A Clinical Development Paradigm for Cancer Vaccines and Related Biologics

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Summary: Therapeutic cancer vaccines are a heterogeneous group of complex biologics with distinctly different clinical characteristics than cytotoxic agents. The current clinical development paradigm used for oncology drug development is based on criteria developed for cytotoxic agents. More flexible and focused developmental guidelines are needed to address the unique characteristics of therapeutic cancer vaccines. Over the course of 1 year, the Cancer Vaccine Clinical Trial Working Group, representing academia and the pharmaceutical and biotechnology industries with participation from the US Food and Drug Administration, defined in a consensus process the cornerstones of a new clinical development paradigm for cancer vaccines and related biologics. Four major topics were addressed: (1) end points for clinical trials, (2) trial designs and statistical methods, (3) technical and developmental challenges, and (4) combination therapy.

The proposed paradigm suggests therapeutic cancer vaccines to be investigated in 2 general types of clinical studies: proof-of-principle trials and efficacy trials. Proof-of-principle trials, which introduce a novel cancer vaccine into humans, should include a minimum of 20 or more patients in a homogenous, well-defined population in an adjuvant setting or without rapidly progressive disease in a metastatic setting to allow vaccines adequate time to induce biologic activity and should incorporate immune and molecular markers. Objectives should include initiation of a safety database, determination of dose and schedule, and demonstration of biologic activity as proof-of-principle. Biologic activity is defined as any effect of the vaccine on the target disease or host immune system using biologic markers as study end points, for example, clinical, molecular, or immune response. Immune response is demonstrated if determined in 2 separate, established and reproducible assays at 2 consecutive follow-up time points after the baseline assessment. If proof-of-principle trials show such immune response, or other biologic or clinical activity, efficacy trials may be initiated. If none of these end points is met, the clinical development plan should be reevaluated to decide if further development is warranted. Efficacy trials formally establish clinical benefit either directly or through a surrogate and are encouraged to be randomized studies. This is in contrast to single-arm phase 2 trials used for cytotoxic agents, which often use tumor response rate as the primary end point and historical controls as a comparator. Efficacy trials may use prospectively planned adaptive designs to expand from randomized phase 2 into phase 3 studies if well-defined trigger-point criteria are met, but the cost of incorporating such design elements should be carefully evaluated. Efficacy trials can also be exploratory randomized phase 2 trials or conventional phase 3 trials. In addition, conventional clinical end points can be adjusted to account for biologic features of cancer vaccines. The concept of efficacy trials allows for an early assessment of vaccine efficacy based on credible prospective data. This 2-phase developmental paradigm supports a more flexible, expeditious, and focused clinical developmental process with early and informed decision making. In addition, this report addresses clinical development challenges and issues for combination therapies.

Key Words: cancer vaccines, clinical development, paradigm, clinical trial, trial design

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SCOPE

Therapeutic cancer vaccines represent a heterogeneous group of biologic agents,[1,2] whose clinical development can be hampered due to the frequent application of the conventional oncology drug development paradigm established for cytotoxic agents. There is considerable need for a clinical development paradigm for cancer vaccines and related biologics based on consensus between a wide range of stakeholders in the cancer immunotherapy field.

This document summarizes the positions of the Cancer Vaccine Clinical Trial Working Group (CVCTWG) regarding the following topics: (1) end

points for clinical trials, (2) trial designs and statistical methods, (3) technical and developmental challenges, and (4) combination therapy. The CVCTWG consists of a group of over 50 experts from academia, regulatory bodies, and the biotech/pharmaceutical industry from America and Europe. All positions were based on the current state of knowledge and were reached in consensus between participants throughout 5 group discussions per topic on the phone and 3 Workshops conducted between November 2004 and November 2005. Results were presented to a wide audience of about 200 stakeholders in cancer immunotherapy development at the concluding Workshop in November 2005 in Alexandria, VA. The results are presented here.

BACKGROUND

The conventional clinical drug development paradigm in oncology involves 3 phases and was implemented for conventional cytotoxic drugs. It is based on several assumptions that are less or not relevant to the development of therapeutic cancer vaccines. These include that antitumor activity of an agent inevitably is connected to serious toxicity risks and that maximizing dose should maximize efficacy. Hence, the compelling requirement to determine the maximum tolerated dose (MTD) underlies the design of conventional phase 1 dose-escalation trials. However, cancer vaccines are generally much safer than cytotoxic agents, and the dose that yields sufficient immunogenicity and biologic activity is unlikely to confer significant toxicity. Justification of the vaccine dose selected for later phase studies is not based on the safety profile, but rather on biologic or clinical activity and possibly practical factors. Another conventional phase 1 goal is characterization of the pharmacokinetics (PKs) of the experimental agent. This concept only applies to systemic agents whose absorption, distribution, metabolism, or excretion parameters can be reliably measured. Cytotoxic agents are usually absorbed, metabolized, and excreted, the PKs of their active and precursor species can be measured and often are related to their toxicity profile. In contrast, the PK behavior of cancer vaccines injected intradermally or subcutaneously or even cells injected intravenously at present cannot be meaningfully assayed for many immunotherapy products. An example is the injection of disease-specific peptide antigens into the intradermal space aimed for uptake by dendritic cells and induction of a systemic T-cell response via MHC pathways initiated in dendritic cells. The processing of the peptides and systemic effects of resulting T-cell activity are not quantifiable with present methods and there is no established theory for a linear relationship between dose of peptide administered and the magnitude/potency of a potentially resulting T-cell or clinical response.

Conventional phase 1 trials in oncology often enroll patients with various tumor types at a late stage of disease with one secondary objective being the identification of a tumor type with antitumor activity. Often anecdotal cases of response in a given tumor type lead to further development of the agent in that tumor type. In contrast, selection of the appropriate target patient population is inherent in the first step of most cancer vaccine trial designs due to the disease-specificity of the vaccine. Examples are the selection of autologous or allogeneic tumor cells, or tumor-specific antigens, from which the vaccine will be manufactured. Conventional short-term response criteria based on shrinkage of established tumor mass (eg, Response Evaluation Criteria In Solid Tumors[3]) are the cornerstone of trials investigating cytotoxic drugs. In contrast, they are not always applicable to cancer vaccines or other immunotherapeutic agents because the absence of tumor shrinkage may not be reflective of the relevant biologic or clinical activity of the vaccine. For conventional chemotherapeutic drugs, an antitumor effect in form of tumor shrinkage is expected soon after exposure to the cytotoxic agent. In contrast, the mechanism-of-action for vaccines involves immune activation and building of an immune response over time. An immune response has the potential to translate into a long-term clinical impact on the target disease and may be better assessed as disease stabilization or survival improvement. It is currently assumed, immune effects induced by vaccines may less likely reduce bulk of tumor but more likely target small quantities of cancer cells or minimal residual disease (MRD). Thus, single-arm trials using historical control data as the comparator and short-term end points like tumor response may not reflect the full extent of the product to induce clinical activity. Instead, end points in early trials with cancer vaccines should reflect parameters of biologic activity. Clinical end points adjusted for the biologic features of cancer vaccines will also be important.

