ies a same combination could demonstrate synergism or antagonism across different model systems.

The variable results of the same combination across different tumour models is reflective of the heterogeneity of cancers, pointing to the importance of patient selection. However, most targeted agents were developed in unselected patients and the activities were defined by the population average, often without knowledge of the predictive markers. For combination regimens with more than one targeted agent, the lack of patient selection would not only compromise the efficiency of the clinical studies but also make the outcome data misleading. For example, improved efficacy of a combination may not be detectable in the overall patient population if synergism is dependent on a specific molecular context that is only present in a small subset of patients. Conversely, an improvement in the overall response rate or progression free survival may not necessarily mean benefit of the combination in individual patient, as the results may simply reflect the summation of the outcomes of individual components in different subsets of patients.

Also at issue is the limited guidance for optimal doses for the combination regimens. Specifically, if dose reduction of individual agents is required for combination therapies due to safety issues, would the combination still perform better than single agents at full dose? In addition, it is possible to differentially reduce the doses of the two agents and multiple MTDs may be defined for the same combination. It is however difficult to determine which dose ratio would be optimal.

In addition the sequence of agent administrations is often critical to the outcome of the combination, given the unique mechanisms of actions of targeted agents. Indeed synergism of many combination regimens has been found to be sequence-dependent. However, not uncommonly, different tumour models may produce conflicting results regarding the optimal sequence for the same combination. Without knowledge of the molecular contexts and clinical relevance of the preclinical models, it is difficult to apply these observations to clinical studies.

IMPROVING PRECLINICAL STUDIES: Clearly, more and better preclinical and nonclinical studies are needed for overcoming these barriers. Such non-clinical studies have the potential to enhance our knowledge of the individual agents and their combination, the mechanisms of actions, and markers for responsiveness or resistance, all of which critical to optimizing the strategy for clinical development of combination regimens. Nevertheless, the limitations of preclinical studies must also be appreciated in order to appropriately use the model systems.

Some ideas to improve preclinical studies were offered. A systematic effort is needed to molecularly characterize the human tumours and preclinical models. Experiments for specific combinations should be carried out in multiple tumour models and include clinically relevant doses and exposures. The single-agent control should be based on the full dose for comparison with the combination regimen. More importantly, results should be interpreted in the molecular context of the models to maximize translatability to the clinical settings.

One also cannot overemphasise the importance of correlative studies for the search of predictive and pharmacodynamic markers. These correlative studies are not only important in clinical trials but should start from non clinical studies, including those on cell lines and animal models.

CONFLICT OF INTEREST STATEMENT: Dr. Helen Chen is an employee of Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI) and it can be confirmed that there is no conflict of interest involved in this paper, nor in her participation in this entire event.

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doi:10.1016/j.ejcsup.2007.09.030

A CLINICAL DEVELOPMENT PARADIGM FOR CANCER VACCINES AND RELATED BIOLOGICS

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INTRODUCTION: Cancer vaccines present unique developmental challenges. Some potential solutions exist, but they are not widely known nor is there any consensus about their use. The Cancer Vaccine Clinical Trial Working Group (CVCTWG), a joint initiative of the Cancer Vaccine Consortium (CVC) and the international society for biological therapy of cancer (iSBTc), has proposed a new clinical development paradigm for cancer vaccines and immunotherapies through workshops conducted between October 2004 and November 2005.

The goal of CTCVWG was to use collective knowledge in the field to synthesize a flexible and applicable paradigm, reach a

consensus on practical recommendations to improve cancer vaccine development, and offer an accepted, practical approach to cancer vaccine development. To achieve these goals, 200 academic leaders, biotechnology/pharmaceutical drug developers, and regulators attended three workshops and worked together over the course of more than a year.

RATIONALE BEHIND A NEW PARADIGM FOR CANCER VACCINE DEVELOPMENT: Cancer vaccines have distinctly different biologic characteristics compared to cytotoxic agents and, therefore, required an adjusted developmental approach. For example, cancer vaccines do not pose serious toxicity risks, and there is no proof of a linear dose-potency relationship for cancer vaccines. Therefore, it is not necessary to conduct a conventional dose-escalation to establish maximum tolerated dose (MTD). Dose and schedule are not determined through escalation based on toxicity. Because cancer vaccines are not usually metabolized, it is not necessary to conduct conventional pharmacokinetic studies. Many cancer vaccines are designed to address one tumour type, obviating the need to performed mixed tumour trials for target selection. Conventional short-term response criteria (e.g., RECIST) are not very applicable to cancer vaccines, and historical control comparisons on response rates are not useful. Proof-of-principle endpoints should reflect biologic activity, including immunogenicity. Some standard trial designs lack the flexibility to translate new learning into late-phase trials.

In Table 1, the CVCTWG's proposal for a new paradigm for development of cancer vaccines is shown.[1]

In this paradigm, exploratory studies serve the purpose to demonstrate proof-of-principle. Once proof-of-principle is established, efficacy trials should begin. Ideally, such studies should be phase II or III randomized trials. The paradigm is also applicable for combination trials of vaccines and biologics or immunomodulators.

Cancer vaccines generally exhibit little toxicity, but first-in-man studies should include adequate toxicity testing without overly extensive screening for unexpected toxicities. Efficacy trials must be designed with stopping criteria. Generally, there is no need to establish an MTD, but it is desirable to determine the optimal biologic dose.

