, and
- Preliminary evaluation of the clinical data supports a determination that the product may be effective.

# Rolling BLA: Procedure

- Schedule for submission of information agreed upon
- Submission of complete sections (unless agreed on in advance and meaningful review can be conducted)

# Regulatory References

- Guidance for Industry Fast Track Drug development Programs- Designation, Development, and Application Review, revision 1/06, found at <http://www.fda.gov/cber/gdlns/app4>.
- CBER SOPP 8414: Fast Track Drug Development Programs: Designation and Review Programs
- Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics  
<http://www.fda.gov/cder/guidance/6592dft.htm>
- References for the Regulatory Process for the Office of Cellular, Tissue, and Gene Therapies (OCTGT)  
<http://www.fda.gov/cber/genadmin/octgtprocess.htm>

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