DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
AD HOC TRANSLATIONAL RESEARCH STRATEGY SUBCOMMITTEE MEETING

Summary of Meeting
May 8, 2019

Webinar

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The first meeting of the 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 Wednesday, May 8, 2019, at 10:00 a.m. ET. The TRSS chairs, Dr. Davidson and Dr. Dang, presided.[1] The meeting was adjourned at 10:54 a.m.

Co-Chairs
Chi V. Dang
Nancy E. Davidson

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

Ex Officio Members
James H. Doroshow, NCI

Executive Secretary
Peter Ujhazy

Presenters
Walter J. Curran, Jr., MD, Executive Director, Winship Cancer Institute of Emory University
Chi V. Dang, MD, PhD, Scientific Director, Ludwig Institute for Cancer Research; Professor, Wistar Institute
Nancy E. Davidson, MD, Senior Vice President, Director and Full Member, Clinical Research Division, Fred Hutchinson Cancer Research Center
James H. Doroshow, MD, Deputy Director, Clinical and Translational Research; Director, Division of Cancer Treatment and Diagnosis, NCI

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

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I. Welcome and Opening Statement

Peter Ujhazy, MD, PhD
Nancy E. Davidson, MD

Dr. Ujhazy called the first TRSS meeting to order and welcomed participants. He confirmed that a quorum of at least six subcommittee members was present.

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.

II. TRSS Overview and Purpose

James Doroshow, MD

Dr. Doroshow reminded TRSS that in 2016, the Specialized Programs of Research Excellence Evaluation Working Group of the National Cancer Advisory Board and Board of Scientific Advisors recommended that NCI form a subcommittee to identify the most important translational research opportunities. NCI therefore formed TRSS, whose members come from NCI's advisory boards—the Clinical Trials and Translational Research Advisory Committee (CTAC), the Board of Scientific Advisors, and the National Cancer Advisory Board.

TRSS is tasked with surveying scientific horizons broadly and giving advice to NCI's advisory boards and NCI leadership on enhancing and broadening the Institute's overall translational research portfolio. Specifically, TRSS will identify the following:

- The most provocative and impactful translational research questions
- The most important opportunities for applying new technologies to translational research
- Translational research knowledge gaps

The subcommittee's meetings are open to the public. The subcommittee has two working groups:

- The Glioblastoma Working Group, chaired by Dr. Curran and Dr. Dang, would report on its activities later in this TRSS meeting.

- The co-chairs of the Radiation Oncology Working Group are Adam Dicker, MD, PhD, and Silvia Formenti, MD. The working group plans to meet in person in the fall of 2019. It is anticipated that the working group will present its report to TRSS in the winter of 2020.

TRSS will review each working group's report before these documents are presented to CTAC for final approval. TRSS will also use the experiences of these two working groups to inform NCI leaders about whether this process is effective and valuable and whether other translational research topics should undergo a similar process.

III. TRSS Glioblastoma Working Group Update

Walter J. Curran, Jr., MD
Chi V. Dang, MD, PhD

Background and Treatment Challenges. Dr. Dang explained that glioblastoma multiforme (GBM) is the most common malignant brain tumor, with approximately 13,000 new cases diagnosed in

the United States each year. In spite of numerous attempts, progress in developing effective treatments for this disease has been limited. Median survival is about 15 months, with a 5-year survival rate of around 3 percent.

GBM has a unique biology in that malignant cells infiltrate the brain and the tumors have no well-defined border. As a result, the ability to resect negative surgical margins without compromising neurological and physical function is limited. Other challenges to treatment include limited ability of drugs to cross the blood-brain barrier, intra- and intertumoral genomic heterogeneity that limits the ability to develop targeted therapies, and a microenvironment that is not amenable to immunotherapy.

Developing effective GBM therapies will require a better understanding of GBM biology and animal models that recapitulate human disease. Other needs are rigorous evaluations of drugs at both preclinical and early clinical trial stages, a better understanding of therapeutic vulnerabilities and mechanisms of treatment resistance, and a well-integrated pathway to connect preclinical to clinical research.

GBM Working Group. Dr. Curran explained that the goal of the GBM Working Group is to identify critical research gaps and opportunities for improving the outcomes of patients with GBM. The working group was charged with focusing on therapeutics for adults with GBM, and it will deliver recommendations for research capabilities and other needs that are critical for improving GBM therapeutics. The working group members represent a broad range of medical specialties and areas of expertise.

