

Cancer Vaccine Clinical Trial Working Group

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Cancer Vaccine Clinical Trial Working Group

A Clinical Development Paradigm for Cancer Vaccines and Related Biologics

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Working Group Summary

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Cancer Vaccine Clinical Trial Working Group

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CVCTWG Issues

- Cancer vaccines have unique developmental challenges.
- Some potential solutions exist.
 - Not widely known.
 - No consensus.
- Need for a flexible and adequate clinical development paradigm.

CVCTWG Goal

- Utilize collective knowledge in the field.
- Synthesize flexible and applicable paradigm.
- Reach consensus.
- Offer accepted, practical approach to CV development.
- Not “lowering the bar” for vaccine approval.

CVCTWG – A Consensus-building Process

- > 1 Year Process
- Comprehensive Expertise, Collaborative Spirit:
 - Academic Leaders
 - Biotechnology/Pharmaceutical Drug Developers
 - Regulators
- > 60 International Participants, ~200 Workshop Attendees
- 3 Workshops, Various Conference Calls
- Consensus Reached on Practical Recommendations to Improve of Cancer Vaccine Development

CVCTWG Workstreams

1. Clinical Endpoints
2. Trial Design Methodologies
3. Technical Challenges
4. Combination Therapy

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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

- Mostly 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 pharmacokinetics.**
- 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.**
- Standard trial designs lack flexibility to translate new learning into late-phase trials.

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 as feasible
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:**
 - Minimum sample size adequate to initially assess safety ($N > 20$)
 - 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: 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
- 2) Assessments for vaccine-specific toxicities unique for the investigated product based on toxicity expectations from pre-clinical models (including autoimmunity as applicable)
- 3) Collection of serum and other relevant samples at defined time points. Storage 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
- No need for most products to establish a MTD; **optimal biologic dose** is desirable
- 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 if no adequate models exist

Proof-of-Principle Trials: Biological Activity

Biological Activity:

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

Potential parameters:

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

Immune Response:

- Collection of **maximum number of justifiable sample material** per patient
- Samples taken sequentially
- **≥ 3 assay timepoints**: baseline and two follow-up timepoints
- Immune **assays** should be **established, reproducible and technically validated** in the laboratory where used; no clinical validation is required
- Minimum of **two such assays** should be applied
- **Adequate immune response**: ≥ 2 assays are positive at ≥ 2 follow-up timepoints
- **Prospectively defined frequency and magnitude** of immune response for the population under study

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
- Consider clinical relevance of data in the absence of clinical activity data
- If **no signal of activity** (all three are negative) - stop program and re-evaluate

Adjustment of Clinical Endpoints

Characteristics of clinical benefit for CV:

- Immune response to be built before clinical activity
- Delayed onset of clinical activity
- Slowing of progression or SD may be more relevant than shrinkage of bulky disease

Delayed Benefit:



Continuation of vaccination therapy at first progression:

If progression is not rapid but „clinically insignificant“

If no other therapy immediately required

If no effective therapy available

Crucial: choice of population, rapidity of progression

Adjustment of Clinical Endpoints

Response Rate:

Caveats:

- PD before detectable benefit
- Delayed benefit may lead to premature discontinuation
- No tumor shrinking but slowing of progression
- Response may require better quantifiable parameters (biomarkers)

Prospective Modification of Response Assessment:

If response is detected after initial progression, evaluation should either

- not consider PD prior to reponse **OR**
- reset baseline to largest tumor volume after start of treatment

Define time window in which delayed reponse must occur

PFS / DFS / TTP:

Caveats:

- PD before detectable benefit
- Delayed benefit may lead to premature discontinuation

Prospective Modification of Response Assessment:

If response is detected after initial PD, evaluation should either

- not consider PD prior to reponse
- baseline remains at start of therapy

Define time window in which benefit reponse must occur

Overall Survival: “Gold Standard”

Surrogate Biomarker Endpoints

“Objectively measured parameter to indicate normal or abnormal biological processes”

Single markers or composites of markers (genomic profiles, matrix of immunological parameters)

Validation:

Proof-of-principle trials: **unvalidated** surrogates or biomarkers to establish biological activity.

Efficacy trials: **clinically 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 **minimal residual disease (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.

Surrogate Biomarker Endpoints

Utilize Biomarkers **as Frequently as Possible**
to Support their Validation in Clinical Trials

➔ Expand Repertoire of Clinical Endpoints for
Efficacy

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
- Utilize **adaptive designs**
- Designs:
 - *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 Phase 2 Trials with adaptive design



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:

- May be expanded and data combined if stringent criteria are met
- 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 if population changed
- 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

REVIEW

A Clinical Development Paradigm for Cancer Vaccines and Related Biologics

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CVCTWG – Workshop Faculty

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Thank you.

