Meeting Report

Cancer Immunology Research

# Report on the FDA-AACR Immuno-oncology Drug Development Workshop

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## Abstract

The FDA-AACR Immuno-oncology Drug Development Workshop was held in Washington, DC, from October 13 to 14, 2016. This interdisciplinary forum included government, industry, and academic leaders in pharmacology and oncology. The aim of the meeting was to discuss methodologies in nonclinical and clinical research, safety monitoring, efficacy endpoints, and statistical evaluation of cancer immunotherapy products. This summary highlights topics and viewpoints raised by the presenters and discussants and should not be viewed as the conclusions or recommendations of the workshop as a whole. *Cancer Immunol Res; 5(4); 282–5. ©2017 AACR.*



## Introduction

The meeting was introduced by Marc Theoret (FDA) and Suzanne Topalian (Johns Hopkins) with overviews on recent advances in the field of tumor immunology. The immunotherapy of cancer has a long history, but the modern era of immunotherapy commenced approximately 30 years ago with the advent of cytokine therapies that demonstrated antitumor responses, often coupled with significant toxicity. Although the initial responses to IL2 and IFN treatment seen in diseases such as melanoma and renal cell cancer were promising, most other tumors tested did not respond well. The complexity of the cytokine response leads to a constant interplay between innate and adaptive immune cells within the tumor microenvironment, with some benefit noted at a cost of significant, potentially fatal, toxicity. This stalled development and interest in the field as a whole.

This paradigm was challenged with the development of immunotherapeutic drugs that antagonized the regulatory molecules, called checkpoint inhibitors, within the immunological synapse. Increased survival times of up to 10 years in patients treated with ipilimumab (Yervoy, Bristol-Myers Squibb), an antibody targeting the cytotoxic T lymphocyte antigen-4 (CTLA-4) pathway, highlighted the benefit of this approach. Unfortunately, only a minority of patients show any demonstrable clinical effect, and adverse events on therapy have been severe and unpredictable. Many factors can affect the potential for both toxicity and response to treatment, including genetics, age, and varying target antigens. Agents targeting the immune checkpoints of programmed cell death-1 (PD-1) and programmed cell death ligand 1 (PD-L1) have been more tolerable with fewer side effects overall. The activity noted in early trials of PD-1 and PD-L1 inhibitors led to the large number of clinical trials across many cancer histologies. Despite these advances, an increased understanding of the biological mechanisms of immunomodulatory products and the tumor response is needed in order to continue development of these and similar agents and to advance patient care.

## Preclinical Evaluation of Immunotherapeutics for Cancer

Regulatory oversight of cancer immunotherapy products is administered through two FDA divisions: the Center for Drug Evaluation and Research (CDER) and the Center for Biologic Evaluation and Research (CBER). In support of regulatory protocols, nonclinical models are designed to provide safety data and support an appropriate starting dose. However, translational challenges exist with immunotherapeutic products with respect to species relevance. Thresholds for immune activation may be species-specific and therefore dependent on individual target expression, biology, distribution, or a combination of these factors. Receptor occupancy assays also depend on host genetics. *In vitro* cytokine release assays from peripheral blood mononuclear cells are often used as surrogates for intratumoral immune cells, but this may not represent responses within the tumor microenvironment. Differences in reactivity may also exist between juvenile and adult animal models and be dependent on the stage of tumorigenesis.

> "Challenges include a lack of a fully functioning immune system in tumor models, the potential of nonspecific reactivity to self proteins in healthy tissues, and the stage of tumorigenesis."

