Introduction

In September 2009, FDA published a draft guidance document,  
“Guidance for Industry: Clinical Considerations for Therapeutic  
Cancer Vaccines” (1), and called for comments from the broader  
community. C-Change (2), an organization founded in 1998 to  
mobilize key cancer leaders from the private, public, and not-for-  
profit sectors on a mission to eliminate cancer as a public health  
problem through prevention, early detection, and treatment,  
requested from the authors of this article a critical review of the  
draft guidance. The primary concern was the unnecessarily narrow  
focus on only therapeutic vaccines at the time when promising  
results were being reported from clinical trials of preventive  
vaccines in individuals with premalignant lesions (3, 4). In August  
2011, C-Change submitted to the FDA the comments with specific  
recommendations that are presented and discussed below. Our  
goal was to encourage the addition of preventive vaccines to this  
new Guidance because they have many issues in common with  
therapeutic vaccines, except that they are focused primarily on  
reducing the risk of progression to invasive cancer. On the other  
hand, because of the increasing recognition of the importance of  
developing preventive vaccines to reduce the risk of cancer in  
healthy populations, for example, in individuals who have  
increased cancer risk due to germline mutations, C-Change  
encouraged FDA to alternatively address such preventive or pro-
phylactic vaccines in a separate Guidance. The final guidance was  
published in October 2011 without the addition of prophylactic  
vaccines (5). Because the field of preventive cancer vaccines has  
continued to develop, now 4 years later there is an even stronger  
reason to either revise the 2011 guidance to encompass all cancer  
vaccines or to draft a new guidance specifically focusing on  
preventive vaccines.

Here, we revisit the recommendations submitted to the FDA  
addressing a number of topics that we hope will be taken into  
consideration in future revisions of the subject Cancer Vaccine  
Guidance or in a new separate Guidance on Preventive Cancer  
Vaccines. We recognize that other important cancer-related Gui-  
dances also exist and that they cannot all be referenced here in the  
context of our comments. The agency’s “Guidance for Industry:  
Clinical Trial Endpoints for the Approval of Cancer Drugs and  
Biologics” (6) is an example that is especially relevant. We  
nonetheless believe that the recommendations we provided  
regarding Therapeutic Cancer Vaccines Guidance are still gener-
ally applicable, even with respect to the related Guidance named  
above and others. They are as follows:

1. Broaden the Guidance to address the use of cancer vaccines  
to not only treat established cancer but also to prevent or to  
decrease the high risk of invasive cancer in patients with  
premalignant disease.

2. Define the term "cancer vaccine" in an explicit and detailed  
manner.

3. Address considerations relevant to the safety, antitumor  
immunologic activity, and therapeutic activity in phase I  
trials for preventive cancer vaccines.

4. Encourage the selection of a relatively homogeneous  
population of patients for early-phase trials (best achieved

Abstract

Cancer vaccines based on antigens derived from self mole-
cules rather than pathogens have been under basic and clinical  
investigations for many years. Up until very recently, they  
had been tested primarily in the setting of metastatic disease  
with the goal to engage the immune system in slowing down  
disease progression. Many therapeutic vaccine trials, either  
investigator initiated or led by pharmaceutical companies,  
have been completed and many are currently ongoing, fol-

The FDA Guidance on Therapeutic Cancer  
Vaccines: The Need for Revision to Include  
Preventive Cancer Vaccines or for a New Guidance  
Dedicated to Them

Olivera J. Finn¹, Samir N. Khleif², and Ronald B. Herberman†

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¹Department of Immunology, University of Pittsburgh School of Med-
icine, Pittsburgh, Pennsylvania. ²GRU Cancer Center, Georgia Regent  
University, Augusta, Georgia.  
†Deceased.

Corresponding Author: Olivera J. Finn, University of Pittsburgh School of  
Medicine, E040 Biomedical Science Tower, Pittsburgh, PA 15261. Phone: 412-  
648-9816; Fax: 412-648-7042; E-mail: ojfinn@pitt.edu  
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by focusing on premalignant disease) and the careful selection and specification of particular assays for immunologic monitoring.

5. Encourage the design of phase I clinical trials that will result in better understanding of the complex set of possible interactions among a variety of components of the immune system, which influence whether a cancer vaccine might lead to induction or augmentation of effective antitumor immunity or to undesirable inflammatory processes and immunosuppression.