There is often a linear dose-potency relationship for cytotoxic drugs, which allows for titration of dose for further study. For cancer vaccines, there may not be any linear association between dose, immunogenicity and clinical end points, possibly due to a multistep, leveraged process of immunologic and subsequent clinical responses. Therefore, dose and schedule of vaccination can be studied in early phase trials, but optimization of dose should remain flexible at this stage. More often, especially for autologous vaccines, practical concerns will justify the selection of dose for later phase trials. As an example, similar levels of immune response may be induced at distinctly different dose levels, whereas immune response, as measured with currently available assays, may not be associated with clinical outcome (particularly if objective tumor shrinkage is the clinical outcome).

In summary, the early phase of cytotoxic drug development in oncology involves aspects of reduced relevance to therapeutic cancer vaccines. Absent the need to establish the MTD, characterize PKs, or identify the appropriate target population, early phase cancer vaccine trials need to focus on other goals that may permit more rapid assessment of therapeutic potential. Paramount is the establishment of an active dose regimen providing proof-of-principle and the generation of sufficient safety data to permit the rational design of randomized trials

that would yield registration quality data; that is, data that determines efficacy of the vaccine in the target population. An alternative development paradigm more appropriate for therapeutic cancer vaccines and related biologics is outlined below.

A CLINICAL DEVELOPMENT PARADIGM FOR CANCER VACCINES AND RELATED BIOLOGICS

The intention of the clinical development paradigm for therapeutic cancer vaccines proposed herein is to introduce flexibility in the developmental process. The proposed paradigm does not aim to provide strict guidelines or replace the standard paradigm in cases where the standard may be more appropriate. The proposed paradigm suggests investigating cancer vaccines in 2 phases corresponding to 2 general types of clinical studies: *proof-of-principle trials* and *efficacy trials* (Table 1). It supports a more flexible, expeditious and focused clinical developmental process with early and informed decision making through prospectively defined "go" or "no go" decision points, use of biologic end points, adjusted clinical end points, early use of randomized trials and adaptive design components, where applicable.

Proof-of-principle Trials

Proof-of-principle trials are exploratory trials, which combine some aspects of conventional phases 1 and 2 trials. They introduce a novel cancer vaccine or related biologic agent into humans and generate the data necessary to plan efficacy trials. It may be desirable to perform one or more proof-of-principle trials, based on the nature and sequence of the outcomes to be measured.

Objectives

Three lead objectives should be addressed: investigate safety and initiate a safety database; investigate dose and schedule; demonstrate proof-of-principle through biologic activity (including immune response) or clinical activity.

General Characteristics

Proof-of-principle trials should be conducted in defined patient populations, which may resemble the target population for efficacy trials and should investigate disease-specific biologic parameters (eg, molecular

markers) to demonstrate biologic activity. The investigated population should include a minimum of 20 patients allowing for sufficient data to assess safety (acute, common toxicities). The general statistical objective should be to document the nature and estimate the likelihood of toxicities, determine the presence and frequency of a biologic effect, and estimate the association between dose and/or schedule and signals of biologic effect. Due to the heterogeneous nature of signals of biologic effects formal narrow statistical criteria guiding the decision to move forward in the development plan are not specified in this general paradigm. Patients should not have rapidly progressing disease to allow for sufficient time for biologic and potential clinical activity to develop. In such populations, it may be appropriate to continue therapy beyond early, clinically nonsignificant disease progression to allow for a late response to occur. A patient population, in which patient withdrawal based on early disease progression can be minimized, should be chosen. This should allow for a minimum number of vaccine doses to be administered and/or a minimum time interval from initiation of therapy to have elapsed, so a delayed response, which may follow initial progression can be detected.

Toxicity

Cancer vaccines are generally much safer than cytotoxic agents. In a proof-of-principle study, the following steps would allow for adequate toxicity testing/screening:

1. conduct a standard safety panel of examinations/tests to cover major organ systems as used in general oncology drug development;
2. address vaccine-specific toxicities unique for the investigated product based on toxicity expectations from preclinical models; this should include autoimmunity as applicable;
3. allow for investigation of unexpected toxicities through collection of serum and other samples from patients at predefined time points, and ad-hoc when toxicity occurs. These samples will be used for further laboratory testing in case unexpected toxicity is being observed throughout the proof-of-principle study.

Such approach would allow reacting to safety needs in an ongoing proof-of-principle trial without extensive

TABLE 1. New Clinical Development Paradigm for Cancer Vaccines and Related Biologics

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 immune assays
No rapidly progressing disease	Dose/schedule of vaccination investigated as feasible
Discuss continuation with relevant regulatory authorities	
Efficacy trial(s)	Expansion of safety database
Randomized trials	Establishment of efficacy
Allow prospective adaptive designs	

prospective screening. Criteria for stopping the trial for unexpected toxicity should be included in the design.

Pharmacokinetics

Cancer vaccines generally are not metabolized in reliably measurable ways and therefore conventional PK measurements are of limited use. However, vaccines that involve measurable drug products such as transfected tumor cells producing cytokines may have different requirements if a measurable effect or product is clinically meaningful. Therefore, PK study requirements should be individually defined for the product investigated.

Biologic Activity

In general, biologic activity should include the demonstration of an impact of the vaccine on the immune system of the patient or impact on the disease under investigation. End points, which could be used to determine biologic activity, might be T-cell immune response to target antigens, regulatory T-cell activity, molecular response (MRD), cytogenetic response (where applicable), or conventional tumor response (where appropriate) in both the adjuvant or the advanced disease setting. Such end points could allow for rapid assessment of biologic activity. For the individual vaccine product, such end points should be included in proof-of-principle trials.

