Cancer Vaccine Clinical Trial Working Group

Workstream 2

Design Methodologies in Cancer Vaccine Clinical Trials

Workstream 2 - Participants

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CVCTWG Workstream 2 Topics:
Design Methodologies for Cancer Vaccine Trials

- The cancer vaccine clinical development paradigm
- Objectives for early trials: toxicity, biological activity, clinical activity
- Investigation of dose and schedule
- Bridging the gap between early and late phase development
- Adaptive trial designs for Phase 2 and 3 development
- Surrogate endpoints for clinical activity in early trials

Conventional Oncology Drug Development Paradigm

Phase	N (variable)	Purpose
1	20 to 80 healthy volunteers, or patients (may or may not have target disease)	Determine safety, dose range, MTD, DLT Characterize pK If mixed population, find target
2	100 to 300 patient volunteers with targeted disease	Evaluate effectiveness, look for side effects. May provide estimate of effect size for Phase 3
Discuss continuation with Regulatory Agencies		
3	500 to 1,000 patient volunteers	Verify effectiveness, monitor adverse reactions from long-term use.
4	Large numbers of patients	Post-marketing surveillance

[Modified from Cheney T. & Kaspar P. Overview of Clinical Research, 1996.]

Reasons for the Need for a Different Paradigm for Cancer Vaccines

- Usually there are no serious toxicity risks and no proof for a linear dose-potency relationship for cancer vaccines (CV): no need for conventional dose-escalation to establish MTD.

- Dose and schedule are not determined through escalation based on toxicity.

- CV usually do not get metabolized: no need for conventional pharmakokinetics.

- Many CV are designed to address one tumor type: no need for mixed tumor trials for target selection.

- Conventional short-term response criteria (e.g. RECIST) are not well applicable to CV and historical control comparisons on RR are not useful: proof-of-principle endpoints should reflect biologic activity including immunogenicity.

Proposed Development Paradigm for Cancer Vaccines

Phase of Development	Purpose
Proof-of-Principle Trial (Exploratory Trials) N>20 Well-defined population No end-stage disease	Safety database initiated Proof-of-Principle: immunogenicity, biologic activity, clinical activity Use established and reproducible immune assays Dose and schedule of vaccination
Discuss continuation with Regulatory Agencies	
Efficacy Trial(s) (Randomized Trials) Allow flexibility through prospective adaptive designs	Expansion of safety database Establishment of efficacy
Post-Approval Trial	Post-marketing surveillance

Proof-of-Principle Trials

- Assumptions: - Sufficient evidence to initiate human studies
  - Immunoassays are established and reproducible

- Objectives:
  - Start building safety database (descriptive toxicity)
  - Define dose and schedule as feasible
  - Proof-of-principle: immune response, biologic activity, clinical activity.
  - Development of necessary knowledge allowing for rapid initiation of *efficacy trials*.

- Characteristics:
  - N>20
  - Defined patient population (possible target population in *efficacy trials*)
  - No end-stage disease
  - Investigate disease-specific biologic parameters to demonstrate biologic activity
  - No mandate to investigate exact mechanism of action
  - No need for demonstration of statistical significance for any comparisons

Proof-of-Principle Trials

- **Dose and Schedule**
  - Cohort design to determine dose and schedule
    - Each cohort should receive a single dose for safety: if no signal for toxicity, then each cohort will receive multiple doses as either :
      - predetermined number of doses
      - variable number of doses to be determined by a target parameter such as maintenance of immune profile
    - Cohort size is determined by estimates of immune response or other biologic parameters but should have a minimum of 6 patients
    - Dosing aim: Number of doses can be determined by immune profile results with goal of sufficient number of doses to maintain stable immune response
  - Patient withdrawal based on toxicity or disease progression following a minimum time period or number of doses to allow for delayed response (WS1)

Proof-of-Principle Trials: Toxicity

CV have generally low toxicity. A first-in-man study should include adequate toxicity testing without overly extensive screening for unexpected toxicities:

1) Standard safety panel of exams/tests to cover major organ systems (standard)
2) Vaccine-specific toxicities unique for the investigated product based on toxicity expectations from pre-clinical models; including autoimmunity as applicable;
3) Investigation of unexpected toxicities through collection of serum and potentially other samples from patients at defined time points. These samples will be stored for further laboratory testing if unexpected toxicity is observed.

Characteristics:

- Allows to react to safety needs in an ongoing study without extensive screening.
- Criteria for stopping the trial for toxicity must be part of the design.
- Applicable also for combination trials between vaccines and biologics or immunomodulators
- No mandate to enter first-in-man trials with combinations based on animal data because of limited availability of relevant animal models; however, if available relevant animal models are to be utilized.
- No need for most products to establish a MTD.

Proof-of-Principle Trials: Endpoints

Biological Activity:

Impact of the vaccine on immune response or impact on the disease under investigation.