6. More fully acknowledge several major limitations of the results from prior preclinical or clinical studies that are used to support a new clinical trial.

7. Add considerations related to the disease setting when designing late-phase efficacy trials.

8. Emphasize more the value of phase II clinical trials and the relative safety profile of early-phase vaccine trials.

9. More explicitly address several issues pertaining to the preventive as well as therapeutic clinical trial design.

10. Endorse more definitively the plan for accelerated approval regulations, where licensure of vaccines can be based on surrogate endpoints, such as immunologic markers, that are reasonably likely to predict clinical benefit.

**Review of the Recommendations and Discussion**

In Section I of the published guidance, it is explicitly stated that the products discussed “are therapeutic cancer vaccines intended to result in specific responses to a tumor antigen, and are intended for the treatment of patients with an existing diagnosis of cancer.”

**Recommendation no. 1**

Broaden the Guidance to address the use of cancer vaccines not only for treatment of established cancer but also to prevent or to decrease the high risk of invasive cancer in patients with premalignant disease.

Many of the tumor antigens targeted by therapeutic cancer vaccines are also expressed in premalignant lesions and immune responses against them can be detected (7–14). In addition, all of the proposed mechanisms of action of therapeutic vaccines, such as development of tumor antigen–specific cytotoxic T cells or antibodies and formation of immune memory, are the same as those that are expected of vaccines focused on reducing the risk of developing invasive cancer (15–17). Many of the clinical trial design issues should, therefore, be very similar. The immunologic aspects of cancer lie on a continuum, with more immunologic similarities shared between premalignant disease and successfully treated cancer with no evidence of disease (NED) than between early-stage cancer and advanced metastatic disease, when immunologic functionality is often compromised. This would be particularly true for the competence of the immune response to recognize and react against the vaccine antigen and later against malignant or premalignant cells. Cancer vaccines designed to be used for primary prevention in healthy populations are more likely to be substantially divergent, as would be the design of studies to demonstrate their efficacy. A separate Guidance should, therefore, be developed at the appropriate time to address considerations related to preventive or prophylactic cancer vaccines for healthy populations who are at increased risk for developing premalignant disease and subsequent cancer.

Section I continues to clarify that the current Guidance “does not apply to vaccines for preventative and therapeutic infectious disease indications, to products intended to induce or augment a non-specific immune response, or to products intended to prevent, or decrease the incidence of cancer in individuals without a prior history of that cancer.” In anticipation that the FDA might revise this Guidance to include preventive vaccines, we put forward the second recommendation:

**Recommendation no. 2**

Define the term “cancer vaccine” in an explicit and detailed manner.

In general, preventive or prophylactic vaccines are considered to be synonymous with microbial vaccines, and we deem it to be very important to distinguish cancer vaccines from vaccines against a virus or a bacterium that causes cancer, for example, Hepatitis B or human papillomavirus vaccines, or from products that inhibit immunoregulatory cells (e.g., T regulatory cells or myeloid-derived suppressor cells) or block T-cell activation checkpoints allowing pre-existing specific antitumor immunity to become manifested. We suggest a definition of a cancer vaccine as a “product which when administered to an individual induces or augments (boosts) antigen specific antitumor immunity.” This definition would include the use of immunologic adjuvants used in combination with tumor antigen(s). It would also include adoptive transfer of effector cells, such as T lymphocytes, natural killer cells, or antibody-producing B cells, antibodies, oncolytic viruses, and other treatments that kill tumor cells and might release antigens that elicit immune responses. This definition applies equally to therapeutic as to the preventive (including prophylactic) vaccines.

Section III of the Guidance covers many issues related to the clinical trial design. Although many of these can apply to both therapeutic and preventive vaccines, there are some clear advantages provided by the preventive setting that might allow more accurate evaluation of a vaccine and the clinical trial design. This in turn would facilitate the testing of both in vivo delivery of specific antigen(s) to DCs. It would exclude, however, adoptive transfer of effector cells, such as T lymphocytes, natural killer cells, or antibody-producing B cells, antibodies, oncolytic viruses, and other treatments that kill tumor cells and might release antigens that elicit immune responses. This definition applies equally to therapeutic as to the preventive (including prophylactic) vaccines.

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with metastatic diseases versus patients with no evidence of residual disease or minimal burden of disease."