Immune Response

Immune assays can possibly provide a rapid and quantitative measurement of the relative immunogenicity of well-defined cancer vaccines and are a measure of biologic activity. In general, immune assays should be standardized and thus allow for comparisons of results from different clinical trial centers and enable rapid progress in optimization of vaccination strategies for example, dose, route, schedule, antigen/adjuvant combination, boost, heterologous prime/boost, among others. Frequently used immune assays include cytotoxicity assays, intracellular cytokine assays, tetramer assays and the ELISPOT assay.[4,5] However, these assays are rarely technically validated in the respective laboratory, no standardization within the immunotherapy community is established and there is still considerable variability of results between laboratories. These assays do not necessarily need to be clinically validated to be useful. The following criteria are recommended to allow for an immune response to be identified by one of the above assays: (1) the maximum justifiable amount of sample material per patient should be collected to perform the assay and permit for repeat testing; (2) samples should be taken sequentially; (3) a minimum of 3 assay time points should be investigated: baseline and at least 2 follow-up time points; (4) assays should be established, reproducible, and technically validated in the respective laboratory (no proved correlation with clinical outcomes should be required); (5) a minimum of 2 such assays should be applied; (6) the frequency and magnitude of an immune response should be prospectively defined for the popula-tion under study. Under these conditions, an immune response (single marker or composite of markers) is identified if it was seen in at least 2 assays at 2 consecutive follow-up time points after the baseline assessment.

Clinical Activity

Clinical activity constitutes any improvement in clinical outcome using established definitions such as response (tumor regression), progression-free, recurrence-free, or overall survival. Standard patients in conventional phase 1 clinical trials in oncology have end-stage disease, have relapsed or progressed on previous therapies and may be immune compromised. In such patients, cancer vaccines are unlikely to demonstrate conventional signals of clinical activity such as measurable shrinkage of bulky disease, or prolongation of time to recurrence, progression, or death in single arm studies. Therefore, it is proposed to:
1. identify the appropriate patient population considering the end points of the proof-of-principle trial (which may lead to less frequent use of end-stage patients) and
2. not to emphasize clinical activity as a measure of success in proof-of-principle trials but focus on biologic activity.

Dose and Schedule

Dose and schedule should be investigated in proof-of-principle trials, however, a definitive answer on the optimal setting for further trials should not be expected from a first-in-human study. Although preclinical studies have limited relevance to the selection of dose and schedule, they can help defining the starting dose for first-in-human studies, and their value must be assessed on an individual basis. In the first-in-human trial, a cohort design similar to that used for conventional phase 1 trials is recommended. This trial would not be focused on the MTD paradigm but rather on assessing the relationship between dose and schedule and a biologic outcome with careful monitoring for relationships to observed toxicities. The outcome could be biologic activity measures (defined above) or clinical end points (described below). The safety outcome for each cohort should be evaluated before initiation of the next cohort with each subsequent cohort having some systematic variation of dose and/or schedule. This may either be a predetermined variation, or the dose/schedule of the next cohort could be based on biologic activity measures from previous cohorts (eg, maintenance of immune response). Cohort sizes and the number of cohorts will depend on balancing between (1) minimizing risk to the patient, (2) obtaining data contributing to the assessment for potentially rare events, (3) the expected variation of the measures of biologic outcome, (4) the number of biologic outcome measures, (5) the magnitude of meaningful differences between biologic outcome measures. As a starting point cohort sizes of at least 6 patients per cohort are suggested. Unfortunately, the body of literature for optimizing the size of conventional phase 1 trials has little applicability to designing a proof-of-principle cohort trial

because of the differences in the types of outcome measures and objectives. The withdrawal of patients from a proof-of-principle trial should primarily be based on toxicity or clinically significant disease progression after a minimum time period and number of vaccinations to allow for a delayed response to occur. When the presumptive dose and schedule are attained for a given cohort, the trial design should allow for expansion of that cohort as appropriate. Another consideration regarding the size of the first-in-human trial is the degree to which the types of biologic activity outcomes to be assessed could benefit from randomized assignment to dose and/or schedule regimens. If the differences between biologic activity outcome measures for dose/schedules regimens are expected to be subtle then randomization may be important to eliminate confounding outcome difference with regimen group differences. If randomization between dose/schedule groups (including possibly a 0 dose group) is desirable then the size of first first-in-human proof-of-principle trials should be adjusted with the goals of subsequent studies in mind.

Decision Criteria to Advance into Efficacy Trials

If proof-of-principle and safety have been demonstrated, development may move forward into randomized trials focused on the demonstration of efficacy. If proof-of-principle in the respective patient population is solely based on immune response the decision about moving forward should be an assessment of the risk/benefit ratio in comparison with the existing standard of care by the vaccine developer.

Efficacy Trials

Efficacy trials in this paradigm establish clinical benefit or the likelihood thereof either directly or through a surrogate and in general should be randomized clinical trials. Efficacy trials may use prospective adaptive designs to expand from randomized phase 2 into phase 3 studies if well-defined trigger-point criteria are met. These trials are intended to be a direct follow-up to proof-of-principle trials and bridge over the gap of the no longer recommended conventional phase 2 trials. They will confirm the data obtained in proof-of-principle trials and demonstrate efficacy. Their design can either be like conventional phase 3 trials, or comparative randomized phase 2 trials with adaptive component to be expanded into phase 3, or other designs able to produce credible clinical data to demonstrate efficacy. Depending on the developmental path of the product under study and findings from earlier trials, more than one efficacy trial may be needed. The concept of efficacy trials allows for an early assessment of vaccine efficacy and a more rapid and informed development of cancer vaccines. Examples for efficacy trial designs and definitions relevant to the developmental paradigm are described below.

Randomized Phase 2 Trials

Randomized phase 2 trial can be the following:

Noncomparative Randomized Phase 2 Trials

Under the strictest definition the randomized phase 2 study is a collection of single-group historically controlled trials where subjects are allocated randomly to the trials.[6] These single-group historically controlled trials are performed in parallel and have a higher degree of comparability between patients assigned to each trial (arm). Each single group historically controlled trial should be evaluated separately because the statistical power to compare the outcomes between trials is limited due to small sample sizes and may not allow definitive conclusions about superiority of one arm. Criteria to decide the outcome in these trials are based on meeting the statistical goals for each trial.

Comparative Randomized Phase 2 Trials

These trials are powered to show a statistically significant difference between 2 arms in a well-defined patient population using a well-defined primary outcome measure. They may also be stratified to achieve additional balance for known prognostic factors. The outcome measure may not be what will be ultimately used in phase 3. For example, biologic outcomes (biomarkers) often give smaller trial size requirements and shorter study durations than do dichotomous or time-to-event outcomes. Projected differences between arms can be set as relatively large compared with those used in phase 3 and may not always be achieved even if the product has activity; the intent would be to carry forward with phase 3 even for suggestive but not statistically significant results. If positive and well conducted, evidence of efficacy can be provided by comparative randomized phase 2 trials.