Potential parameters for biological activity:

- Regulatory T-cell activity or immune response against target cells
- Molecular response (minimal residual disease)
- Any form of clinical activity

Immune profile:

- Sequential samples
  - Minimum of 3 assay timepoints: baseline and two follow-up timepoints
  - Minimum of two established and reproducible assays for immune profile
    - **Adequate immune response**: ≥ 2 assays are positive at ≥ 2 follow-up timepoints

Clinical Activity:

No mandate to demonstrate clinical activity with conventional Oncology endpoints in Proof-of-Principle trials.

If investigated: No end-stage patients, homogenous population.

Pharmacokinetics:

Generally not required for CV. Must be product dependent.

Proof-of-Principle Trials: Decision Points

- If signal of activity of either clinical response **or** biologic activity **or** immune response is detected based on pre-specified parameters, move forward

- If no signal of activity (all three are negative), program is stopped and re-evaluated

Efficacy Trials

- Direct follow-up to *proof-of-principle trials*
- Bridge the gap of the not recommended *conventional Phase 2 trial*
- Demonstrate efficacy
- Recommended to be randomized trials
- Design:
    - *Conventional Phase 3 trials*
    - *Comparative randomized Phase 2 trials*
    - *Comparative randomized Phase 2 trials with adaptive component*
    - Other designs able to produce credible prospective data to demonstrate product efficacy

Efficacy Trials: Randomized Trials

Randomized Phase 2 Trial Concepts

Non-comparative randomized Phase 2 trials

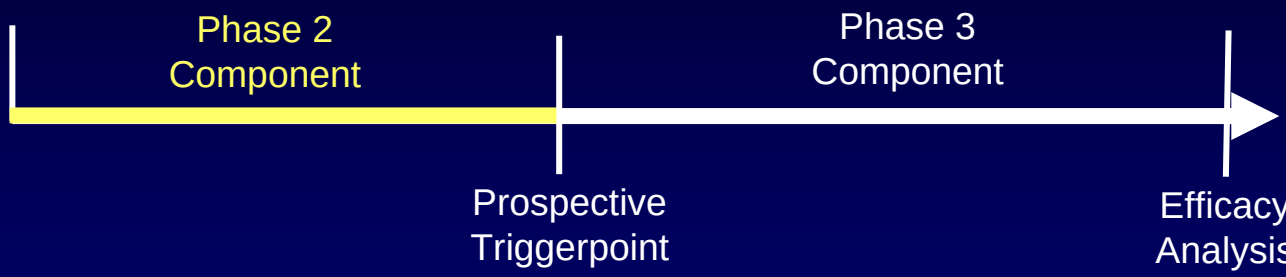
- Collection of parallel single-arm historically controlled trials with random patient allocation.
- Higher degree of comparability between patients in each trial (arm) due to randomization.
- Each trial evaluated separately; outcome criteria are like single-arm trials.
- Exploratory nature; need for confirmatory trials.

Comparative randomized Phase 2 trials

- Randomized +/- stratified clinical trials done in Phase 2.
- Powered for statistically significant difference between two arms in a well-defined population using a well-defined primary outcome measure.
- Outcome measure may be surrogate (e.g. biologic activity).
- Projected differences may be relatively large compared to Phase 3.
- If positive and well-conducted, *comparative randomized Phase 2 trials* can provide evidence of efficacy.

Efficacy Trials

Randomized Phase 2 Trials with Adaptive Component



Objective: Introduce a clinical trial design option that allows additional flexibility for development

Triggerpoint characteristics:

- Must not be fully statistically powered to demonstrate superiority ($p\alpha$ or $p\beta$)
- Separate, independently powered endpoints for both analyses: e.g. less definitive triggerpoint and more definitive efficacy endpoint

Flexibility aspects:

- Allow for sample size re-calculation based on triggerpoint data
- Allow for modification of eligibility criteria for Phase 3 component to focus on a specific population
- Allow for start of Phase 3 trial either through continuation without change or protocol amendment

Other characteristics:

- Data from Phase 3 component not to be pooled with Phase 2 data
- All designs and potential changes of criteria must be prospective (as far as possible)
- If intended for product approval regulatory consensus or SPA should occur prior to initiation

Surrogate Endpoints in Trials with Cancer Vaccines

Proof-of-principle trials: unvalidated surrogates or biomarkers to

- determine biologic activity,
- support PK and PD studies as applicable
- allow for more rapid vaccine development
- applies to single markers as well as composites of markers (genomic profiles, matrix of immunological parameters).

Efficacy trials: validated surrogates or biomarkers as efficacy endpoints.

Types of surrogate markers: Requirements for prospective validation

- Associated with the disease (prognostic factor):

  Validation needs proof-of-correlation between outcome and biological marker in single-arm or randomized studies.
- Associated with the therapeutic intervention (e.g. immune response):

  Validation needs randomized trial showing that intervention-induced surrogate correlates with outcome.

Molecular response as a surrogate endpoint

- CV are expected to work best in MRD populations.
- Molecular markers allowing uniform assessment of MRD and the impact of a vaccine on the target disease can function as a measure of biological and/or clinical activity.
- Examples: CML: well-defined canonical chromosomal abnormality (BCR-ABL) detectable by RT-PCR

  AML: multiple heterogeneous chromosomal abnormalities not present in all patients, requiring an array of markers to determine biological activity in a non-selected group of patients.

Thank you.