DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
39th CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC) MEETING

Summary of Meeting
July 17, 2019

NCI Shady Grove, Seminar 110
9609 Medical Center Dr.
Rockville, MD 20850

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
Summary of Meeting
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The 39th meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was on Wednesday, July 17, 2019, at 8:30 a.m. The CTAC chair, Dr. Loehrer, presided.[1] The meeting was adjourned at 2:52 p.m.

Chair
Patrick J. Loehrer, Sr.

CTAC Members
Debra L. Barton
Walter J. Curran, Jr.
Janet Ellen Dancey
Nancy E. Davidson
Timothy J. Eberlein
Howard J. Fingert
David M. Gershenson (absent)
Anne-Marie R. Langevin (absent)
Michael L. LeBlanc
David A. Mankoff
Lynn M. Matrisian (absent)
Neal J. Meropol
Augusto C. Ochoa
Roman Perez-Soler (absent)
Gloria M. Petersen
Steven T. Rosen (absent)
Dan Theodorescu (absent)

Ad Hoc Members
David F. Arons

Ex Officio Members
William L. Dahut, NCI
James H. Doroshow, NCI
Paulette S. Gray, NCI
Michael J. Kelley, U.S. Department of Veterans Affairs
Anthony Kerlavage, NCI
Richard Pazdur, U.S. Food and Drug Administration (absent)
Katherine B. Szarama, Centers for Medicare & Medicaid Services (absent)

Executive Secretary
Sheila A. Prindiville, NCI

Presenters
Alex A. Adjei, MD, PhD, Professor of Oncology and Pharmacology, Consultant in Medical Oncology, Mayo Clinic
Walter J. Curran, Jr., MD, FACR, Executive Director, Winship Cancer Institute of Emory University
Chi V. Dang, MD, PhD, Scientific Director, Ludwig Cancer Research; Professor, The Wistar Institute
James H. Doroshow, MD, Deputy Director, Clinical and Translational Research; Director, Division of Cancer Treatment and Diagnosis, NCI
Howard J. Fingert, MD, FACP, Consultant, Alacrita Consulting, Inc.
Laurie E. Gaspar, MD, MBA, Professor Emeritus, Department of Radiation Oncology, University of Colorado Denver
M.K. Holohan, JD, Director, Office of Government and Congressional Relations, Office of the Director, NCI
Michael L. LeBlanc, PhD, Member, Fred Hutchinson Cancer Research Center, University of Washington

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

Patrick J. Loehrer, Sr., MD, Director, Indiana University Melvin and Bren Simon Cancer Center; Associate Dean for Cancer Research, Indiana University School of Medicine

Douglas R. Lowy, MD, Acting Director, NCI

Lisa Meier McShane, PhD, Acting Associate Director, Division of Cancer Treatment and Diagnosis Biometric Research Program, NCI

Neal J. Meropol, MD, Vice President of Research Oncology, Flatiron Health

Lynne Penberthy, MD, MPH, Associate Director, Surveillance Research Program, Division of Cancer Control and Population Sciences, NCI

Malcolm A. Smith, MD, PhD, Associate Branch Chief, Pediatrics in the Clinical Investigations Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health Bethesda, MD

Rajeshwari Sridhara, PhD, Division Director, Division of Biometrics V, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

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I. Call to Order and Opening Remarks

Patrick J. Loehrer, Sr., MD

Dr. Loehrer called the 39th meeting of CTAC to order and welcomed participants.

Dr. Loehrer reviewed the confidentiality and conflict-of-interest practices required of CTAC members during their deliberations. He invited members of the public to send written comments on issues discussed during the meeting to Dr. Prindiville within 10 days of the meeting.

National Institutes of Health (NIH) Events Management videocast the meeting, and the videocast became available for viewing at http://videocast.nih.gov after the meeting.

Motion. A motion to accept the minutes of the 38th CTAC meeting, held on March 6, 2019, was approved.

II. Acting Director's Update

Douglas R. Lowy, MD

Dr. Lowy—Acting NCI Director since Norman E. Sharpless, MD, became Acting Commissioner of the U.S. Food and Drug Administration (FDA)—said he will continue the initiatives of Dr. Sharpless and of the previous NCI Director, Harold E. Varmus, MD.

CTAC devoted a moment of silence in memory of CTAC member Paul A. Godley, MD, PhD, MPP, of the University of North Carolina School of Medicine, who passed away in March. He was Vice Dean of Diversity and Inclusion at the university and the Rush S. Dickson Distinguished Professor of Medicine, Hematology/Oncology. Dr. Godley worked tirelessly in many domains, especially in the field of health disparities. He was the inaugural chair of the NCI Cancer Care Delivery Research Steering Committee and worked on behalf of the NCI Community Oncology Research Program, acting as chair of many data and safety monitoring boards. He became a CTAC member 2 years ago. He was admired and respected by both his peers and patients.

National Trends in Cancer Death Rates. Dr. Lowy shared data from the Annual Report to the Nation on the Status of Cancer showing the annual percentage change in death rates of many cancers. Since 2015, the mortality rate for melanoma has gone down faster than for any other cancer, likely because of new targeted treatments as well as immune checkpoint inhibitors. The data are from the Surveillance, Epidemiology, and End Results (SEER) Program, indicating that these population trends are nationwide and not just a subset of the population treated at major cancer centers. This finding suggests that these treatments are disseminated widely, and all segments of the population are benefitting from these advances. However, there is still a long way to go, as some cancer mortality rates have continued to rise.

NCI Budget. NCI has seen substantial increases in its budget beginning in fiscal year (FY) 2015, in part from the 21st Century Cures Act's Cancer Moonshot, as well as increases in Congressional appropriations. The President's FY 2020 budget proposed a total of about $5.3 billion for NCI. The House proposed about $6.4 billion. Both budgets included funding for the Childhood Cancer Initiative and the 21st Century Cures Act. The Senate had not released its FY 2020 budget at the time of the CTAC

meeting. Also, Congress had not resolved the debt ceiling, which would need to be done to complete the appropriations process.