As a result of these various factors, Rodney Prell (Genentech) indicated that the no-observed-adverse-effect level (NOAEL) is an inappropriate approach in evaluating immunotherapeutic agents (1). This also leads to challenges in translating *in vitro* to *in vivo* data and calculating the minimum anticipated biological effect level (MABEL) for selection of a first human dose in clinical trials. To address these problems, Alan Korman (Bristol-Myers Squibb) described past and current nonclinical models regarding targeted

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antibodies to T cells (2). Autoimmune-prone mice are often used to understand if antibody treatment can worsen autoimmunity, because inbred mouse models tend to have few toxicities when using antibodies to immune checkpoints. For example, antibodies to PD-1 can induce rapid diabetes in the nonobese diabetic (NOD) mouse model, whereas antibodies to CTLA-4 do not. Drugs developed for these receptors also need to be evaluated with respect to their properties (e.g., fully human, humanized, isotype, specificity) to avoid unintended immune-related adverse reactions. Insight into these mechanisms will benefit monotherapies and combined research with additional antibodies, DNA plasmids encoding tumor-associated antigens, or cytotoxic therapeutics. Murine models capable of mounting a human immune response may also aid in discovery, as was detailed by Kristina Howard (FDA).

With respect to adoptive cell transfer–based approaches, similar species-specific and translational problems arise in nonclinical models. Timothy MacLachlan (Novartis) described the use of patient-derived T cells with genetically engineered T-cell receptors (TCR) that recognize specific tumor-associated peptides within the MHC proteins of target cells as well as the use of genetically engineered chimeric antigen receptors (CAR). These approaches do help create more individualized therapies, but the high potential of nontarget responses requires a deep understanding of human T-cell function, differences between human and animal T cells, and the exact target specificity of the adoptively transferred T cells. RNA and protein assessment of tissue, and assessment of possible cross-reactivity of the TCR or CAR, may enhance target specificity. Building safety switches into CARs, such as the requirement for two antigen targets to avoid normal tissue reactivity, may also be an option. David Clarke (Pfizer) described the use of anti–CTLA-4 therapy coupled with an adenovirus containing DNA plasmids encoding tumor-associated antigens (e.g., prostate-specific antigen, prostate stem cell antigen, prostate-specific membrane antigen) in an effort to expand and maintain the T-cell response. Challenges include a lack of a fully functioning immune system in tumor models, the potential of nonspecific reactivity to self-proteins in healthy tissues, and the stage of tumorigenesis (e.g., certain stages may not be able to induce an immune response). Careful evaluation of these various factors may lead to better outcomes in phase I trials.

## Dosing Immunotherapeutics

Several speakers argued that the relatively small number of patients employed in traditional 3+3 dose-escalation designs could lead to an increased risk in selecting a nontolerable recommended phase II dose for cancer immunotherapeutic agents. Eric Rubin (Merck) described the alternative strategy of toxicity probability-interval design where the dose is continued, escalated, reduced, or terminated depending upon toxic responses involving a larger number of patients (3). Mark Ratain (University of Chicago Medicine, Chicago, IL) described another approach for phase I trials of combination therapies that utilizes randomized dose escalation, in which a subset of each dose cohort is randomized to monotherapy for safety. Ratain also favored randomized dose trials for the evaluation of both safety and efficacy simultaneously (4). David Feltquate (Bristol-Myers Squibb) showed evidence from the experience of Bristol-Myers Squibb in ipilimumab (Yervoy) and nivolumab (Opdivo) combination trials (5). Although the use of traditional designs was considered feasible, the evaluation of the different doses and schedules of these combinations certainly benefits from larger sample sizes. Hong Zhao (FDA) highlighted the need to evaluate actual body-weight dosing versus flat dosing in relation to drug clearance. Additional insight regarding individualized dosing for specific patient groups (e.g., pediatrics, geriatrics, hepatic, or renal-impaired patients) may also assist in helping to optimize regimens and avoid adverse events.

## Evaluating Immune-Related Adverse Events

Immunotherapy advances have been accompanied by an intense interest in immune-related adverse events, both to better manage toxicities occurring in patients and to better understand the nature of the immune system's interaction with a variety of potential target tissues. David Berman (AstraZeneca) noted that with immune checkpoint inhibitors, an array of inflammatory reactions, including hepatitis, enterocolitis, hypophysitis, and nephritis, have been noted. Pathologically, these immune-related adverse events were observed to be distinct from, but similar to, graft-versus-host disease and autoimmune disease of the target organs (6, 7). Adverse events in CAR T-cell therapy have also generated significant interest. These toxicities may include tumor lysis syndrome, neurologic toxicity (in the case of CD19-targeting agents), and cytokine release syndrome.