Comparative Randomized Phase 2 Trials With Adaptive Component

Such trials are the phase 2 component of a phase 2/3 trial aiming to demonstrate efficacy of a novel product. They have the stringency, prospective design and planned conduct of a conventional phase 3 trial. The phase 2 component has a specific finish at a prospectively defined trigger point of efficacy. If a prospectively defined efficacy goal is achieved, it will trigger the activation of the full phase 3 trial. If the prospectively defined efficacy goal is not achieved, the study will be terminated. The definition of the trigger point and the parameters to measure it is crucial. Trigger points are prospectively defined and may be relatively complex. For example, a less definitive end point in the first phase (eg, molecular response) triggering expansion of the study and a more definitive end point (eg, overall survival) in the second phase demonstrating efficacy in the expanded study may be used. Trigger points may not be fully statistically powered to demonstrate superiority ($p\alpha$ or $p\beta$) and may be independent from the primary efficacy end point. Independence of end points may avoid paying a statistical penalty. Adaptation of such trial may not only entail an adjustment in sample size. It may also allow for modification of eligibility criteria to focus on a specific population, which benefited particularly from the investigational agent in the first

phase of the study. Such adaptive design is only acceptable if it was prospectively specified that criteria identified in the early phase could lead to a change in population. It is not required to specify the precise criteria at the beginning of the trial because this may not be feasible before having data from the earlier phase. Adaptation may also allow for sample size recalculation based on interim data. The adaptive later-phase component can either be activated through continuation from the earlier phase without change, or through a protocol amendment if changes were implemented. If the adaptive component is not activated, comparative randomized phase 2 trials with adaptive component will generally have the characteristics of a comparative randomized phase 2 trial. If the adaptive component is activated they will transform into a conventional phase 3 trial. For formal demonstration of efficacy, data from the later phase 3 component cannot be pooled with the earlier phase 2 data except when the used end points are different.

Conventional Phase 3 Trials

These are usually large-size randomized clinical trials with definitive or surrogate clinical end points designed to demonstrate superior efficacy or noninferiority of the product under investigation in comparison with the present standard of care. They are statistically fully powered to support the specified difference between both arms and often also have the power to discriminate between stratification variables in the final analysis. They often specify additional secondary analyses for full exploration of the product effect on the treated population.

Tandem Proof-of-principle and Efficacy Trials

Under certain circumstances it may be appropriate to design a combined proof-of-principle trial with clinical end points and an efficacy trial so that they are executed in tandem. Such a trial will be prospectively designed and planned and usually be a randomized trial. Whether such a design is optimal in any given situation will depend on many factors, including: the complexity of the clinical setting, the potential for obtaining data that would result in unplanned modifications to the randomized trial, the potential for advances to induce unplanned modifications, and whether the time spent planning the tandem trial would truly result in a savings of time, administrative burden, and developmental resources given the previous considerations.

CLINICAL TRIAL END POINTS

Any clinical study of therapeutic cancer vaccines must take into account the unique characteristics of the vaccine and the patient population under study. Conventional measures of efficacy have served the drug development community in the setting of cytotoxic drug development but the use of these same efficacy measures may require modification when applied to trials using cancer vaccines.

Patient Selection

In any clinical study designed to support licensure, the population studied must support the proposed use of a product. In clinical studies of cancer vaccines the inclusion criteria should reflect the population that has the potential to benefit from the therapy, based on proof-of-principle studies. Enrichment strategies may be considered that use biomarkers and other surrogate markers for prognosis even if these markers have not been validated as surrogates for efficacy. For example, patients with prostate cancer and short prostate-specific antigen doubling times or patients with completely resected stage IV melanoma are at high risk for recurrence. Time to event studies including these patients would likely reach study objectives relatively quickly.

Survival

Of the existing efficacy measures, survival is most easily applied to both conventional chemotherapeutic trials and cancer vaccine trials. Demonstration of a survival benefit (ie, time to death irrespective of cause) is the accepted "gold standard" for products to demonstrate clinical benefit for the treatment of cancer.[7] However, when using survival as the primary end point, one must balance the need for a reasonable follow-up period with the need for a patient population that is most likely to respond to a vaccine. Survival is subject to confounding by subsequent therapies, and may not be the most appropriate end point for the demonstration of clinical benefit in the initial therapy for many cancers. Patients with advanced cancer, bulky disease, and limited life expectancy may also exhibit immune suppression that may make them inappropriate for evaluation of a product that depends on an effective immune system for activity.

Other Time-to-event End Points

Delay in the onset of cancer recurrence or progression might be expected to lead to improvements in survival and other clinical benefits. Time-to-event end points other than survival, such as disease-free survival (DFS) in the adjuvant setting, and progression-free survival (PFS) in the advanced and metastatic disease setting, have increasingly seen acceptance as surrogates for clinical benefit.[7] Therapeutic cancer vaccines pose the possibility of a delayed onset of activity. This is based on the time required to mount an effective immune response and the time for that response to be translated into an observable clinical effect. As such, patients may experience early tumor progression before eventual tumor regression. If the conventional definition of DFS or time-to-progression (TTP) is used, there is a possibility for premature treatment discontinuation in a patient who could ultimately experience benefit from a cancer vaccine. This might be avoided by modifying the definition of progression requiring confirmation on at least 2 observations or by not considering early progression within a prospectively defined time-interval (eg, 3 mo from therapy start). In those patients who ultimately respond after an early period of progression, the date on which to base the

subsequent calculation of DFS or TTP would remain the date of the start of therapy. Any improvement in DFS or TTP may also constitute a clinical benefit if it is indicated by a low-toxicity cancer vaccine and leads to the delay of toxic therapies.

Response Rate

Response or tumor shrinkage, commonly used as a measure of clinical activity in the setting of cytotoxic therapeutics, may be a less relevant measure of vaccine efficacy in the treatment of solid tumors. As noted previously, early tumor progression may occur before the onset of clinical effects after a slowly developing antitumor immune response. Furthermore, a cancer vaccine may fail to induce tumor shrinkage yet still be effective in slowing the rate of progression. If not anticipated by the study design, such situations could lead to the premature discontinuation of therapy in a single patient and cancellation of the development for an otherwise active product. Adjustments to the definition of response can be made to render this end point more suitable for cancer vaccine trials. In a manner similar to DFS or TTP, an allowance can be made for the continuation of treatment of the face of early and clinically insignificant progression. Patients who experience tumor regression after initial tumor progression might be scored for response based on the largest tumor volume measured after the start of treatment, not necessarily from the baseline tumor volume. This may result in a response rate that more accurately reflect the efficacy of the vaccine under study, provided that durability of these responses is also demonstrated.