Dr. Lowy continued by describing four areas of added emphasis for NCI: research on childhood cancers, investigator-initiated research, health disparities, and drug resistance.

Childhood Cancers. The NCI–Children's Oncology Group (NCI-COG) Pediatric MATCH (Molecular Analysis for Therapy Choice) Trial began in 2017. It was estimated that 10 percent of the children enrolled would be eligible for one of the 10 treatment arms. Those data were an underestimate; so far, about 25 percent of enrollees are eligible to receive treatment. As of July 2019, 645 patients had enrolled, and the trial is accruing about 27 patients per month. About 10 percent of the children eligible for a treatment arm of the trial have enrolled.

NCI accounts for about 80 percent of NIH awards for pediatric cancer research. The number of NCI pediatric cancer awards has increased from about 500 to more than 800 awards between FY 2014 and FY 2018. The President's FY 2020 budget proposal included $50 million per year over the course of 10 years for the Childhood Cancer Research Presidential Initiative.

Data sharing is the key to success. The Childhood Cancer Data Initiative (CCDI) will focus on facilitating the sharing of childhood cancer data by building interoperable databases; identifying opportunities to align and integrate multiple data sources to make data work better for patients, clinicians, and researchers; and maximizing opportunities to improve treatments and outcomes for children with cancer. The CCDI will hold a scientific planning meeting July 29–31 at which advocates, and experts can provide input on the initiative's next steps.

Investigator-Initiated Research. Dr. Lowy discussed the low paylines for research program grants for FY 2020 at a recent joint meeting of the National Cancer Advisory Board and the Board of Scientific Advisers. NCI remains committed to increasing paylines for FY 2020, budget permitting.

Health Disparities. Over the past two decades, U.S. cancer mortality rates have declined for all racial and ethnic groups except American Indians. NCI has provided additional supplemental funding and taken other steps to change this trajectory for American Indians and maintains research efforts to study health disparities for other groups.

In 1975, the incidence of cervical cancer among African American women was twice the incidence among white women. Today, there is a similar incidence of cervical cancer among white and African American women, primarily due to cervical screening through Pap smears. However, the mortality rate among African American women is about 50 percent higher compared with white women, likely because African American women are diagnosed at a later stage of disease than white women. Current cervical cancer screening research could lead to FDA approval of a self-sampling test to allow for earlier identification of women who need treatment, including women who do not have access to health care. This possibility illustrates how technology may help overcome health disparities.

Geographic health disparities illustrate that ZIP code might be more important than genetic code. In 1999, the cancer mortality rates for the people who lived in metropolitan areas were about the same as for those who lived in nonmetropolitan areas. Today, mortality rates are higher in nonmetropolitan areas, likely due to multiple factors, including lifestyle and access to prevention, early diagnosis, and treatment.

In FY 2018, NCI held a conference on rural cancer control and provided supplements to 21 cancer centers to focus on rural populations. NCI also issued funding opportunity announcements (FOAs) related to cancer disparities, including projects related to American Indians.

Primary and Acquired Drug Resistance. Most cancer deaths occur because of either primary or acquired drug resistance. The focus of the NCI Drug Resistance and Sensitivity Network (DRSN), part of the Cancer Moonshot, is to understand and overcome primary and acquired resistance, identify drug combinations and other approaches to improve outcomes for patients, and promote collaborations among various networks such as the Experimental Therapeutics Clinical Trials Network and the Immuno-Oncology Translational Network. The DRSN will focus on multiple myeloma, lung cancer, prostate cancer, acute myeloid leukemia, colorectal cancer, and melanoma.

Leadership transitions. NCI recently appointed Dinah S. Singer, PhD, as the Deputy Director for Scientific Strategy and Development; Anne Lubenow, MPH, as the Chief of Staff to the Acting Director; Eric Cole, MS, FACHE, as Deputy Executive Officer; Tony Kerlavage, PhD, as the Director of the Center for Biomedical Informatics and Information Technology; Jeff Shilling as the Chief Information Officer; Jonas S. Almeida, PhD, as the Chief Data Scientist of the Division of Cancer Epidemiology and Genetics; and Weston Ricks, MBA, as the Budget Director.

Questions and Discussion

Dr. Loehrer noted that 25 percent of patients were eligible to enroll on a treatment arm on the Pediatric MATCH trial but that only 10 percent joined. He asked about the low accrual rate, given 80 percent of eligible pediatric cancer patients take part in clinical trials. Dr. Doroshow said that because eligible patients are having their tumors sequenced and are receiving appropriate agents outside of the study, not all patients join the treatment arm of the trial.

Dr. Petersen asked whether NCI continues to consult with Dr. Sharpless. Dr. Lowy said that he and Dr. Doroshow continue to communicate with Dr. Sharpless.

III. Legislative Update

M. K. Holohan, JD

Budget and Appropriations. In FY 2019, the Labor, Health and Human Services, Education, and Related Agencies (Labor-HHS) appropriations bill, which includes the NIH budget, was passed and signed into law before the beginning of the fiscal year, the first time in 22 years. An on-time appropriation helps NCI plan its spending. Last year, the Labor-HHS bill was paired with the defense spending bill. FY 2019 included a $2 billion increase to NIH, including a $74 million increase for NCI. In addition, NCI received $400 million for the Cancer Moonshot.

The President's FY 2020 budget was released in March and proposed a 12 percent decrease for NIH and a 14.6 percent decrease for NCI, although there was $50 million for the new Childhood Cancer Data Initiative. The President's budget is written at the level specified by the Budget Control Act, which sets caps on defense and nondefense discretionary spending.

Since the Budget Control Act was passed in 2011, Congress has raised the cap three times and declined once, when sequestration went into effect. Should the caps remain in effect, the law would

require a $597 billion cut from nondiscretionary pool. Congress would still need to reach a budget deal, even if budget caps are negotiated.

