DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
AD HOC TRANSLATIONAL RESEARCH STRATEGY SUBCOMMITTEE (TRSS) MEETING

Summary of Meeting
March 29, 2021

Webinar

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
***AD HOC* TRANSLATIONAL RESEARCH STRATEGY SUBCOMMITTEE**
Summary of Meeting
March 29, 2021

A meeting of the *ad hoc* Translational Research Strategy Subcommittee (TRSS) of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was held by webinar on Monday, March 29, 2021, at 1:00 p.m. The TRSS chairs, Drs. Davidson and Dang, presided.[1] The meeting was adjourned at 2:00 p.m.

Co-Chairs
Chi V. Dang
Nancy E. Davidson

TRSS Members
Francis Ali-Osman
Walter J. Curran, Jr. (absent)
David A. Mankoff
Lynn M. Matrisian
Roman Perez-Soler
Kevin M. Shannon
David A. Tuveson
Kevin P. White (absent)
Max S. Wicha

Ex Officio Members
James H. Doroshow, NCI

Executive Secretary
Peter Ujhazy, NCI

Presenters
Francis Ali-Osman, DSc, Margaret Harris and David Silverman Distinguished Professor of Neuro-Oncology Research; Professor of Surgery, Professor of Pathology, Department of Surgery and Pathology, Duke University Medical Center
Chi V. Dang, MD, PhD, Scientific Director, Ludwig Institute for Cancer Research; Professor, The Wistar Institute
Nancy E. Davidson, MD, Senior Vice President, Director, and Full Member, Clinical Research Division, Fred Hutchinson Cancer Research Center

[1]A roster of TRSS members and their affiliations is included as an appendix.

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Monday, March 29, 2021

I. Welcome and Opening Statement

Chi V. Dang, MD, PhD
Nancy E. Davidson, MD

Dr. Davidson reviewed the confidentiality and conflict-of-interest practices required of TRSS members during their deliberations. She invited members of the public to send written comments on issues discussed during the meeting to Dr. Ujhazy within 10 days of the meeting.

Dr. Dang reminded the TRSS that during its last meeting on January 14, 2021, the subcommittee discussed the TRSS charge and research opportunities in gastric and esophageal cancers; a CTAC working group on gastric and esophageal cancers is in the process of being formed. TRSS plans to meet quarterly in 2021, and members will identify translational gaps and opportunities for the subcommittee's consideration. At each meeting, a member will give a brief presentation to frame a selected topic, followed by discussion with TRSS members. The subcommittee will present recommendations to CTAC and the NCI director twice a year. NCI and TRSS will reassess this process after one year. Dr. Dang listed several questions for TRSS to consider during its deliberations on proposed topics, such as whether the topic has the potential to enhance NCI's translational research portfolio and whether TRSS recommends that NCI take certain actions on the topic.

Upcoming TRSS meetings and topics are as follows:

- Thursday, June 17, 11:00 a.m. to 12:00 p.m. ET: translational potential of organoid cultures and animal tumor models
- Thursday, September 9, 11:00 a.m. to 12:00 p.m. ET: to be determined
- Thursday, December 16, 3:00 p.m. to 4:00 p.m. ET: to be determined

In response to a question from Dr. Shannon, Dr. Davidson explained that TRSS is a subcommittee of CTAC, which was briefed on the activities of TRSS during its March 17, 2021 meeting.

II. Discussion of Opportunities and Gaps in Translational Research

Resistance to Immunotherapy

Francis Ali-Osman, DSc

Cancer immunotherapy is an exciting new frontier in oncology that has led to some dramatic responses in very advanced cancers, including leukemias, lymphomas, and solid tumors. The hypothesis underlying immunotherapy is that host immune surveillance plays a key role in suppressing oncogenesis by recognizing and eliminating tumor cells; in addition, the tumor escapes immune surveillance and then grows and progresses by developing an immune-evasive phenotype.

Different types of immunotherapy target or exploit different components of the immune system. For example, various types of antibodies are used to target the passive immune system, whereas several types of therapies (including checkpoint inhibitors, vaccines, and viruses) target or exploit the active immune system.