End Point Modifications

Continuation of treatment in the face of early progression, although generally considered inappropriate in a study using cytotoxic chemotherapy, may be justified in the setting of a vaccine trial if the vaccine causes minimal toxicity and if delaying alternative treatment does not disadvantage the patient. Examples include the use of a vaccine in an adjuvant setting where the appearance of a small new lesion (conventionally considered an indication of progression), may not mandate an immediate switch to alternative treatment. The precise and prospective definition of this period must be cognizant of the rates of tumor growth and immune response generation. Risk-benefit considerations must also take into account the availability and proven benefit of therapeutic options in the patient population under study. In those patients who ultimately respond after an early period of progression, the date on which to base the subsequent calculation of DFS or TTP would remain the date of the start of therapy. The precise definition of progression might be based on observations made during the proof of concept phase of clinical development. For example, if a proof-of-principle study showed that most responses occurred within 3 months of therapy initiation, then if early progression occurred and no clinical effect was observed after 3 months of cancer vaccine therapy the patient would be scored as having progression at the time progression was initially observed. If a response were to be observed within the 3 months, then the initial progression would not be scored. In general, these "time-to-event" end points should incorporate death as an event (PFS not TTP) unless it can be shown that death from events other than the disease under study are likely to confound results.

Patient Reported Outcomes and Quality of Life End Points

Improved patient quality of life is viewed as a clinical benefit by US and European regulatory agencies, however, demonstration of this benefit in the context of clinical trials in oncology has proved problematic. Quality of life measures need to be prospectively validated and analysis plans thoroughly discussed before study initiation if efficacy is to be based on patient reported outcome measurements.[8]

Biologic Markers

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal or abnormal biologic processes. These biomarkers can be useful in terms of defining a study population, and are in various stages of validation as surrogates for efficacy.[9] Although it is currently not acceptable to base an efficacy trial to be used for product registration on nonvalidated biologic markers as surrogates for efficacy, it is important to use meaningful biologic markers, which can be measured with established and reproducible tests, before such efficacy trials. This applies to single markers and composites of markers such as genomic profiles or a matrix of immunologic parameters.[10] Early use of biomarkers may also contribute to their validation. A surrogate end point based on biologic markers could be validated through the composite analysis of multiple phase 2 studies or randomized trials. The most important element of validation would be to show correlation between clinical outcome and the biomarker in a prospective fashion. However, there are 2 types of markers, which may require different levels of validation. The first is associated with the disease itself and therefore could be a prognostic factor, and a surrogate end point. The second is a markerlike immune response, which is related to the therapeutic intervention rather than the disease itself. For the first type, validation could consist of proof-of-correlation between outcome of the disease and the biologic marker, which possibly can be demonstrated in single-arm studies. For the second, validation includes randomized trials aiming to demonstrate an increased immune response is correlated with better outcome but may be very complex.[11]

Cancer vaccines are currently expected to have the best clinical benefit in populations with MRD.[12] Therefore, molecular markers that can be used for a relatively uniform assessment of MRD and the impact of a vaccine on the target disease may function as a measure of biologic and/or clinical activity in clinical trials. An example

is chronic myeloid leukemia, in which a well-defined canonical molecular abnormality, the Philadelphia chromosome, can be measured via well-established real time-polymerase chain reaction methods to determine biologic and clinical activity.[13] This is in contrast to many other cancer indications, where molecular makers may exist but are not uniformly present in all patients. Therefore, an array of markers representing multiple molecular abnormalities would need to be used to determine biologic activity. This may not necessarily be feasible for a pivotal phase 3 trial as a clinical end point but potentially to determine biologic activity in proof-of-principle trials and trigger initiation of efficacy trials.

Biomarker information should be incorporated into clinical trial designs wherever possible to retrospectively analyze whether particular biomarkers were associated with clinical benefit.[12] This includes the frequent collection of patient sample materials such as blood from peripheral circulation or bone marrow (as appropriate), lymph node or tumor tissue, tumor infiltrating lymphocytes, vaccine-site, or delayed-type hypersensitivity injection site biopsies, among others. Patient consent forms should specifically request donation of blood and tissue for research and permission for such future, unspecified studies using the necessary precautions for preserving patient anonymity.

DEVELOPMENT CHALLENGES

Criteria for Clinical Development

Several major decision points are encountered during cancer vaccine development, and each presents unique issues due to their novelty and complexity. These decision points include: (1) selection of the product candidate, (2) initiation of nonclinical development, (3) initiation of proof-of-principle trials, and (4) initiation of efficacy trials. Each decision to move forward involves a considerable increase in the required resources. Consequently, such decisions should be made in the context of a thorough assessment of the program to avoid costly set-backs at later stages.

At each of these checkpoints it is important to evaluate and revise the complete product development plan, which should, at every step, include an assessment of issues related to Chemistry, Manufacturing, and Controls as well as Toxicology/Safety, Pharmacology, and Clinical/Regulatory strategy. The long-range logistical, regulatory, and commercial implications of each issue identified at each development step should be considered. For instance, issues such as the presence of undesirable genetic sequences, the necessity for poorly characterized raw materials for production, or the product manufacturability at the desirable scale need to be assessed at the stage of product candidate selection. Other issues, such as the feasibility of developing a given vaccine product in the selected patient population, and assessment of the maximum feasible dose for further development (because safety concerns are unlikely to drive dose selection) should be addressed during early

clinical development. Before initiation of efficacy trials, a plan for validation of the manufacturing process and the product characterization and release criteria tests should be developed.

Product Standardization and Characterization

Due to the generally complex nature of cancer vaccines, standardization of the vaccine manufacturing process and characterization of the vaccine product are a considerable and continuous challenge. Control of the vaccine component materials is a critical first step in product standardization. This includes maintenance of a derivation history for all vaccine components (especially bovine products) and avoidance—whenever possible—of undesirable, unstable or poorly characterized raw materials, cell lines or process intermediates. For many products, especially those of autologous nature, the manufacturing process defines the product, so the impact of process changes on the final product requires careful evaluation, and determining how much and how soon to standardize the process during product development is challenging.