The working group developed several preliminary recommendations. An overarching recommendation is to develop a national infrastructure for preclinical testing and qualification of novel therapeutics for patients with GBM that is seamlessly integrated into an early-phase clinical trials program. The national infrastructure should have the following capabilities:

1. Conduct preclinical qualification studies of new agents that target GBM
2. Conduct early-phase clinical trials driven by molecular pharmacodynamics and imaging
3. Develop novel immunotherapy strategies
4. Create approaches to improve radiation sensitivity and overcome radiation resistance
5. Focus on enhancing the quality of life for patients and family members

Dr. Curran listed several other overarching recommendations as well as more detailed recommendations for each of the five capabilities listed above.

The working group's next steps are to incorporate the TRSS feedback into the draft working group report and finalize the document. The group will circulate the final draft to TRSS for its review, and TRSS will discuss this draft before it is forwarded to CTAC for its approval. The GBM Working Group chairs will present the final report to CTAC at its July 17, 2019, meeting.

Questions and Discussion

Highest-Priority Recommendations. Dr. Davidson praised the report. She asked whether the recommendations have equal weight or whether some have higher priority than others. Dr. Dang replied that enrolling patients into clinical trials is not a problem in the GBM research field and that the biggest challenge is with the therapeutic pipeline. Models are another important need, as is a set of shared guidelines for advancing therapeutic agents from the bench to the clinic. Dr. Dang noted that these recommendations have higher priority than the other preliminary recommendations. Dr. Curran agreed,

adding that if the highest-priority capability had to be identified, he would choose capability 1. If efforts to address this capability are successful, the next step would be to implement capability 2.

Leveraging NCI Resources. Dr. Matrisian commented that although the recommendations list potential contributions by the Cancer Therapy Evaluation Program (CTEP), other NCI programs have resources or capabilities that could help address the recommendations. Dr. Matrisian wondered whether these resources could be linked together to ensure that all of the steps to develop a new GBM drug, for example, are completed successfully. Dr. Curran said that CTEP has many of the needed capabilities, but the working group's report should identify other resources appropriate for GBM that could be leveraged to support implementation of the recommendations. Examples include the Cancer Immune Monitoring and Analysis Centers, the Experimental Therapeutics Clinical Trials Network, the National Clinical Trials Network (including the groups and lead academic participating sites that conduct GBM research), and NCI-designated cancer centers.

Dr. Davidson asked whether there is an NCI program specifically focused on brain tumor clinical trials. Dr. Doroshow replied that NCI sponsors the Adult Brain Tumor Consortium and the Pediatric Brain Tumor Consortium. The adult consortium conducts phase II clinical trials and is separate from the National Clinical Trials Network. However, this group lacks the resources for and is not designed to focus on small, intensive pilot studies of pharmacodynamic-guided or image-guided approaches for translation from preclinical to clinical studies. NCI needs to determine whether to develop a new brain tumor resource based on TRSS recommendations and, if so, what relationship to existing resources this new resource would have.

Dr. Matrisian wondered whether it is possible to expand the capabilities of the existing consortium instead of building a new resource. Dr. Doroshow said that many members of this consortium would probably participate in a new program. However, to address the recommendations of the working group, this new program would need a different structure and type of support.

Focus of the Recommendations. Dr. Perez-Soler pointed out that the recommendations do not address early detection. He asked whether a radiographic method or circulating tumor cell–based markers could be used to identify GBM at an early stage and whether the disease is more treatable at this stage. He also asked about the characteristics of the 3 percent of patients who survive longer than 5 years and noted that early detection is particularly important for malignancies for which effective treatments are lacking. Dr. Curran reported that some research has focused on syndromes that increase the risk of GBM in certain families, but members of these families account for only a small proportion of patients with GBM. There are currently no available biomarkers that could be used for broad population screening. Longer-term survivors typically have good performance and neurologic status, complete resection of the tumor, appropriate response to radiation and adjuvant treatment, and less bulky tumors. Dr. Davidson added that the working group's charge is to focus on therapeutics.

Dr. Shannon asked why the working group is not addressing pediatric brain tumors. Dr. Doroshow explained that NCI is planning to form a separate working group focused solely on pediatric brain tumors. Dr. Shannon commented that the biology of pediatric brain tumors might inform research on the biology of adult tumors and vice versa. Furthermore, discussions between adult and pediatric experts have been helpful in leukemia. Dr. Curran noted that the working group has some members with pediatric expertise, but its charge is to address GBM occurring in adolescents, young adults, and adults.