Most immunotherapies used to date have been monotherapies, so research is needed on combinations of two immunotherapies or combinations of immunotherapies and other cancer treatments. Also, as with other cancer treatment modalities, inherent and acquired tumor resistance to immunotherapy is an ongoing challenge. Mechanisms of immunotherapy resistance that need further research include extrinsic factors related to the tumor microenvironment (e.g., immunosuppressive T-regulatory cells that kill T cells and antigen-presenting cells, T-cell exhaustion, and altered coinhibitory and costimulatory

receptors and factors) and intrinsic, tumor-related factors (e.g., host genetics and epigenetics, immune response pathways, and altered cell signaling).

Opportunities for TRSS to explore include:

- Molecular mechanisms, genetics, and cellular basis of response and resistance to immunotherapy
- Identification and validation of biomarkers of response and resistance to immunotherapy
- Development of rational, mechanistically based strategies for combinations of immunotherapies with other immunotherapies, targeted therapies, radiation therapies, and chemotherapies
- Development of immunotherapeutic agents, small molecules, delivery systems, and regimens to reduce immune suppression, enhance T-cell activation and reactivation, and induce immunogenic tumor cell death
- Evaluation of the relationship between tumor mutational burden and response or resistance to chemotherapy
- Development of precision (personalized) immunotherapy guided by genomics or biomarkers

Discussion

Immunotherapy Combinations. Dr. Shannon said that by far the lowest-hanging fruit in the cancer immunotherapy field is understanding intrinsic resistance (e.g., CD19 chimeric antigen receptor [CAR] T cells that stop expressing the antigen), which has been challenging for conventional agents as well. In addition, obtaining approval for combinations has been challenging for targeted therapies, especially if both combined therapies are targeted. Combining agents that also target the immune system with immunotherapies will be equally challenging. Dr. Shannon recommended studies that determine a patient's characteristics before they become resistant, after they respond to the treatment, and then after they develop resistance. This type of comparison has been very informative for targeted therapies.

Dr. Ali-Osman noted that both radiation therapy and chemotherapy were believed to be immunosuppressive, but more recent data show that the opposite can be true; these treatments program the tumor to be more responsive to immunotherapies. For example, radiation therapies can cause double-strand DNA breaks that, when released from the tumor, can induce the interferon pathway. Bringing experts from both sides together to examine the data will open up exciting possibilities.

Preclinical Models. Dr. Wicha called for good preclinical models so that the therapies to combine are chosen on a rational basis grounded in an understanding of the immune system. Research has been conducted primarily in xenograft and immunosuppressed animals. Although this approach has been useful, a great deal has been missed. Investments are therefore needed in the development of immunocompetent preclinical models and organoids with immune systems. In addition, for the first time, some patients are developing durable responses to immunotherapies, and a few appear to be cured. Studies should examine patients who have long-term, durable responses to immunotherapy to determine how they differ from other patients.

Dr. Dang asked whether any studies in preclinical models have assessed the effects of chemotherapy on the immune system using the latest technologies, including single-cell analyses in immunocompetent models. Dr. Doroshow replied that such studies are needed, not only for chemotherapies but also for targeted agents and their effect on the microenvironment in the context of immune competence with various checkpoint inhibitors. NCI is developing plans to molecularly characterize hundreds of syngeneic models developed in the 1960s and 1970s and stored at the Frederick National Laboratory for Cancer Research. NCI is also developing a program to examine phosphorylation events. Assays are now available or soon will be available for a study of combinations of durvalumab with six different chemotherapy drugs. However, not all of the analytes developed work in mice, so NCI

is identifying new analytes for studies in syngeneic mouse systems. The lack of models leads to clinical trials of combinations that turn out to be very toxic or ineffective.

Dr. Shannon said that studies that do not use patient-derived xenograft (PDX) models cannot obtain funding. The mindset has to change so that non-PDX preclinical models can be developed and used.