Many of these issues do not apply to the setting of premalignant disease where the immune system is not yet compromised to the same degree as in cancer and time to progression from a premalignant lesion to invasive cancer is more predictable. Our recommendation is to include the premalignant disease setting in these considerations, as it might very much facilitate evaluation of the highest potential of all cancer vaccines and serve as the gold standard for immune responses, safety, and efficacy in other disease settings.

Recommendation no. 3
Address considerations relevant to the safety, antitumor immunologic activity, and therapeutic activity in phase I trials for preventive cancer vaccines.

There has been a long track record for cancer vaccine safety in the past 20 years. Most have a safety profile that is better than that of traditional cancer chemotherapy, with clinically significant adverse events being either not observed or only mild (18–20, 21). This of course is predicated on the ability to elicit a strong immune response in the setting of cancer. Toxicity of the vaccine is linked to either the sub-acute or long-term immune effect of the antigen or the acute toxicity effect of the vehicle/adjuvant. Accordingly, testing for acute toxicity in a phase I safety trial would be needed in the following categories: (i) any vaccine with substantial toxicity observed in preclinical toxicity studies; (ii) classes of vaccine platforms with toxicity demonstrated in previously conducted clinical trials; and (iii) new vaccine platforms or other vaccine components (e.g., adjuvant) with potential vital organ toxicity (21). Because induction of autoimmunity is one of the safety issues that have been associated with some cancer vaccines, assessment of this issue in the earliest stage or NED patients with greater immune competence is much more likely to be informative. This may not be possible to accomplish with phase I or early-phase trials in all cases, but early-phase trials might provide limited data that can be expanded in later-phase trials. For vaccine platforms with expected acute toxicity, for example, certain viral or bacterial delivery vehicles, or combination adjuvants, it may be necessary to first perform clinical safety studies in advanced cancer patients with limited life expectancy with the understanding that specific toxicities are the primary endpoints, rather than immunogenicity and efficacy.

Immunologic activity of vaccines is the most important issue and the key purpose of phase I studies should be to test the ability of a cancer vaccine to induce adaptive immunity. Because phase I dose-escalation studies of cancer vaccines do not determine toxicity or biologically active dose in the vast majority of the vaccines tested, another feasible goal of a phase I study in the premalignant setting, where individuals are expected to respond, could be to find a dose and a schedule that induces high levels of T helper 1 cell (TH1) and CTLs toward tumor antigens while avoiding, to the extent possible, induction of immune suppressor cells (21). Therefore, in contrast with early-phase trials with chemotherapy drugs, the most appropriate disease setting should involve patients who are not immunosuppressed and are capable of mounting a strong immune response to the vaccine. Such phase I trials should not take any longer to perform in the setting of premalignant disease than in patients with advanced disease. These trials in the premalignant setting would be much more informative as they would be much more likely to provide the needed demonstration of immunologic activity in a shorter amount of time (22).

To evaluate therapeutic and clinical benefit of a cancer vaccine, it will clearly take longer in patients with early-stage disease or NED compared with patients with advanced, measurable disease. On the other hand, in phase I trials in advanced disease, the ability of a vaccine to induce antitumor immunity has been observed only in a minority of patients leading to these trials being characterized as failures. We consider it unfortunate to discount a particular vaccine without a further phase I study performed in immunocompetent patients with premalignant disease or NED, followed by a therapeutic efficacy trial in the same disease setting.

Section III.A.1.b also addresses the issue of patient population and tumor heterogeneity. It acknowledges that, “although it may be acceptable to test heterogeneous patient populations with a common antigen in early phase trials, this approach is unlikely to provide interpretable evidence of efficacy for the purposes of licensure. In addition, there are particular challenges with the approach of enrolling patients with heterogeneous tumor types and stages into early phase trials of cancer vaccines. Differences in the clinical stage of the disease and prior treatments can affect the potential response to the cancer vaccine. This is especially problematic with vaccines that are made from autologous patient materials, as each patient and tumor histology are different, resulting in different vaccine preparations. As a result, interpretation of trial results from a heterogeneous patient population can be especially challenging, and the objectives of the trials may not be achieved. Thus, in selecting the patient population for cancer vaccine testing in early phase trials, careful consideration should be given to the heterogeneity of the patient population.”