As of the date of the meeting, the House had passed 10 of the 12 spending bills, including the Labor-HHS bill. The House bill provided a $300 million increase for NCI, including the $50 million for the CCDI. The Senate has indicated it will not pass any bills until a deal on the budget caps is reached. The last time the Senate had not marked up any bills before August was 1987. That year, there was a 1-day government shutdown, as well as a December omnibus spending bill.

Dr. Lowy testified before the House and Senate Appropriations Labor-HHS Subcommittees in April.

Legislation. The Recalcitrant Cancer Research Act of 2012 required NCI to develop scientific frameworks for two recalcitrant cancers. The statute defined recalcitrant cancers as those with a 5-year survival rate of less than 20 percent that cause at least 30,000 deaths per year.

In FY 2014, NCI developed the scientific framework on two recalcitrant cancers—pancreatic ductal adenocarcinoma cancer (PDAC) and small cell lung cancer (SCLC)—and submitted them to Congress. The law also required NCI to review and update the frameworks within 5 years. NCI submitted the updated PDAC framework to Congress and will submit the SCLC framework in June. NCI must also report on the effectiveness of the frameworks in FY 2020.

The Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act was passed in 2018 and focuses on childhood, adolescent, and young adult cancer survival rates and biobanking resources for biospecimens. NCI has rapidly begun implementation of this legislation. In January, NCI released a request for applications (RFA) that aligns with the STAR Act and is currently reviewing those applications. In May, NCI convened a meeting of representatives from the cancer and advocacy communities to focus on challenges and opportunities in biobanking for childhood cancers and is identifying additional efforts to enhance biospecimen collection and biobanking across childhood cancer research programs.

Congressional Briefings. Congress appreciates and enjoys interactions with cancer advocates and cancer researchers, including young researchers and students. Recent Congressional briefings that NCI attended covered e-cigarettes, artificial intelligence (AI) and cancer clinical trials, and human papillomavirus–related cancers. NCI representatives were also preparing to attend a reception for Glioblastoma Awareness Day and to host members of the Congressional Cancer Survivors Caucus.

Questions and Discussion

Dr. Davidson asked Dr. Lowy about funding for investigator-initiated research, given the current status of the budget. Dr. Lowy said that NCI has been investing more funds in the research program grants (RPG) pool since FY 2014. NCI is giving more awards than ever before, but the application rate has gone up far faster than the budget, so the payline has gone down. In FY 2017, NCI received 500 more applications for R01s compared with FY 2016. In FY 2018, NCI received 600 more applications than in FY 2017. There was also an increase in FY 2019, but it was not as large as in the previous 2 years. If NCI receives an appropriation close to what the House has recommended, that could substantially increase the

payline. NCI has added $400 million to the total RPG pool between FY 2014 and FY 2019. The total increase to the NCI budget during that time was $800 million.

Ms. Holohan added that members of Congress are very interested in visiting cancer centers and cancer researchers in their own states and districts, as well as seeing progress for patients and learning more about that progress.

Dr. Loehrer said that NCI RPG applications have risen but that applications at other NIH Institutes have not risen nearly as much. He asked whether some of the increase is due to the NCI cancer centers, which naturally look to NCI for funding. Dr. Lowy said that the cancer centers have not been a major driver of the increased applications. NCI is changing the wording for the cancer center support grants to make it more explicit to applicants that other NIH Institutes can also fund cancer research.

Dr. Curran asked whether there are any NCI themes, aside from the pediatric cancer initiative, that would help enact favorable legislation in Congress. Dr. Lowy said that primary and acquired resistance piques interest. At a White House meeting related to the CCDI, Vice President Mike Pence remarked on the number of children who were cancer survivors who had responded to treatment, but then relapsed. One of the CCDI's goals is to learn to predict which children are likely to have a recurrence, so that physicians can design appropriate treatment programs. Another thing that has surprised and impressed Congress is the increase in RPG applications. Finally, members of Congress often ask about rare cancers and cancer disparities.

Ms. Holohan said that Congress has been concerned about workforce development and that junior researchers are leaving the field. The 21st Century Cures Act contains provisions to level the playing field for junior investigators. Congress is also interested in patient-specific stories and in seeing that research funding is distributed around the country.

Dr. Mankoff asked whether the economic benefits of research make an appealing argument in requests for funding and whether there is anything that NCI can do to make that argument even stronger. Ms. Holohan said that there is strong interest in the Small Business Innovation Research (SBIR) program, and that NCI recently received an award from the Small Business Administration for its SBIR efforts. Advocacy and professional organizations also focus on how cancer centers and clinical trial networks bring economic benefits to particular areas. Some of the appeal to members of Congress is that people in their districts have access to treatments, and for others it is that people in their districts are employed by biomedical research organizations.

Dr. Lowy said that subcommittee members are more oriented toward the health issues. They know that the cost of cancer care is high and that the economic investment in research helps drive the U.S. economy.

IV. Progress in Small Cell Lung Cancer Research Working Group Final Report

Alex Adjei, MD, PhD
Laurie Gaspar, MD, MBA

The charge of the Progress in Small Cell Lung Cancer (SCLC) Research Working Group was to review progress in SCLC research in light of the FY 2014 frameworks. The working group met in February 2019 and agreed that progress has been made in the initiatives outlined in the scientific

framework. The initiatives included increasing the understanding of the biology and genetics of SCLC; developing models to understand treatment response and predictive biomarkers of SCLC; prevention, screening, and diagnosis of SCLC; and approaches to treatment and resistance. The working group thought the teams that NCI grant funding brought together have truly accelerated the research. There has also been at least one new immunotherapy and chemotherapy treatment change for SCLC.

The working group concluded that the FY 2014 initiatives remain relevant and should continue, with added emphasis in the areas of biospecimens, models, and screening. The working group initially presented its draft report during the March 2019 CTAC meeting, and their feedback was incorporated into this final report.