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David Porter (University of Pennsylvania, Philadelphia, PA) noted that in order to understand the nature of these toxicities in reporting clinical trials, case definitions must be standardized and published alongside clinical results. Biological mechanisms that mediate immune-related adverse events need to be studied to predict individuals at risk and identify onset. Common grading criterion to categorize severity, particularly in CAR T-cell therapy, is needed to more effectively convey outcomes. Mario Sznol (Yale School of Medicine, New Haven, CT), Diko Kazandjian (FDA), and Ke Liu (FDA) all focused on the categorization and management of immune-related adverse events and the need to improve and standardize management (8). Increased investigation of anti-inflammatory agents in treating adverse events is warranted, and particular attention should be paid to any potential modulation of the efficacy of clinical response to therapy. Adverse events will occur with any effective anticancer therapy, and it is imperative to work with patients and multidisciplinary teams of healthcare providers to quickly identify and treat adverse events as patients present to the clinic or the emergency department. In addition, Elad Sharon (NCI) noted that studying immune-related adverse events could help gain insight into, and possibly help develop therapies for, similar autoimmune conditions in cognate target tissues. The careful monitoring and tracking of immune-related reactions in patients may also increase our understanding of how these therapeutics function, and consequently help, accelerate drug development.

## Choosing Appropriate Endpoints

Maitreyee Hazarika (FDA) provided an overview of the regulatory pathways for approval of new anticancer agents. The FDA

examines data in the context of disease, line of therapy, other available therapies, study design, endpoints, and the magnitude of evidence. Endpoints that have supported past approvals in randomized control studies include overall survival (OS), tumor assessment endpoints, progression-free survival (PFS), relapse-free survival, and patient reported outcomes (e.g., quality of life, physical functioning, tumor-related symptoms). With the advent of immune-based anticancer agents, additional endpoints need to be considered given that some of these drugs may exhibit low objective response rates (ORR), but can still appear to benefit patients if the duration of responses is prolonged. Rajeshwari Sridhara (FDA) discussed situations in which traditional assessments of objective responses based solely on tumor measurements may not be as useful in assessing the benefit of immunotherapy agents. For example, tumor enlargement following initiation of anti–PD-1 therapy may on occasion be a reflection of inflammation and not tumorigenesis. Many observers call this phenomenon "pseudo-progression," given that in some cases, enlargement is followed by regression at a subsequent tumor assessment. Axel Hoos (GlaxoSmithKline) suggested that some new lesions that emerge on therapy with immune agents may represent a micrometastatic collection of tumor cells, or an initial growth of a tumor, prior to an antitumor response. The complexity is enhanced in that the time to progression or pseudo-progression may vary. Progression alone may not necessarily translate into an eventual treatment failure, as OS may improve in the absence of changes in ORR or PFS (9).

Lawrence Schwartz (Columbia University Medical Center, New York, NY) reviewed the various new criteria being promulgated as improvements on the traditional RECIST system for tumor assessments (10). Standardization of these criteria is sorely needed. Both he and Sumithra Mandrekar (Mayo Clinic, Rochester, MN) discussed methods of evaluating tumor response kinetics that might better capture the effect of immunotherapeutics. Utilizing new techniques, such as radiomics, to correlate quantitative molecular imaging with genetic expression patterns, in association with consistent records detailing the reasons for progression (e.g., increase in target lesion size or appearance of any new lesions), may improve on current methods of tumor assessment (11). Optimizing and standardizing novel metrics and criteria will aid in efforts in drug development. Nicholas Latimer (The University of Sheffield, Sheffield, United Kingdom) suggested modeling survival curves independently with flexible parametric models, cure models, or a mixture, to account for atypical trends linked to immune-based antitumor agents (12).