Product characterization, when conducted throughout all stages of vaccine development, can provide invaluable information on how to determine vaccine potency, predict clinical outcome, determine the effect of a manufacturing change, or determine the stability of the product. Characterization of purity and potency can be particularly challenging. If the product is composed of heterogeneous components (eg, autologous blood or tumor-derived vaccines) attention should be paid to characterizing the "other" cells in the product as part of the purity evaluation. Establishment of potency assays is especially difficult for cancer vaccines due to the lack of established biologic surrogates of efficacy and/or appropriate in vivo models. Therefore, one should evaluate potency markers early in development to establish a database in support of the potency marker(s) eventually selected. Efforts to correlate an analytical test (eg, surface marker expression on a cellular product) with a relevant biologic activity may allow one to replace a complex biologic assay with a simpler analytical test.

Cancer Vaccine Implementation Into the Clinic

Among therapeutic cancer vaccines currently in development, patient-specific, autologous products pose the greatest technical, logistical, and regulatory challenges for implementation, whereas allogeneic, nonpatient-specific products offer a somewhat clearer path forward. Issues to consider early in development include: (1) minimization of manipulations at the clinical site of tissue and final product, (2) careful evaluation of conditions required for product shipment and storage and the commercial implications of such requirements, (3) the impact of product "hold times" associated with shipping and handling on final product characterization, (4) centralization and throughput of the manufacturing process, and (5) the impact of vaccine release turnaround time on initiation of treatment in late stage cancer

patients. In addition, if resection of autologous tumor is required for vaccine manufacturing the safety, feasibility, and financial compensation for such tumor procurement procedures should be considered. Final product heterogeneity is inherent with patient-specific vaccines that are, by definition, unique. Early discussion with regulators to balance the desire for product consistency with an acceptable range for critical product release testing parameters is critical. In general, autologous tumor-derived vaccines are most feasible in diseases where tumor cells are readily available in the bloodstream (eg, acute and chronic leukemias) or tumor resection is clinically indicated in the setting of metastatic disease (eg, renal cell carcinoma).

Regulatory Interactions

At the relevant decision points throughout the development process, such as the introduction of a vaccine into proof-of-principle trials or after the completion of proof-of-principle trials, consultation with the relevant regulatory authorities is encouraged. All interactions, particularly about the overall developmental plan should occur early in the process. This should happen in the form of proposals for development plan review meetings. Thus, the proposed cancer vaccine clinical development paradigm allows for regulatory interactions in accordance with existing practice.

COMBINATIONS OF THERAPEUTIC CANCER VACCINES AND OTHER AGENTS

Antitumor immunity is a complex process involving multiple checkpoints at which successful tumor rejection might be interrupted. Generating adequate number of tumor-specific lymphocytes by active immunization addresses the afferent arm of the immune response. However, multiple downstream tumor escape mechanisms impede the efferent arm or effector phase of the antitumor immune response. Future tumor immunotherapy may therefore involve possibly 2 (or more) interventions, one to generate immune effectors (a cancer vaccine), and another to overcome tumor resistance, resulting in a situation where 2 (or more) agents that possess little or no efficacy individually may be effective therapeutics if used together.

Regulatory approval of combinations of therapeutic agents has usually required definitive demonstration of the independent contribution of each component for fixed combination products. Such a demonstration presents practical and ethical problems in patients with lethal diseases such as cancer, especially when one or both components may have limited independent activity. As well, ownership and institutional issues create barriers to creating promising combinations. This section addresses the regulatory, practical, and administrative barriers to the clinical development of such combinations with therapeutic cancer vaccines.

Definitions

Preventive anti-infective vaccines in common use, consisting of a single or multiple immunogens, a simple adjuvant, and inert excipients physically mixed and administered together, have been regarded as a single product from the point of view of preclinical and clinical testing, rather than a combination requiring definitive evaluation of the independent contribution of all 3 components. The definition of a therapeutic cancer vaccine follows the concept for all discussions below. A combination with a cancer vaccine consists of the vaccine itself, as defined above, given with another combination agent, with the intention of generating better cancer treatment outcomes than could be obtained with either agent alone. In this section the 2-component definition above (vaccine plus one combination agent) is used, however, the principles can be applied to combinations of vaccines with more than one combination agent.

The clearest case occurs when the vaccine and the combination agent(s) have different physical and biologic characteristics and are given by different routes or at different times. At times it may not be clear whether a combination agent is independent of the vaccine or is part of the vaccine itself (eg, an adjuvant), and therefore not subject to combination testing; these cases should be clarified in discussions with regulatory authorities.

Preclinical Safety Testing

Therapeutic cancer vaccines of many different types have generally been safe in human use. In addition, animal model systems that replicate the clinical situation of slow development of tumors in the setting of an intact immune system, that can be used to predict the effects of cancer vaccines in humans, and, more importantly, the effects of combination with other agents, are of very limited use. Nonetheless, certain aspects of cancer vaccine use (such as the use of viral vectors), and the potential for the toxicity of new, highly immunologically active, agents that might be combined with cancer vaccines necessitates a suitable approach to preclinical safety testing to support clinical trials. Given the scientific uncertainties, it is proposed to adopt a flexible approach, performing studies likely to be most informative while avoiding tests that contribute little valuable information. Sometimes careful phase 1 clinical testing in the absence of relevant animal models may obviate the need for further preclinical testing of the combination, or conversely indicate a potential risk requiring further assessment. Data on cancer vaccines or combination agents of a similar type or mechanism of action may also be of predictive value. We also recommend obtaining relevant safety data obtained from research studies performed primarily to assess biologic effects as an economical approach to preclinical safety evaluation. Consultation with regulatory authority staff or an experienced toxicologist is recommended in designing such "double-duty" studies.

The investigation of toxicity as described for proof-of-principle trials of vaccine monotherapies earlier in this document may also be applicable for combination trials

TABLE 2. Major Considerations in Setting Dose and Schedule for Combination Therapy Trials

- Type of vaccine
- Nature and mechanism of action of combination agent
- Prior nonclinical experience (safety, dose range, activity, induction of immune responses, schedule dependence and interactions, pharmacokinetic profile and interactions) with the vaccine, the combination agent, and both combined
- Prior clinical experience (safety, biologic activity, clinical activity) with the vaccine, the combination agent, and both combined
- Prior clinical and nonclinical experience with similar agents or agents in the same "class"

between vaccines and other biologics or immunomodulators.

Component Dose and Schedule Finding in Early Clinical Testing

Because of the different types of vaccines and potential combinations, a variety of potential approaches exist how to establish dose and schedule of a cancer vaccine and a combination agent in early clinical trials. Table 2 lists several major considerations in designing the initial and subsequent trials of a vaccine in combination with another agent.