Questions and Discussion

Dr. Mankoff said that the National Lung Cancer Screening Trial was successful in changing practice in how low-dose computed tomography is used. That trial resulted in a reduction in non–small cell lung cancer mortality, but it had no observable impact on SCLC outcomes. Improvements in computed tomography technology will enable coupling molecularly targeted blood-based agents with molecularly targeted imaging. The availability of molecularly targeted agents and biomarkers of early response are particularly important given that choosing the right therapy early is especially important in SCLC.

Dr. Loehrer remarked that 50 years ago both testis cancer and SCLC had very poor survival outcomes, but the advent of platinum chemotherapy in the 1970s produced a dramatic increase in cure rates for testis cancer. The introduction of platinum doublet therapy for SCLC in the 1980s also produced an increase in survival but it was only modest in comparison, and this plateau has not been surmounted. The hope remains that an agent could be found that would produce a similar breakthrough for the treatment of SCLC.

Dr. Lowy said that the advances in non–small cell lung cancer have not accrued to SCLC. It is still not known whether the newly approved immune checkpoint inhibitors will have an impact on patient outcomes. SCLC patients often respond to initial treatment but then become resistant. Understanding the biology of resistance will be key to advancement.

Dr. Davidson noted that Congress required this 5-year review and asked whether there is a plan to review the progress again. Dr. Prindiville said that the law required that NCI reevaluate the framework at the 5-year mark and evaluate the process's effectiveness. That evaluation is due in 2020.

Dr. Davidson asked whether NCI has plans to review the impact of the initiatives that were started based on the recommendations of the working group. Dr. Doroshow said that there will be two RFA-equivalent program announcements that establish consortia for screening and therapy and for the development of models. Progress, which has already been substantial, will be reviewed when funding for the consortium is considered for renewal.

Dr. Dancey asked whether there are plans to build on the progress of checkpoint inhibitors in SCLC, given that this is the first class of agents in a generation that has affected SCLC treatment. She went on to question whether the report highlighted the inhibitor and immuno-oncology appropriately, and if the report could be amended to reflect that. Dr. Adjei responded that the working group discussed the

paradox of SCLC having a high mutation rate but only modest results using checkpoint inhibitors. The working group did not make a specific recommendation about immunotherapy but concluded that there is a need to better understand the biology of the disease, including the immune milieu; develop better models; and understand SCLC biology. Dr. Gaspar added that there are several SCLC clinical trials using immunotherapies.

Dr. Curran commented that while much has been learned about the molecular subclasses of non–small cell cancer and how to circumvent resistance, the report should reflect that progress in the treatment of SCLC has been limited.

Motion. A motion to accept the report passed unanimously.

V. Recognition Ceremony

Cancer Clinical Investigator Team Leadership Awardees
James Doroshow, MD

Dr. Doroshow announced this year's the Cancer Clinical Investigator Leadership Award (CCITLA) recipients. The awards recognize clinical investigators who are actively involved in NCI-funded collaborative clinical trials at NCI-designated cancer centers. Candidates for the award must be full-time faculty in the oncology clinical setting and must have practiced for 3 to 8 years post-fellowship.

Each year, NCI provides 10 to 12 two-year awards of $60,000 per year. The funding gives the awardee protected time—at least 1 day per week—to focus on clinical trial-related activities. Ninety-five percent of the recipients who have completed the award have remained in academic clinical research positions. As the initial CCITLA recipients are now 10 years out from receiving the award, NCI plans to assess the program to ensure that it is productive from the point of view of NCI and the cancer centers, and to determine whether NCI could improve the program.

The 2019 recipients are as follows:

- Gabriel A. Brooks, MD, MPH, Norris Cotton Cancer Center, Dartmouth University
- Lara E. Davis, MD, Knight Cancer Institute, Oregon Health & Science University
- Kristin A. Higgins, MD, Winship Cancer Institute of Emory University
- Katherine M. Moxley, MD, Stephenson Comprehensive Cancer Center, University of Oklahoma
- Paul E. Oberstein, MD, MS, Laura and Isaac Perlmutter Cancer Center, New York University School of Medicine
- Paul K. Paik, MD, Memorial Sloan Kettering Cancer Center
- Daniel E. Spratt, MD, Rogel Cancer Center, University of Michigan
- Victor M. Villalobos, MD, PhD, University of Colorado Cancer Center
- Ira S. Winer, MD, PhD, Barbara Ann Karmanos Cancer Institute, Wayne State University
- Dan P. Zandberg, MD, Hillman Cancer Center, University of Pittsburgh Medical Center

Retiring CTAC Members
Douglas R. Lowy, MD
James Doroshow, MD

Dr. Davidson was recognized for her service as chair of CTAC from 2015 to 2018. Drs. Curran, Mankoff, and LeBlanc were recognized for their service as they are rotating off CTAC.

VI. Glioblastoma Working Group Final Report

Walter J. Curran, Jr., MD, F.A.C.R.
Chi V. Dang, MD, PhD

Drs. Curran and Dang chaired the Glioblastoma Working Group of the Translational Research Strategy Subcommittee (TRSS). This working group was convened to help identify the most provocative and impactful translational research questions in glioblastoma to advance treatment, identify opportunities for the application of new technologies, and identify gaps in translational research knowledge. This report represents the working group's deliberations and recommendations to NCI.

Glioblastoma Multiforme (GBM) Treatment Challenges. GBM is the most common type of malignant brain tumor, with approximately 13,000 newly diagnosed patients every year in the United States. Limited progress has been made in the development of curative therapies. Despite aggressive therapies, the median survival for GBM is 15 months, with a 5-year survival rate of 3 percent. Dr. Dang went on to comment that GBM treatment outcomes have been limited by the lack of a strong research pipeline for the development of curative therapies.