Exceptional Responders. Dr. Dang asked NCI staff to discuss longitudinal studies in responders to immunotherapy in NCI networks and research on chemotherapy's effect on the immune system. Dr. Ujhazy replied that NCI-supported research on the effect of chemotherapy on the immune system several years ago, and some research on this topic is ongoing. Many individual grants are addressing these issues. For example, the Specialized Program of Research Excellence program has approximately 40 immunotherapy projects, including some that are studying resistance.

Percy Ivy, MD, Associate Chief of the Investigational Drug Branch and Program Director of the Experimental Therapeutics Clinical Trials Network at NCI, was the principal investigator of the Exceptional Responders Initiative. Results from this study and a description of the study's methods were recently published. For this study, investigators submitted information on patients enrolled in early-phase clinical trials who were exceptional responders, but only a small number of these patients had been treated with immunotherapy. Many case reports in the literature have described exceptional responders to immunotherapy, but these cases were not included in this study.

Helen Chen, MD, Associate Chief of the Investigational Drug Branch in the Cancer Therapy Evaluation Program, said that the Cancer Immune Monitoring and Analysis Centers Network will analyze thousands of specimens from immunotherapy trials. A meta-analysis might be conducted to more systematically examine exceptional responders and exceptional nonresponders (patients with tumors that usually do respond to a given immunotherapy). Other initiatives can collect specimens from these patients. A major question is how to combine chemotherapy and radiation therapy, which are the standard of care, with immunotherapy. Whether chemotherapies are immunosensitizing or suppress the immune system is not clear, and different types of chemotherapy might have different effects on the immune system. Some clinical trials are conducting serial biopsies to address this issue.

Dr. Ali-Osman noted that when a tumor is introduced into an animal that is not immunocompromised, the tumor is rejected, and this process needs to be understood. He asked whether, for example, any studies have inserted a variety of tumors into healthy animals and assessed levels of rejection to understand intrinsic mechanisms of immunosurveillance. Furthermore, research is needed on why high doses of chemotherapy kill T cells but low doses have the opposite effect. Similarly, high doses of radiation therapy have a different effect than low doses, and the mechanisms of these effects might be different. Duke University is studying a recombinant poliovirus therapy for glioblastoma that had not responded to chemotherapy. After receiving the recombinant virus treatment, many patients responded to chemotherapies that had not been effective before. Perhaps the immune system has been changed or the tumor has been reprogrammed to become responsive to chemotherapy. Another research question about combination therapy is whether to start chemotherapy (or radiation therapy) or immunotherapy first and which doses of chemotherapy (or radiotherapy) to use.

Dr. Perez-Soler said that "exceptional responders" are probably the norm in some diseases. In the last few years, 20 percent to 30 percent of patients with lung cancer have survived for a long time after immunotherapy. As a result, thousands of people survive for years after immunotherapy. A study should enroll perhaps 500 patients with lung cancer before treatment to help researchers understand the mechanism of sensitivity, which is as important as resistance.

Microbiome Research Questions. Dr. Dang asked about NCI efforts to study the impact of immunotherapy on the tumor microbiome and recent evidence showing dramatic responses with microbiota treatment in patients who had not responded to other therapies. Dr. Davidson agreed that not much research is being done in this area.

Other Research Gaps. Dr. Tuveson commented that patients who do not respond to immunotherapy innately or who acquire resistance tend to have substantial disease burden, resulting in hormonal imbalance, cachexia, and other systemic effects that might modulate the immune system in the wrong direction. Lack of consideration of the systemic effects of cancer is interfering with the ability to understand the impact of immunotherapy.

Another challenge is the difficulty of obtaining biopsies (except for liquid biopsies). Dr. Tuveson asked whether noninvasive imaging technologies have been developed to monitor immune response. Dr. Mankoff said that efforts are underway to use imaging for immune cell activation. A challenge for imaging the effects of immunotherapy is the fact that the characteristics of immune activation (e.g., increased glycolysis or glucose metabolism) resemble those of tumors, and the ability to distinguish tumors from signs of immune activation is limited. However, significant advances have been made in imaging the effects of common monoclonal antibodies in preclinical models and even in patients.