The major goals of early trials of vaccine combinations are to establish safe doses and schedule for each agent, and to determine the dose and schedule that optimizes biologic interactions of the vaccine with its combination partner (eg, whether the immune response to vaccine is enhanced by the combination partner). Theoretically, the dose/schedule of the combination that increases tumor-specific immune responses compared with either agent alone will also be the best dose/schedule for producing an antitumor effect. If the combination partner produces antitumor responses by non-immune mechanisms, early trials should at least establish that the combination partner does not diminish vaccine-induced immune activation. Subsequent trials would determine if the combination has antitumor activity (or better antitumor activity than expected for either component) sufficient for large scale, efficacy-directed clinical trials.

For most cancer vaccines, it is reasonable to begin with certain assumptions that will then guide subsequent trial designs: the vaccine acute safety profile is not dose-dependent, and the vaccine produces the desired biologic effect across a broad-dose range; the vaccine is unlikely to have pharmacologic interactions with the agent proposed for combination; and the major adverse toxicity interaction, if any, is likely to be manifest as a late autoimmune event. Therefore, for establishment of a tolerated dose and schedule, dose-ranging exploration for the vaccine may not be necessary, particularly if the biologically active dose of the vaccine is already known or can be extrapolated from clinical experience with similar products. There are some notable exceptions where dose ranging of the vaccine may be important to establish a safe dose for subsequent study, for example, com-binations of chemotherapy with certain live vectors that might alter the toxicity profile (perhaps related to in vivo replication and dissemination) of the vector.

Similarly, dose-ranging for the vaccine combination partner may not be necessary if the safety profile and active biologic doses were previously established in clinical trials. Perhaps the most common setting in clinical development is one in which a tolerated and biologically active dose is known for both the vaccine and the combination partner. Based on the assumptions described above, it would be reasonable for the initial trial of both agents to be conducted with the "full" doses of both agents. The goal of such an initial trial would then be shifted away from a safety evaluation to explorations of schedule effects on immune response, because schedule of administration of each agent, and secondarily the dose of the combination "partner," are more likely to influence biologic activity in vivo. In such a study, different cohorts might be used to explore schedule variations that are predicted to influence biologic effect. Several study designs are possible, including randomization to the different arms. Presuming that a measurable end point is known and feasible (immune response to vaccine), the schedule chosen for phase 2 (or phase 3) trials would be that which produced the greatest increment in the desired end point (or did not diminish immune activation in the case where the combination partner produces tumor responses by nonimmune mechanisms), compared with historical controls or to cohorts receiving only vaccine and/or only the combination partner (because the combination partner could also induce tumor-specific immune responses by nonspecific immune activation). These trials will likely require larger sample sizes than typical phase 1 trials. Unlike typical phase 1 trials, the cohorts can be accrued simultaneously (possibly randomized) rather than sequentially. If accrual is sufficient, the trials could also simultaneously be designed to evaluate antitumor effect. If there are concerns related to induction of autoimmune toxicity, patient follow-up should be extended for several months before further clinical development.

If dose finding for the vaccine is required within the context of a combination (eg, if no prior clinical experience with the vaccine), the better end point of the initial trial is "immune response," and not acute toxicity, for the reasons noted above. If there is no prior clinical experience with the vaccine partner, then the requirement for prior standard single agent phase I trials of the partner, and for dose-ranging of the partner with the vaccine, depends on the agent and the expected outcome in the clinic with regard to immunologic effects and antitumor activity. In the latter case, it could be acceptable to simultaneously initiate dose-ranging phase I single-agent trials of the proposed vaccine partner and dose-ranging phase I trials in combination with a specific vaccine. When both vaccine and partner have not been evaluated in the clinic, and both are expected to be inactive outside of a combination, the starting dose and schedule must be extrapolated from preclinical and

toxicology data. It may be necessary to test various dose ratios with a fixed schedule to find the correct doses that produce the intended biologic effects (ie, tumor-specific immune response ± any additional biologic effect of the vaccine partner). Because of the many potential variations, it may not be possible to explore both dose and schedule simultaneously. If in any of the scenarios above, the vaccine combination partner is associated with clinically relevant toxicities, novel trial designs for the combination could be considered, for example, in which the dose of the "toxic" agent for the combination is lowered progressively in successive cohorts to determine if tumor-specific immune "enhancement" is maintained while reducing overall toxicity.

Appropriate statistical input is required during the design of any trial to assure adequate power to detect meaningful biologic differences. The discussion so far presumes that the biologic end point (immune response) for finding an optimal dose/schedule could be expected to correlate with clinical outcome. As noted in other sections of this manuscript, immune response to the cancer vaccine is difficult to measure and parameters which are associated with tumor response are often not known. If dose ranging for safety is not necessary as is the case for most conceivable combinations with vaccine, and a biologic correlate predictive of antitumor effect is not available, then the end point of the initial combination study (eg, to select schedule) may need to be antitumor activity (objective response or PFS). These are likely to be larger trials and require careful planning and statistical input to derive meaningful data and conclusions, particularly if conducted as part of a phase 2 evaluation to select a regimen for definitive randomized phase 3 trials. The design of the study will be dependent on what is already known about the antitumor activity of the individual agents in the combination.

Because of the lack of validated immune response correlates of antitumor effect, dose and schedule explorations may be bypassed altogether in many potential vaccine combinations. The initial study of the combination could use full doses of each agent in some predetermined schedule, possibly extrapolated from preclinical studies. The goal of the phase 2 trial would then be to assess the antitumor effect of the combination, in comparison to a predetermined level of activity which is considered sufficient for continued development, or to the antitumor activity of the active agent in the combination (presumably the vaccine combination partner). The difficult issues related to evaluation of combinations in phase 2 trials, which are intended to provide sufficient evidence of activity to proceed to definitive large randomized trials, are not unique to vaccines or biologics.

Controlling for the Effect of Separate Components in the Clinical Development of Cancer Vaccine Combinations

In combination development of agents for nonlife-threatening conditions such as combination antihyper-

tensives or combinations of inhaled therapies for asthma, the independent contribution of each combination agent to efficacy and safety has often been established in large phase 3 trials. In oncology, many combination chemotherapies have been accepted based upon studies demonstrating the benefit of the combination itself with less data formally addressing the contribution of individual components. A similar approach is recommended for combinations with cancer vaccines, where either agent may have little independent activity and, at least for the vaccine, safety is not a significant issue. Some combinations may have preclinical biology that justifies developing the combination as if it were a single agent from the beginning. The CVCTWG believes that, in other cases, it is necessary to control for any vaccine or combination agent that could account for the desired magnitude of efficacy alone, so as to avoid an ineffective agent "free riding" with an effective one. Clinical testing should, however, minimize the exposure of patients to plausibly ineffective vaccines or combination agents.