The diffuse infiltrative nature of GBM tumors makes them difficult to resect completely, even with the use of contrast-enhanced imaging. Even though tumor cells are not visible on the scans, they could still be present in the non–contrast-enhanced areas surrounding the tumor. Another challenge in treating GBM is the location of the tumor. Radiation therapy for the non–contrast-enhanced area of the brain is limited because normal brain tissue lacks tolerance to radiation. Systemic therapies have to overcome the blood–brain barrier to reach their target, and targeted agents are limited in their effectiveness based on intra- and inter-tumoral heterogeneity. To date, immunotherapy has not been very successful in treating GBM, likely because it is a largely "cold" tumor.

The key considerations in treating GBM are a better understanding of the biology of the disease, particularly in understanding tumor infiltrates in the surrounding normal parenchyma; animal models that recapitulate human disease; a pathway to evaluate drugs at the preclinical and clinical stages; and a better understanding of therapeutic vulnerabilities and resistance.

Dr. Curran said that the focus of this working group was on improving therapeutics for adult GBM. He described the process that led to the working group's final report and summarized the recommendations for CTAC members. Briefly, the working group made overarching recommendations that include developing a national infrastructure for preclinical testing and qualifying novel therapeutics for patients with GBM that seamlessly integrates with an early-phase clinical trials program and leverages existing NCI resources; leveraging industry support and public-private partnerships in the development of GBM therapeutics; expanding the NCI Cancer Therapeutics Evaluation Program's portfolio of drugs available for preclinical and clinical testing; and bridging the basic neuroscience research conducted and funded by the National Institute of Neurological Disorders and Stroke with NCI's portfolio of GBM

research. In addition to the overarching recommendations, the working group made specific recommendations for infrastructure capabilities and research needs within five areas of special emphasis: preclinical qualification of new agents, clinical trials, immunotherapy, radiation therapy, and quality of life.

The working group's recommendations address the most important challenges that must be overcome to ensure rapid progress in the development of new treatment strategies and improving outcomes for patients with GBM. Lastly, the working group developed a model for the seamless integration of preclinical and early clinical trial testing to provide a robust set of information that can serve as a foundation for decisions for further clinical development.

Questions and Discussion

Dr. Loehrer commented that it appears that the tumor microenvironment plays an important role in GBM and asked whether the working group had discussed it. Dr. Dang said that the working group addressed the microenvironment in its report and that the recommendation to expand the understanding of the tumor biology is inclusive of research into the tumor microenvironment.

Dr. Lowy asked about the blood–brain barrier and whether it might pose an obstacle for therapy. Dr. Curran said it is unknown how much of a role the blood–brain barrier plays in resistance to therapy. The working group recommended that performing multiple biopsies of a tumor over time could lead to better understanding of permeability and resistance.

Mark Gilbert, MD, NCI Center for Cancer Research and ex officio member of the working group, said that many factors affect the permeability of the blood–brain barrier. Some agents are too large to cross the barrier, and others are transported out by well-known mechanisms of resistance. It is critical to prescreen agents in preclinical models and during early-phase clinical trials. Appropriate models are needed to predict what agents are likely to cross the blood–brain barrier.

Dr. Dang asked Dr. Gilbert about the need for better imaging of the drug's accessibility to the tumor. Dr. Gilbert said that there is a need for imaging to validate whether the drug reaches the tumor, and it is important to know whether there is interpatient variability in the drug's permeability. Patients could then be screened for a clinical trial based on pretreatment evidence of delivery.

Mr. Arons said that there have not been enough early-phase clinical trials that helped determine which subset of patients is most likely to benefit from a drug, consequently impacting clinical trial failures. He emphasized the need for research resulting in novel therapies to treat GBM.

Mr. Arons said that a recently published study found that the timing of immunotherapy delivery may also be key. The study found a greater survival benefit when immunotherapy was given as a neoadjuvant therapy at the time of recurrence. There is also an emerging class of imaging agents that can be used in early-phase trials and could lead to lower doses of radiation and enhance radiation's effects.

Dr. Barton applauded the inclusion of quality-of-life outcomes in the report. It is critical to capture those outcomes in databases so that they can be used in the development of models using artificial intelligence and machine learning. The more comprehensive the database, the more useful the models will be.

Dr. Barton commented that the model for the seamless integration of preclinical testing and early clinical trials, especially the inclusion of non-disease-related outcomes that the working group presented, captured all key areas and should be considered in every disease portfolio going forward. As the population of cancer survivors increases, it is important to consider the psychosocial and physiological costs to the patient. The NCTN has patient-reported outcomes committees that can be helpful in that area by working in parallel during trial design and development to include non-disease-related outcomes.

Terri S. Armstrong, PhD, NCI Center for Cancer Research, said that GBM is both a cancer and a neurologic disease. GBM significantly affects the patient's function, which, in turn, affects the patient's outcome. NCI, FDA, and the European Medicines Agency developed key constructs to measure across clinical trials and clinical care that fit well with the report's quality-of-life framework.

Dr. Petersen asked whether liquid biopsy for tumor products of brain tumors could identify potential biomarkers. Dr. Gilbert said that it would be ideal to be able to use a blood test to identify disease status because it is easier on the patient. So far, these types of liquid biopsy studies have not been effective, but new research suggests that the cerebrospinal fluid (CSF) might hold promise. Molecular technologies are rapidly improving, and even small pieces of DNA in CSF can now be detected and studied. These studies could be incorporated into future clinical trials. Dr. Curran added that there are funded studies looking at tumor byproducts in the blood. Dr. Mankoff said that most of the positive studies to date have involved CSF.

Dr. Loehrer said that most clinical trials appear to be in patients with a recurrent tumor. What percentage of trials involve early therapy? Mr. Arons said that most of the trials are for recurrent GBM, and that there is a need to focus more on early therapy. In 2018, the National Comprehensive Cancer Network advocated clinical trials for treatment from the time of diagnosis. Dr. Curran said the key for clinical trials of frontline treatments is to have the preliminary early-phase data to show that it can be successful.

Dr. Gilbert said that treatment with temozolomide and radiation has changed the standard of care for GBM. The GBM 5-year survival rate is 10 percent to 15 percent, and the 2-year survival is 30 percent to 35 percent which is an improvement; a small number of patients who received standard of care therapy have lived beyond a decade. It would be important to study outcomes in patients to be able to identify those most likely to benefit from the treatments.