## Surrogate Efficacy Endpoints

Prospective analysis of clinical trials commonly relies upon RECIST-based assessments of ORR or PFS, as well as OS in evaluating an experimental regimen, but, as discussed above, may not be optimal analytical endpoints. OS is the gold standard for many patients with metastatic disease, but the extended length of time necessary for obtaining data on survival has long motivated researchers interested in surrogate endpoints. Sirisha Mushti (FDA) offered a possible solution: simply reassessing and relaxing the definition of progression may modify ORR or PFS enough to help develop new therapies. Daniel Chen (Genentech) suggested that reassessing a patient's baseline at the point of progression could achieve the same purpose while extending the potential benefit of a new experimental therapy that can cause pseudo-progression. Xin Gao (FDA) discussed using alternative intermediate endpoints. By assessing an intermediate endpoint at predetermined intervals, predictive outcomes and additional insight regarding tumor dynamics may be derived. Antonio Ribas (University of California, Los Angeles, Los Angeles, CA) discussed the idea of a durable response rate as an endpoint, or more specifically, evaluating the long-term response of a given treatment. Jan Bogaerts (EORTC) discussed data generation obtained from studies of large patient groups and the importance of conveying standardized information that is relevant and current (13). Evaluating the probability of an endpoint (e.g., PFS, OS) at a specific landmark time point of 2 or 3 years was an option discussed by Keaven Anderson (Merck) and Tai-Tsang Chen (Bristol-Myers Squibb; ref. 14). This milestone survival analysis, which can be incorporated *a priori* in a study design or *post hoc* in the study report, allows for both the relative and absolute measures of true mean effect over time.

## Novel Trial Designs and Combination Trials

Ed Korn (NCI) described a biomarker-stratified phase III trial in which a biomarker's pretrial credentials determined possible efficacy (15). A biomarker, such as tumor PD-L1 expression, has strong credentials when significant evidence indicates a benefit to treatment. Evaluation of a biomarker's credentials can be done through various approaches. Understanding which technique to use is important in ensuring the most effective treatment for all subgroups. Increased efficiency with these techniques will aid in drug combination studies. Lillian Siu (University of Toronto, Toronto, Ontario, Canada) discussed techniques to generate supportive data for therapeutic combinations (16).

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Collectively, establishing a systematic approach with which to gather data and evidence is required to move forward to trials involving multiple therapeutic strategies. John Kirkwood (University of Pittsburgh, Pittsburgh, PA) highlighted the complexities in handling phase III studies and suggested an adaptive trial approach that examines multiple combinations based on state-of-the-art biomarkers in a collaborative phase II study that could potentially evolve into a concurrent phase III trial. This adaptive statistical methodology encourages collaborations globally and across disciplines, including biostatisticians, academic investigators, and regulators. Kirkwood's approach would require fewer patients per arm, reduce the cost to sponsors, and possibly foster improved efficiencies compared with traditional trial designs. David Rimm (Yale University, New Haven, CT) highlighted the need for the critical evaluation of diagnostic assays. In particular, one must control the preanalytic conditions for a given assay and provide for standardized processes to assure the validity of assay results. Specimens may become altered by the extraction, handling, and preparation of a sample for analysis. Rapidly fixing and staining specimens and using monoclonal, not polyclonal, antibodies can reduce alterations in antigenicity. Increased use of quantitative fluorescence techniques, metabolic blood assays, RNA signatures, and genetic analysis platforms is anticipated to be helpful in identifying patient subgroups, with the aim being to ensure reproducibility (17).

## Conclusions

In summary, the modern era of cancer immunotherapy has progressed significantly in the last 30 years leading to the development of an array of agents currently in use and in development. Understanding underlying biological mechanisms will be key to addressing clinical applications and evaluating next-generation immunotherapies. Development of nonclinical models that more accurately translate into human applications is sorely needed. Increased research into biomarkers and endpoints that can be readily obtained from circulating blood, tumor tissue, and imaging would also speed drug development efforts and improve patient outcomes. One possible first step in this process would be utilizing existing trials and retrospectively analyzing completed trials with tissue available for analysis. However, as noted in the final session, proper quality control measures must be employed when evaluating correlative assays. The key to moving forward in immunotherapy will be the active participation of all stakeholders in the drug development community.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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