Dr. Wicha said that primitive stem-like cells might drive tumors and downregulate antigen presentation and immune responses. A study in long-term responders could determine whether immunotherapy attacks the cancer stem-like cells in these tumors or whether it targets cells that are more differentiated that are expressing differentiation antigens, which would mean that long-term responders are not completely tumor-free because they still have the stem-like tumor cells. However, as soon as these cells differentiate, they are destroyed by the immune system. These kinds of hypotheses could be explored in long-term responders to identify basic biologic principles that might account for differences in responses.

High-Priority Research Topics. Dr. Doroshow asked TRSS for help identifying a few major projects for NCI to address. Dr. Shannon identified the following potentially high-priority topics in the immunotherapy field:

- Development of immunocompetent preclinical models for immunotherapy research
- Development of murinized versions of human immunotherapies
- Research on combinations of immunotherapy with targeted agents that attack an oncoprotein only (e.g., $KRAS^{G12C}$ inhibitor in lung cancer)

Dr. Dang said that NCI should focus on emerging types of research instead of old models of resistance.

Dr. Perez-Soler commented that immunotherapy is much less effective in patients who have lung cancer and *EGFR* mutations. Research in these patients could be helpful in understanding resistance.

Dr. Davidson approved of the focus on models suggested by Dr. Shannon and the focus on "exceptional responders" suggested by Dr. Perez-Soler. Trials might be designed to study resistance in humans to complement animal studies.

Dr. Dang asked Dr. Tuveson why the mouse model he created produces a wide spectrum of pancreatic ductal adenocarcinoma in mice that have the same genetic aberrations. Dr. Tuveson replied that the diversity of these mice probably begins at the cellular levels. Reducing this diversity would reduce their complexity. The animals have the same *RAS* and *p53* mutations, eat the same food, and have

the same microbiome, but they present a wide spectrum of disease. Dr. Tuveson suggested that TRSS propose preclinical research in addition to clinical research. Examples of research needs include the following:

- Responses to chemotherapy after treatment with immunotherapy
- Microbiota treatment in humans
- Infectious agent immunotherapy in humans
- Noninvasive or only modestly invasive methods to monitor patients treated with immunotherapy

Next Steps. Dr. Dang asked each TRSS member to send a list of five high-ranking research priorities for NCI to consider to Dr. Ujhazy, who will compile the topics into a single list. TRSS will then review the list and narrow it down to a manageable number of topics.

III. Wrap-Up and Adjournment

Peter Ujhazy, MD, PhD

Dr. Ujhazy announced that the next TRSS meeting will be on June 17, 2021 at 11:00 a.m. ET and will focus on models and organoids. Dr. Ujhazy thanked the TRSS members for their valuable input.

IV. Adjournment

There being no further business, the TRSS meeting was adjourned at 2:00 p.m.

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Date Chi V. Dang, MD, PhD, Co-Chair

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Date Nancy E. Davidson, MD, Co-Chair

_____

Date Peter Ujhazy, MD, PhD, Executive Secretary

Appendix

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Clinical Trials and Translational Research Advisory Committee
***Ad Hoc* Translational Research Strategy Subcommittee**

CO-CHAIR
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Scientific Director
Ludwig Institute for Cancer Research, New York
Professor, The Wistar Institute
Philadelphia, Pennsylvania

CO-CHAIR
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Senior Vice President, Director, and Full Member
Clinical Research Division
Fred Hutchinson Cancer Research Center
President and Executive Director
Seattle Cancer Care Alliance
Head, Division of Medical Oncology
Department of Medicine
University of Washington
Seattle, Washington

MEMBERS

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Margaret Harris and David Silverman
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Neuro-Oncology Research
Professor of Surgery
Professor of Pathology
Department of Surgery and Pathology
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Kevin P. White, PhD
President, Tempus Labs
James and Karen Frank Family Professor
Department of Human Genetics
Professor, Department of Ecology and Evolution
Director, Institute for Genomics and
Systems Biology
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Professor, Internal Medicine
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