Dr. Mankoff said that he was intrigued at the report's suggestion of working with NINDS, particularly on the molecular dynamics and imaging components. Drug companies will not invest in neurologic agents without the ability to prove its efficacy through imaging. Both the imaging and the therapeutic agents must get across the blood–brain barrier.

Motion. A motion to accept the report passed unanimously.

The final working group report was posted online following the meeting.
https://deainfo.nci.nih.gov/advisory/ctac/0719/Att_12_GBM%20WG%20Final%20Report%20CTAC%207-17-19_v1.pdf

VII. Pediatric Brain Tumor Consortium (PBTC) Concept Renewal

Malcolm A. Smith, MD, PhD

NCI has supported the PBTC since 1999. The consortium encompasses 11 institutions and is the primary source of clinical trials for children with refractory brain tumors. Dr. Smith is seeking input from CTAC before finalizing the funding opportunity announcement for the PBTC.

Recent PBTC Studies. Molecularly targeted agents are an area of focus, and studies have included histone deacetylase inhibitors (such as vorinostat and panobinostat), PARP inhibitors (such as veliparib), a MET kinase inhibitor (savolitinib), and a MEK inhibitor (selumetinib). Most PBTC studies included pharmacokinetic analyses and neuroimaging, and many also included genomic analyses.

Protocol PBTC-029 is an example of a successful precision medicine clinical trial that began as a phase I study and transitioned to phase II. The study involved selumetinib in treatment of pediatric low-grade glioma, and it included separate strata for molecularly defined subtypes (e.g., *BRAF* alteration and neurofibromatosis type 1 [NF1]-associated disease). Most of the patients in the *BRAF*-altered cohort saw tumor shrinkage, with 36 percent of patients achieving an objective response. All patients with NF1-associated low-grade gliomas had some tumor shrinkage, with 40 percent reaching the criteria for objective response, and a 2-year progression-free survival rate of 96 percent.

One of the PBTC's charges is to transition studies to phase III COG clinical trials. Of the four phase III brain tumor trials that the COG activated since 2014, two arose from PBTC studies. The COG is expected to receive approval within the next 6 months for two additional phase III trials that are based on PBTC study results.

Dr. Smith described the multiple lines of communication that exist between the PBTC and the COG Central Nervous System (CNS) Tumor Committee to ensure a seamless transition from the PBTC to the COG and avoid any duplication of effort.

Operations Accomplishments. Before 2014, the PBTC was not well integrated into the CTEP clinical trials infrastructure. It has since adopted all of the Cancer Trials Support Unit (CTSU) procedures and is affiliated with the NCI Pediatric Central Institutional Review Board (PedCIRB). The PBTC conducts 100 percent source data verification through central monitoring. A rigorous site performance evaluation procedure is in place to evaluate existing PBTC member institutions, allowing new sites to compete for membership to replace lower-performing sites. The PBTC has worked closely with the St. Jude Children's Research Hospital's Clinical Trials Administration department and regulatory affairs team to develop processes and policies that allow St. Jude to serve as investigational new drug sponsor for PBTC trials, facilitating interactions with pharmaceutical companies.

Future Directions. Dr. Smith highlighted three scientific directions for the PBTC and provided several examples for each area. The PBTC plans to build on findings based on the distinctive biology of pediatric brain tumors to bring novel agents into clinical testing, including kinase inhibitors, local therapies such as intrathecal radiotherapy and tumor-treating fields (supratentorial and infratentorial) for children with high-risk brain tumors, and novel immunotherapies like chimeric antigen receptor T cells.

The PBTC has the capability to quickly transition discoveries from the bench to the clinic. Without the federal funding and the multi-institutional collaboration of the PBTC, the cost and expertise required for designing and implementing trials for children with brain cancer would be prohibitive.

The PBTC will work to increase its capacity for clinical trials through additional support for its Operations, Biostatistics, and Data Management Core; increase the number of member institutions to between 16 and 18; and enhance the ability to continue collaborative interactions with the COG CNS Tumor Committee to facilitate more scientific input to the PBTC.

Questions and Discussion

Dr. Loehrer asked about treatment morbidity and survivorship issues. Many patients who survive treatment have significant treatment-related defects. Dr. Smith said that the PBTC is studying only children with relapsed or refractory disease, and that PBTC investigators do not measure long-term treatment effects because most of their patients are not long-term survivors. The COG and the Childhood Cancer Survivor Study are better equipped to monitor long-term effects. For example, the COG may test the long-term toxicity profile of the agents that the PBTC is testing. Also, the COG may study the agents to see whether they can minimize long-term effects of treatment. What the PBTC can do is conduct first-in-children studies of agents that may have fewer side effects.

Dr. Fingert asked whether there are any plans for the PBTC to collaborate with European consortia to accelerate these clinical trials. Dr. Smith said that the COG focuses more on international collaboration. NCI is open to ways to enhance international communication within the COG. The NF1-associated low-grade glioma trial that COG is conducting for selumetinib includes a partnership with AstraZeneca, which is trying to establish the trial with participation from European centers.

Dr. LeBlanc asked how many studies the PBTC Operations, Biostatistics, and Data Management Core activates each year and whether the core activates Medidata Rave. Dr. Smith said that the center activates three or four studies annually, including Medidata Rave. The PBTC has the expertise in Medidata Rave and the infrastructure for it.

Dr. Curran asked whether the PBTC renewal presents an opportunity to more closely align the COG with the PBTC to take advantage of the existing COG infrastructure to conduct a lot of this work. Dr. Smith said that the PBTC is focused on small early-phase clinical trials for pediatric brain tumors and has established an efficient and effective clinical trial infrastructure. The PBTC is distinct but works closely with the COG CNS Tumor Committee.

Dr. Barton encouraged including non-treatment-related outcomes in COG and PBTC studies to better understand the non-disease-related outcomes that families must deal with. Dr. Smith said that PBTC investigators are interested in studying those outcomes as well.