This is another area where testing a cancer vaccine in a preventive setting of premalignant disease can help avoid a problem of increasing heterogeneity as tumors grow, invade and spread, including additional mutations, changes in the tumor microenvironment, effects of therapy, etc. The goal is to obtain needed data from patients with similar stages of disease and similar prior treatments with respect to their ability to mount a substantial antitumor-specific immune response. This will then help to appropriately plan for later-phase efficacy trials both in early as well as late stages of disease.

Recommendation no. 4
Encourage selection of a relatively homogeneous population of patients for early-phase trials (best achieved by focusing on premalignant disease where there is also a lesser problem of tumor heterogeneity) and the careful selection and specification of particular assays for immune monitoring.

The proposed mechanism of action of cancer vaccines is that they mediate their antitumor activities by eliciting or amplifying an immune response. Immune monitoring (23), especially in early-phase clinical trials, has the major goal of establishing proof-of-principle for the proposed immunologic effect and showing immunogenicity of the administered antigens. Monitoring of the immune response to a vaccine can be useful to assess variations in patient immunocompetency that may affect the study results (24). Responses against known immunogens (e.g., the frequently used keyhole limpet hemocyanin or tetanus toxoid) and HLA typing could assess patient population heterogeneity and assess any HLA link/bias to product activity.

In early-phase clinical trials, immune monitoring should serve to optimize the dose and schedule needed to induce the intended
immune responses and aid the decision-making process concerning further product development and later clinical trial design (21). In later-phase clinical trials, it can provide data regarding the types, magnitudes, and duration of response and the possible correlation with clinical efficacy. A clinically effective antitumor response involves a multicomponent process; therefore, multiple monitoring assays may be needed to identify and measure the components of the immune responses. Immune biomarkers for the most important and relevant components of the antitumor response should be developed. If possible, at least two immunologic assays should be used in an attempt to monitor a specific immune mechanism considered to be critical to mediate an antitumor response. Assay standardization should include specific parameters to control for general variability in an immune response across study sites. The assay parameters, such as assay conditions, sensitivity and specificity of the assay, any in vitro amplification step involved, positive and negative controls, cutoff values for determining the positive and negative test results from patients' specimens, and the statistical analytic methods to be used for the test results, should be validated and clearly described in the clinical protocol before the initiation of the clinical trials (25–27). A robust immune system of a patient without cancer is more amenable to testing and validating these assays, which could then be applied to trials vaccinating patients with cancer. Assay choice is key in trying to assess whether some measure of safety or efficacy is being achieved, but it should be noted that although global measures of T-cell immunity may be useful to assess the general immune competence of the patients, such measures are unlikely to be useful indicators of the induction of specific antitumor immunity, which will be the key objective.

Section III B of the current Guidance discusses issues typical for early-phase versus late-phase clinical trials. Even recognizing differences between immune-based trials and standard chemotherapy trials, much is still based on the chemotherapy trial model where phase I trials are mostly directed to toxicity, dosing and schedule of drug administration. Our recommendation here is the following.

Recommendation no. 5

Phase I clinical trials should address the complex set of possible interactions among a variety of components of the immune system that could influence whether a cancer vaccine leads to induction or augmentation of effective antitumor immunity or to undesirable inflammatory processes or immunosuppression. The starting dose, schedule, and also the specific components and route of administration of the cancer vaccine should be carefully considered not as much from the safety angle, but instead to induce a desirable antitumor response, for example, selective stimulation of Th1 and CTL responses, rather than Th2 responses or augmentation of negative immunoregulatory cells (e.g., Tregs or myeloid-derived suppressor cells). These types of dose considerations and other aspects of vaccine development are likely to be different for each type of vaccine. With the increasing complexity of some current cancer treatment regimens, phase I trials should be designed to adequately test all of the vaccine components in combination, using a small number of patients in each trial and short study duration, sufficient to answer these primarily immunologic questions. A key overall principle to consider is that most cancer vaccines will have an acceptable safety profile across a wide dose range, and a MTD is unlikely to be determined (21). Rather, a very important objective in phase I clinical trials of cancer vaccines is to determine, to the extent possible, the optimal dose to induce the desired antitumor immune response (21). Assessment of changes in relevant immunologic parameters that are expected to be induced in patients receiving a range of doses of the cancer vaccine should provide important information for selecting the dose to be used in later-phase efficacy trials.