For proof-of-principle studies, biological activity is defined as the impact of the vaccine on immune response or on the disease under investigation. Relevant parameters include regulatory T-cell activity or immune response against target cells, molecular response (minimal residual disease), or any form of clinical activity (standard or modified parameters). Immunoassays should be established, reproducible, and technically validated in the laboratory where used; no clinical validation is required. Technically validated does not mean clinically validated; rather, it signifies that assay variability has been minimized. With immunoassays, operator inconsistency and lack of standard operating procedures have been identified as problems. A minimum of two such assays should be applied, with an adequate immune response defined as two assays being positive at two or more follow-up time points. Dr. Hoos emphasised the importance of prospectively defining the frequency and magnitude of the immune response for the population under study.

If all the parameters are met, and if a signal of activity of clinical response, biologic activity, or immune response is detected based on prespecified parameters, then one could move forward with efficacy trials.

CLINICAL ENDPOINTS: The characteristics of clinical benefit for cancer vaccines were highlighted. Generally, immune response builds before clinical activity occurs. The onset of clinical activity is often delayed, and slowing of disease progression or an endpoint of stable disease may be more relevant with cancer vaccines than shrinkage of bulky disease.

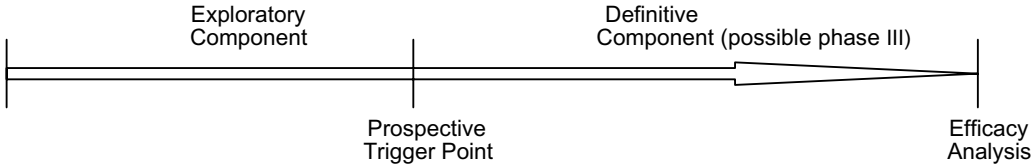
Delayed benefit (response) occurs after disease progression. Therefore, the paradigm calls for continuing vaccination therapy if (1) progression is not rapid and is clinically insignificant; (2) no other therapy is immediately required; or (3) no effective therapy is available. Crucial to this decision are the choice of patient population and the rapidity of progression.

Some caveats are associated with clinical endpoints: for example, for response rates, progressive disease may occur before detectable benefit. Delayed benefit can lead to premature discontinuation. Cancer vaccines might slow progression but not cause tumour shrinkage. Response might require more easily quantifiable parameters, such as biomarkers. The study design can take these factors into account by allowing for prospective modification of response assessment: if response is detected after initial progression, evaluation should either not consider progressive disease prior to response or reset the baseline to the largest tumour volume after the initiation of treatment. The design should also stipulate a time window during which any delayed

Table 1 – Proposed development paradigm for cancer vaccines

Phase of development	Purpose
Proof-of-principle trial(s)	Safety database initiated
(Exploratory trials) $N > 20$	Proof-of-principle: immunogenicity, biologic activity, clinical activity
Well-defined population	Use established and reproducible immunoassays
No end-stage disease	Dose and schedule of vaccination as feasible
Discuss continuation with regulatory agencies	
Efficacy trial(s) (Randomized trials)	Expansion of safety database
Allow flexibility through prospective adaptive designs	Establishment of efficacy
Post-approval trial	Postmarketing surveillance

Reproduced from J. Immunother 2007; **30**:1–15.[1]



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

Trigger Point characteristics:

- Must not be fully statistically powered to demonstrate superiority ($p\alpha$ or $p\beta$)
- Separate, independently powered endpoints for both analyses: less definitive trigger point 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 trigger point data
- Allow for modification of eligibility criteria for phase III component to focus on a specific population
- Allow for start of phase III trial either through continuation without change or protocol amendment

Other characteristics:

- Data from phase III component not to be pooled with phase II 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 special protocol assessment should occur prior to initiation

Fig. 1. Example of a randomized phase II trial with an adaptive component.

response must occur. Most of these caveats also apply to endpoints such as progression-free survival, disease-free survival, and time-to-progression. Overall survival is the gold standard for efficacy trials of cancer vaccines as it is for other anticancer therapies.

Surrogate biomarker endpoints, defined as objectively measured parameters to indicate normal or abnormal biological processes might be used in clinical vaccine development. It is challenging to establish biomarkers that can serve as clinical endpoints. For proof-of-principle trials, unvalidated surrogates or biomarkers may be used to establish biologic activity, but they must be validated to serve as efficacy endpoints. Biomarkers should be used as frequently as possible, at least for proof-of-principle studies, to support their validation in clinical trials. We also need to expand the repertoire of clinical endpoints for efficacy.

Efficacy trials are direct follow-ups to proof-of-principle trials. They bridge the gap of conventional phase II trials (single arm, conventional response rate endpoint historical control comparison, end-stage disease), which are not recommended for cancer vaccines. Adaptive designs my save time (Fig. 1).

One type of design appropriate for cancer vaccines is the comparative, randomized phase II trial with an adaptive component using a prospectively defined trigger point. Sample size can be recalculated at the trigger point. This type of design can help identify patients who might benefit most from the vaccine and alleviates the risk of having a negative phase III study at the end of the development process. Even if the definitive component stands alone as a phase III trial, the development path can be meaningfully accelerated.

CONFLICT OF INTEREST STATEMENT: Dr. Axel Hoos is an employee of Bristol Myers Squibb Inc and it can be confirmed that there is no conflict of interest involved in this paper, nor in his participation in this entire event.

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doi:10.1016/j.ejcsup.2007.09.031