Trial Arms for Definitive Efficacy Trials

For simplicity, this discussion assumes a combination of a cancer vaccine (V) with one other combination agent (A) for which there is significant evidence that the combination is useful. If either the vaccine or the other component are approved or known to be active alone, then the combination can be compared with the single approved component. When neither A nor V is known to be effective or approved for use in the indication, there may be a very strong biologic rationale or single-agent phase 2 data strongly suggesting that neither V nor A will have any efficacy when given by themselves. In these cases 2-arm designs comparing the combination to a control agent (or placebo) are preferred as they minimize exposure of cancer patients to inactive therapies, but place a significant responsibility upon sponsors and regulatory authorities to evaluate carefully the strength of data supporting inactivity of any component. Sponsors may choose to demonstrate such inactivity in appropriately designed phase 2 trials. Where there is strong data that one of the components has no activity, but the inactivity of the second component has not been established, 3-arm studies comparing control, the possibly active single agent and the combination are warranted. Finally, in cases where both components may be active, 4-arm studies may be needed that compare control, each component as a single agent, and the combination. In tumor settings where no control therapy exists, the control arm can be omitted from the above designs. For all randomized trials, where there is an intent for double-blinding, potential unblinding due to the clinical characteristics of the investigated agent(s) should be considered.

Early Stopping

Early stopping is possible when either an experimental arm appears very much better than the control

arm, or when it appears that the experimental arm will never be sufficiently better than control arm to yield a positive trial (futility). Typically, the stopping guidelines will be based on the primary end point of the trial, and the first consideration for early stopping will be when 25% to 30% of the total number of expected events (eg, deaths) have been observed. Although there are different stopping guidelines possible, one can consider early stopping quite often after that initial look at the data, for example, every 6 months. With trials with more than 2 arms, it is possible to stop one of the arms but not the trial. Two other early stopping strategies are possible. One is to use a different biologic end point for consideration of early stopping than the primary end point. The second strategy involves comparing an experimental arm to historical control data to make an early decision concerning that arm. These 2 strategies can also be combined—for example, an experimental arm could be stopped early because there is a less than 10% response rate in that arm (similar to historical response rates for negative agents).

Facilitating Cancer Vaccine Combination Development—Overcoming Barriers

The issues of drug accessibility for combination studies have been widely discussed in editorials and are familiar to most clinical investigators. For agents already in clinical trials, accessibility is limited by the sponsor (owner) for various business, medical, or administrative/ practical reasons. Development of combinations where the intellectual property (IP) is owned by different companies is particularly problematic. Furthermore, the regulatory issues surrounding approval of a combination in which both agents are investigational (or neither agent is approved for the indication) are complex and not yet resolved and thus discourage combination development. In the case where the desired agents are commercially available, the costs to obtain the agents for clinical trials outside their indication are often excessive and are not reimbursed by third party payors.

Another major hurdle to vaccine combination development is the slow or absent process of development of several promising vaccine "partners." In some cases the IP is held by a pharmaceutical company, but development of that agent is delayed or never started for business reasons (other priorities, lack of funding, small market potential, etc.). In some cases lack of a patent position (clearly defined IP) discourages pharmaceutical development. The National Cancer Institute (NCI) has capacity for production of novel compounds, but will not produce agents already owned by another party without express permission from that party. The cost of production of good manufacturing practice material, toxicology testing, and regulatory filing and management are outside the capabilities of almost all academic investigators.

Definitive proposals for solutions to these problems were considered outside the scope of the CVCTWG

deliberations. The CVCTWG recommended that a central government scientific body, such as the NCI in the US, should seek to form a task force composed of academic and industry investigators and Food and Drug Administration staff to continually identify key investigational agents that are not progressing into clinical trials in a timely manner. The task force would prioritize the most important agents and provide guidance to the government science agency staff to begin work leading to the production of the agent for clinical use, which would be made available through a government drug development program such as Cancer Therapy Evaluation Program (CTEP), NCI. The government scientific agency would need to commit adequate resources and staff to preclinical development and production of the identified agents, for example, at a rate of 3 to 5 per year. Such development could be done in partnership with academic collaborators and contractors as necessary. In some countries, legislation may be necessary to permit government production and clinical testing of agents for which the IP is held by private industry, while protecting the IP of the company and granting immunity from liability. If the government work leads to a business benefit for the company, a provision could be in place to obtain reimbursement from the company in return for full access to the data. Many other, and possibly better, solutions may exist, for example, providing certain incentives to the owner of the IP to bring the agent forward into trials and provide the agent to the government agency to increase availability to academic investigators (see below).

It was noted that one possible solution to providing investigational agents for combination trials in the US may reside in the CTEP Division of Cancer Treatment and Diagnosis, NCI, which is committed to facilitating preclinical and clinical studies involving the combinations of anticancer investigational agents originating from more than one pharmaceutical collaborator. CTEP has 150 active Investigational New Drug applications including any cancer vaccines; this puts CTEP in a unique position to facilitate combinations of vaccines and other agents for multiple therapeutic target types. All of the collaborative clinical agreements between CTEP and pharmaceutical or biotechnology collaborators contain provisions to allow for mutually agreeable combination studies, both preclinical and clinical, sponsored by the NCI without additional agreements between the collaborators or CTEP. The CTEP Intellectual Property Option to Collaborator (the "IP Option") offers the first rights of negotiation to an exclusive or nonexclusive license in the event of an invention to the collaborator that supplied the agent for the study. This "Option" is present in all CTEP clinical funding agreements for clinical trials and is also used in all CTEP Material Transfer Agreements for nonclinical studies using agents provided by CTEP under collaborative agreements with pharmaceutical companies.

To expedite the initiation of such studies, a modification of the IP Option has been instituted which

provides all collaborators contributing an agent for a combination study with a nonexclusive royalty free license to any invention that might arise using the combination. Furthermore, this same option applies to preclinical combination studies designed to provide data in support of a clinical trial. The provisions for the sharing of data between collaborators have also been updated to clarify that each collaborator receives the data from such a study for use in the development of its proprietary agent only. No combination study will be initiated unless all collaborators agree to these provisions. These terms have eliminated the need for collaborators to negotiate cumbersome IP or data sharing agreements before approving such studies. This model has also been used successfully by the NCI Cooperative Groups for Group-sponsored studies.

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