Recommendation no. 6

The Guidance should more fully acknowledge some major limitations in the way results from preclinical or prior clinical studies are used. Preclinical studies in primarily mouse tumor models (28, 29) are likely to provide some useful indications about the biologic activity of the vaccine and some general insights about a dose–response relationship for inducing therapeutic efficacy, especially if multiple tumor models are tested and provide similar results. It is unlikely that the antigen dose can be determined; however, dose–response relationships for some components of a cancer vaccine (e.g., adjuvant cytokines) may be determined. More importantly, the effect of the vaccine on the immune system has generally not been dependent on weight or body surface area and accordingly, the dose cannot be predicted on the basis of adjustments for body weight or surface area. Also, some insights might be derived from studies in mouse tumor models regarding the efficacy of specific treatment schedules, but the details are likely to vary considerably and the preclinical models are unlikely to provide clear guidance about the specific schedule of treatments or the starting dose.

Recommendation no. 7

Add considerations related to the disease setting for the design of a late-phase efficacy trials. It seems highly advisable to consider performing phase I trials in the same population of patients that will be subsequently studied for therapeutic efficacy. This approach could entail performing a sequence of trials in neoadjuvant or adjuvant settings for patients with recurrent but surgically resectable cancer, patients whose prior treatment has rendered them with NED, patients with early-phase primary disease, or patients with premalignant disease who are at high risk for disease progression. Adoption of these types of considerations as Guidance will help engender the development of products that would be applicable across the spectrum of disease, from preventive cancer vaccines to cancer vaccines for patients with advanced, metastatic disease.

Recommendation no. 8

Emphasize more the value of phase II clinical trials and the relative safety profile of early clinical vaccine trials. In Sections III B and C, the Guidance implies that randomized phase II trials typically lack statistical power to obtain a conclusive demonstration of a treatment effect but are nevertheless helpful to the design of later-phase confirmatory trials. Rather than focus on statistical power, we urge the Agency to specifically encourage Phase II efficacy trials in the Guidance. Many important questions can be asked from well-designed phase II trials, which can later be incorporated into a larger, well-powered phase III trial. Insofar as late-phase clinical trial designs should be based on safety data primarily from early-phase clinical trials, we wish to emphasize that, although clinically significant and even devastating side
effects are justifiable to expect in the case of some vaccines that rely on antigens with only a weak preference for tumor versus normal cells, such occurrences have been rare. If a cancer vaccine is focused on a tissue-associated antigen or set of antigens, substantial autoimmunity may occur with some frequency, but may not result in clinically significant adverse effects. For example, some melanoma vaccines have induced vitiligo but without significant clinical problems. Rather, vitiligo has been a useful marker for assessing therapeutic responses (30). It is important to recognize that there has been a concerted effort in the field of tumor antigen discovery over many years to identify antigens or antigenic epitopes that are very different on cancerous tissues versus healthy tissues, even for use in therapeutic cancer vaccines. The incentive for this has been not only to avoid undesired autoimmunity, but also to avoid the self-tolerance mechanisms that would prevent or seriously weaken the response to the vaccine. This effort has yielded and continues to yield a large number of antigens (31), even some on premalignant lesions (32), with a better safety profile in preclinical testing that would be expected to carry a lower risk when applied in the clinic for the first time.

**Recommendation no. 9**

Several issues that pertain to the clinical trial design of preventive as well as therapeutic vaccines need to be more explicitly stated.

In some cancer vaccine efficacy trials, disease progression as defined for chemotherapy trials (but without clinically significant deterioration of performance status) has occurred initially but then has been followed by disease stabilization and even complete regression of tumor lesions. Similar observations could be expected in the premalignant setting and should be an acknowledged component in the monitoring of the vaccine effects. With respect to a superiority design compared with a noninferiority design, the threshold for progression is attained when the progression-free survival curve of the experimental group is not continuously lower than that of the control group, with a width of the noninferiority margin that is clinically meaningful.

Our last recommendation (no. 10) is an endorsement of FDA’s plan for accelerated approval regulations, where licensure of vaccines can be based on immunologic markers that are reasonably likely to predict clinical benefit, the same way they have been used in all other vaccines with a much greater history of clinical benefit.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Authors’ Contributions**

Conception and design: O.J. Finn, S.N. Khleif, R.B. Herberman

Development of methodology: S.N. Khleif, O.J. Finn

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): O.J. Finn, S.N. Khleif

Writing, review, and/or revision of the manuscript: O.J. Finn, S.N. Khleif

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**References**


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