Dr. Lowy said that NCI is trying to work internationally with European pediatric researchers. He has been working with the French National Cancer Institute to see whether their pediatric database could be used as part of the CCDI without the legal impediments of the General Data Protection Regulation. NCI is working to share databases with the European Union while protecting patient privacy.

Dr. Dancey said that Dr. Smith illustrated the PBTC's value in having a group of investigators focused on addressing early-phase trials in pediatric brain tumors, but not why it needs its own operations and statistical support. Could the COG infrastructure be used for these early-phase clinical trials? Dr. Smith said that there is a need for a small group to focus on novel approaches to the treatment of pediatric brain tumors. The PBTC is integrated with the clinical trials infrastructure with Medidata Rave, the CTSU, and the PedCIRB. The PBTC is an efficient group that is working well to develop clinical trials for children with brain tumors.

Dr. Davidson said that she hoped that NCI could eventually fold the PBTC into the COG.

Dr. LeBlanc said that Dr. Smith had convinced him of the value of a good relationship between the data management team and clinicians. The program was working well and should be allowed to continue. Dr. Smith said that the COG's focus is on opening larger phase III trials. The PBTC is focused on smaller trials of 10–20 patients, which are not a focus within the COG.

Mr. Arons said that pediatric brain tumor trials are specialized because of the difficult issues of the blood–brain barrier and the unique biology of pediatric tumors. He asked whether the PBTC's work has informed the Pediatric Early Phase Clinical Trials Network (PEP-CTN). Dr. Smith said that it has not, because the PEP-CTN is still in its early phase of developing new clinical trials.

Dr. Davidson asked whether there are other cancer-specific pediatric groups that focus on early-phase trials. Dr. Smith said that there are, but most are philanthropically funded.

Dr. Loehrer suggested bringing pediatric and adult brain tumor researchers together to share ideas that could advance both pediatric and adult tumor research. Dr. Smith agreed that that was a good idea.

Dr. Gilbert said that rare-disease researchers sometimes convene those who specialize in children and those who specialize in adults. The Collaborative Ependymoma Research Network Foundation achieved some major advances in that field when it convened adult and pediatric researchers.

VIII. SEER Program Update

Lynne Penberthy, MD, MPH

SEER was established in 1973 and is now expanding its capacity to support a broader range of research. SEER currently has 16 population-based registries, covering approximately 35 percent of the U.S. population. Through all its registries, it is anticipated that SEER will receive 550,000 newly reported cases of cancer each year. With the new infrastructure the program has put in place, about 85 percent of the cases have at least one real-time electronic pathology report. All of the registries are—or will be—on a common data platform, enabling central linkages. The program will soon issue a request for proposals to further expand the number of registries.

Registries are Health Insurance Portability and Accountability Act (HIPAA) exempt and are required to maintain identifying information for follow-up. They are a valuable resource because they represent data on all cancer patients in a geographic area and consolidate information across many sources. Registries perform active monitoring of all patients, from diagnosis until death; the data collected include patient demographics, characterization of the tumor at diagnosis, treatment, survival, and cause of death.

SEER typically receives patient data from hospital abstracts, physician reports, pathology reports, and death certificates, providing a clinical context for the data. These data are structured when most of the information in electronic health systems are unstructured text. Trained personnel curate the data.

Dr. Penberthy outlined several challenges that SEER faces for capturing clinically meaningful data. Data entry is laborious and costly, and registrars manually extract 250 variables for each case. The data elements are complex, and the largely manual extraction process can take up to 2 years. Patients can receive care from many different health care organizations, and registrars may not have access to the records of all of those organizations. Rapid changes in diagnosis and treatment alter how diagnoses are made and how patients are followed. The pace of new therapies receiving approval has increased, requiring registries to monitor more treatments for more people.

Capturing long-term outcomes such as recurrence, new courses of therapy, and comorbid conditions is difficult. Some of the most intransigent cancers with the highest mortality rates are likely to manifest as recurrent disease. The diagnostic methods used to capture recurrence differ by cancer site and by health care provider, making it difficult to capture recurrence comprehensively. Registrars are unlikely to have access to the data to show evidence for recurrence.

Approaches to Enhancing SEER. SEER's main goals are to create a system representing real-world data to supplement and complement clinical trials to understand the effectiveness of oncology care for patients who do not participate in a clinical trial. SEER is conducting pilot studies to test new approaches to data collection.

One approach to enhancing completeness and expanding the clinical data is to use linkages to other data sources. Linkages are cost-efficient, more accurate, and timely. Another approach is to develop tools for automation, such as natural language processing and machine learning. It may be possible to leverage these activities through collaborations with commercial partners like CVS and Walgreens.

The specific gaps that SEER is addressing are in the area of data capture, including outcomes other than survival and cause of death, and in developing new infrastructures, such as the Virtual Pooled Registry-Cancer Linkage System (VPR-CLS) and the Virtual SEER-Linked Biorepository. SEER is also developing a system that will allow a researcher to rapidly identify patients who may be eligible for their clinical trial.

SEER will partner with organizations to acquire source data, including genomic and genetic testing companies. To capture detailed information on treatment and comorbidity, they will also look to claims sources from large insurers and pharmacies. Six SEER state registries have statewide "all-payer-all-claims" data. In addition to linkages, SEER partnered with technology companies that aggregate and use clinical data.

Dr. Penberthy showed the data sources that SEER already accesses and new sources it is currently piloting. The pilots include biomarkers, pharmacy claims, electronic health record (EHR) data, patient-reported outcomes, administrative medical claims, and surveys.

SEER is collecting data that will permit the tracking of specific treatments over time and beyond the clinical trial setting. With these data, the effectiveness of standards of care in oncology practice can be evaluated, and clinical trial results can be corroborated in the real world.

