Cancer Vaccine Clinical Trials Working Group

# Work Stream 4

## Combinations of cancer vaccines with other agents

# Scope

- Defining a cancer vaccine “combination”
- Proposals for toxicology testing of combinations
- Determining dose and schedule in early clinical testing
- Extent of component control needed in definitive trials
- “Ownership” issues

# Rationale for cancer vaccine combinations

- Cancer vaccines to date:  effect but little efficacy
- Clear evidence of “afferent” immunogenicity
- Checkpoints dampen T-cell expansion/activation
- Multiple tumor escape mechanisms frustrate “efferent” arm of immune response
- Combinations therefore make sense
  - Vaccine to generate immune effectors
  - Other agents to expand immune response and overcome tumor resistance mechanisms

# Definitions

- Vaccine = antigen or antigen mimic + adjuvant + excipients
  - Multiple simultaneous vaccines are not combinations
- Other agent(s) not a vaccine (for simplicity we assume one other agent)
  - Cytokines
  - Immunomodulatory small molecules/Mabs eg, co-stimulatory inhibitors/enhancers
  - Inhibitors of tumor-related immune suppressor mechanisms
  - Treg depletors
  - Cellular therapies (dendritic cells; T cells)
  - Chemotherapy
  - Radiotherapy

# Toxicology testing for cancer vaccines

- Limitations
  - Non-human immune systems
  - Human antigens in animals
  - In practice, little predictive toxicity in animal models, irrespective of vaccine/combination
  - Poor predictiveness for starting dose and tolerable dose range
- Opportunities
  - Improving biological models

# Recommended approach

- Consider prior safety data on components
- Maximize use of safety data from advanced animal models
- Understand the relevant science
- Adopt a flexible approach in discussion with regulatory authorities

# Prior component safety data

- If none, and combination is considered only route forward, combination toxicology only may be considered
- If extensive pre-clinical or clinical component safety data, consider direct progress to Phase I with no/limited combination testing

# Animal biology data

- Newly-developed sophisticated animal models
  - Transgenic animals, knock-ins and knock-outs
  - Partial humanization of relevant systems
- Discuss prospective collection of safety data in these settings in place of “standard” 1- or 2-species toxicology

# Consider the science

- Prior safety data
- Knockout toxic effects
- Plausibility of interactions based on mechanisms of action

# Component dose and schedule – Design issues for early clinical studies

- Type of vaccine
- Agent with which vaccine will be combined
- Prior non-clinical experience with each agent alone and in combination
  - safety
  - dose range
  - activity
  - induction of immune responses
  - schedule dependence and interactions
  - pharmacokinetic profile and interactions
- Prior clinical experience with each agent (safety, activity, induction of immune responses)
- Prior clinical and non-clinical experience with similar agents or agents in the same ‘class’

# Objectives of early clinical trials

- Establish/confirm safety
  - Most vaccines usually lack acute toxicity
  - Vaccine biologic effects often occur across wide dose range
  - Major toxicity interaction predicted to be late autoimmune event
- Optimize biological interactions
  - Dose of agents may be less important than schedule

# Component dose and schedule recommendations

- Dose–ranging of vaccine and/or partner may not be necessary when prior clinical experience is available
- May be important to explore schedule interactions
- Immune and tumor response endpoints
  - Use of non-validated immune endpoint may be considered for go/no-go decision
  - Selection of optimal dose/schedule based on anti-tumor effect is difficult in small early stage studies
- Likely to require larger sample sizes per cohort compared to traditional phase 1
  - Statistical input in study design required
- Longer follow-up prior to phase 2 if autoimmune toxicity is possible/expected

# Component control in larger trials

- Established regulatory approach to combinations: “A vs A+B vs B”
- Cancer and cancer vaccines are different
  - Cancer vaccines safe but minimal efficacy
  - Treatment of large numbers of cancer patients with ineffective therapies asks a high price for largely predictable effects
- For some combinations, ineffectiveness of individual components is clear from the start
- Avoid “free riding” of non-contributing components

# Pivotal trials - what you do depends on what you know

- If vaccine (V) or product (P) are known to be effective:
  - P vs P+V
  - V vs P+V
- V and P known ineffective
  - Control vs V+P
- V is ineffective, P is unknown
  - Phase II trial of P
  - OR, Control vs P vs P+V
- P is ineffective, V is unknown
  - Phase II trial of V
  - OR, Control vs V vs P+V
- V and P are unknown
  - Phase II trials of V and P
  - OR, Control vs V vs P vs P+V

# Early stopping to protect patients from ineffective components

- Stopping guidelines for comparative futility on primary endpoint
  - Can be applied to only one arm (eg, drop P early in a Control vs P vs V+P
- Futility based on non-primary surrogate endpoint
- Compare experimental arm to historical control

# The problem of agent availability and ownership

- Important agents not yet in development
- Restrictive development plans
- Different owners of each component
  - Complex contract and legal issues
  - Compounded if both investigational
  - Regulatory issues in approving two investigational agents together