Biomarkers. Dr. Mankoff commented on the working group's recommendation for pharmacodynamic and response imaging and tissue-based biomarkers (capability 2). NCI programs are

pilot-testing new methods in the late preclinical phase for use in early-phase clinical trials. The ability to measure pharmacodynamic markers of response is limited, and Dr. Mankoff encouraged the working group to extend this recommendation to the preclinical space and take advantage of resources outside of CTEP and clinical trials programs. Dr. Dang agreed that noninvasive biomarkers, such as imaging biomarkers, will be needed to determine whether candidate therapeutic agents have a signal during the preclinical phase.

Other Partners. Dr. Davidson asked about the main patient advocacy groups in this field, noting that such groups could play important roles in public-private partnerships. Dr. Curran replied that the field has a few major advocacy groups and that a representative of one of these groups serves on the working group. This individual recommended that the group narrow its focus and not try to do everything, and his organization and others will be important partners in this effort.

Go/No-Go Decisions. Dr. Matrisian asked how go/no-go decisions for models under development would be made. Dr. Dang said that the working group agreed and noted that guidance that is not overly prescriptive for moving appropriate models forward will need to be developed.

Hypothetical Examples. Dr. Curran asked whether the level of specificity of the preliminary recommendations is appropriate. Dr. Matrisian approved of the broad level of the recommendations. She also suggested that the working group present examples of how to leverage existing resources or develop new ones to implement each recommendation. Dr. Dang said that the report could provide a conceptual framework (such as a flowchart) for a hypothetical example showing the steps that need to be taken and milestones to create the needed pipeline as well as the resources at NCI and elsewhere that could be used at each step. Dr. Matrisian approved of Dr. Dang's suggestion, which would show how to move a candidate therapeutic from preclinical research to clinical benefit, as opposed to building isolated resources.

Bhupinder Mann, MBBS, gave an example of a treatment initially studied in patient-derived xenograft models that demonstrates such a process. The results of the study were used to guide patient selection for phase II clinical trials, and a phase III trial has recently completed enrollment.

Dr. Doroshow agreed that examples would be helpful in the working group report. He suggested including a hypothetical example of an agent that is even earlier than one already in preclinical development and that has not been extensively tested. He also noted that the working group and GBM investigators have called for better infrastructure to develop pharmacodynamic assays, biologic biomarkers, imaging biomarkers, and preclinical models and to test them in early-phase, biomarker-intensive trials for early development. Such infrastructure could entice pharmaceutical companies and others to provide agents for studies and enable agents to undergo testing for GBM earlier in their development. Dr. Matrisian agreed, adding that a barrier to progress in a disease like GBM is the risk pharmaceutical companies would have to take. Reducing this risk and making it easier for pharmaceutical companies to test their compounds would accelerate progress.

Infrastructure Versus Other Needs. Dr. Matrisian pointed out that capabilities 3-5 could leverage the infrastructure established by the first two capabilities. Dr. Curran confirmed that the first two capabilities address core infrastructure needs and that the working group should examine the preclinical infrastructure tools supported by NCI that are not currently applied to GBM. Some clinical trial infrastructure already exists for GBM in adults, so the working group will determine whether to recommend that these programs be augmented or whether new models will be required.

Dr. Shannon asked whether consensus exists in the field regarding the value of existing preclinical models. If existing models are not sufficiently predictive, it might be more important to build better models than better infrastructure. Dr. Dang said that the working group discussed this issue and decided that once it completes its report, the group will gather experts together to assess the predictive value of existing preclinical models and determine whether new ones are needed.

IV. Wrap-Up and Adjournment

Dr. Davidson

Dr. Davidson listed the next steps for TRSS:

- Dr. Dang and Dr. Curran will discuss the TRSS feedback on the GBM recommendations with the GBM Working Group and submit a final draft report to TRSS.
- TRSS will review the final draft GBM Working Group report during a teleconference in June 2019.
- Dr. Dang and Dr. Curran will present the GBM Working Group report to the Clinical Trials and Translational Research Advisory Committee for approval on July 17, 2019.

Dr. Ujhazy thanked TRSS members for participating in this new process. There being no further business, the first meeting of TRSS was adjourned at 10:54 a.m. on Wednesday, May 8, 2019.

11/9/2020 Chi Dang
Date Chi V. Dang, MD, PhD, Co-Chair

11/6/2020 Nancy E Davidson
Date Nancy E. Davidson, MD, Co-Chair

11/17/2020
Date Peter Ujhazy, MD, PhD, Executive Secretary

Appendix

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National Cancer Institute
Clinical Trials and Translational Research Advisory Committee

Ad Hoc Translational Research Strategy Subcommittee

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