SEER is complementing clinical trial results with real-world data. One example is tracking the dissemination of checkpoint inhibitors using oncology practice claims. These real-time data allow SEER to monitor which patients are using these agents and what their outcomes are. The data also show how much off-label use of checkpoint inhibitors takes place for different cancer sites. SEER is also leveraging EHR data and radiological scans to capture more detailed real-time information on radiation site and dose. SEER tracks other data as well—for example, to look for trends in whether patients are refilling prescriptions at the correct intervals.

SEER can also be tapped to monitor standards of care and outcomes. For example, the standard of care for all women who have ovarian cancer includes *BRCA* gene testing, but an analysis of women in California and Georgia showed that there are significant differences among the rates of *BRCA* gene tests of women with ovarian cancer by race and ethnicity. On the other hand, disparities in Oncotype DX testing in breast cancer have nearly disappeared.

Dr. Penberthy showed another example of where SEER data was used to corroborate clinical trial results in the general population. A study using SEER data corroborated the TAILORx (Trial Assigning IndividuaLized Options for Treatment [Rx]) finding that there is an increasing benefit of chemotherapy with higher Oncotype DX risk score.

SEER data can also be used to track incidence and survival by cancer subtypes, such as histologic subtype in lung cancer or molecular subtype in breast cancer when the data are linked with treatment data.

In partnership with the Department of Energy (DOE), SEER is developing resources to support real-time data capture through the use of natural language processing. One of the resources is an application programming interface (API) that will automatically extract five key data elements to facilitate near real-time incidence reporting. For 1 year of data for 11 registries, it would take more than 4,000 hours to screen for cancer site, histology, behavior, laterality, and grade by hand; using the automated process, the screening took 53 minutes. The algorithm coded 43 percent of pathology reports correctly. This method illustrates that real-time incidence reporting is possible and could enable real-time identification of eligible patients for clinical trials. The next planned enhancement would be to appropriately capture disease recurrence and biomarkers.

SEER is working to provide a detailed longitudinal picture of treatment and outcomes for each cancer patient by linking data from multiple sources representing each patient's trajectory over their disease course.

Questions and Discussion

Dr. Meropol asked about linkages between SEER and Medicare data. Dr. Penberthy said that SEER-Medicare is a longstanding partnership, but the data remain separate. SEER and Medicare are discussing whether it would be possible for Medicare to share data—such as treatments, laboratory tests, and comorbidities—to supplement SEER.

Dr. Barton asked whether SEER tracks provider information for individual patient records. Dr. Penberthy said that it may be possible to use the National Provider Identifier to identify information about the specialty provider, and that some registries might capture those data. SEER does not currently contain any provider information.

Dr. Barton asked for more information about the patient-reported outcome survey that Dr. Penberthy mentioned. Dr. Penberthy said that SEER has done pilot studies to contact patients and ask whether they would be willing to share their outcome information. Patients are typically interested in sharing their information in this way. Registries also work with investigators to conduct patient contact studies.

Dr. Ochoa asked how much the planned automation would improve the timeliness of the data. Dr. Penberthy said that the goal is to have near real-time data. For example, SEER will aim to have 2019 incidence data available in February 2020 to allow for any delays in data reporting and statistical modeling. SEER is also trying to standardize information across registries to allow for real-time case ascertainment, so that researchers could recruit patients with a rare cancer from multiple registries simultaneously, for example.

Dr. Dancey asked whether the plans for enhanced data collection and data sources would apply to the entire SEER population or to subsets. Dr. Penberthy said that it applies to subsets but that the longer-term goal is to the include those data for the entire SEER population.

Dr. Dancey said that the new data should represent the U.S. population and should allow researchers to identify and recruit patients for trials. Having a way to link long-term outcomes to trial patients would be very helpful, especially since clinical trial participants are often lost to follow-up. Researchers would also want to capture performance status, response information, and toxicity grades. Dr. Penberthy said getting performance status and data on toxicity is challenging, because it requires pathology and radiology data, including past images. If SEER could access the clinical notes, it may be possible to auto-extract that data. Given that SEER is trying to automate more of the registrars' work, it may be possible to ask the registrars to manually collect those data from the notes.

In terms of the long-term follow-up of clinical trial patients, the VPR-CLS is a system that is being developed to include all of the registries across the United States. The aim is to use the VPR-CLS, which has already been tested in five cohort studies, for clinical trials. Dr. Penberthy offered to provide additional information to CTAC members about the VPR-CLS.

Dr. Fingert said that, in terms of longitudinal follow-up of clinical trials, it is important to think about endpoints other than survivorship. It could be especially meaningful for patients who have good responses to treatment and do not need to progress to another therapy. Time-to-therapy data could add value to the datasets. Dr. Penberthy agreed. SEER is already receiving the longitudinal claims for a subset of the population and could develop a way to provide that information to researchers.

Dr. Mankoff said that the SEER database contains geographic, incidence, stage, treatment, and recurrence data that would be helpful in planning clinical trials. For example, a researcher may want to do a study with a subset of patients and SEER could be queried to find out where those patients lived. Dr. Penberthy said that SEER has worked with DOE to develop graph analytics so that it is possible to find

patients who meet the criteria for a planned clinical trial and identify where the patients live. That task is one of the later goals of the pilot with DOE, but it could possibly be tackled sooner.

Dr. Mankoff said that there are large databases containing images but that few of them have longitudinal outcomes. He suggested it would be meaningful to connect longitudinal imaging data to clinical endpoints. Dr. Penberthy said that SEER has been discussing the possibility of obtaining images, as it is a logical next step, but that data storage is a potential challenge. SEER is already obtaining the text from imaging reports. Dr. Mankoff said that other groups are working on these infrastructure challenges and offered to introduce Dr. Penberthy to members of the various imaging networks. Dr. Penberthy said that she would appreciate those introductions; imaging data would be necessary to capture recurrence appropriately.

Dr. Loehrer said that the location mapping could be helpful in looking at where morbidity and mortality may be the highest to inform researchers about where to conduct screening trial investigations. He also suggested that SEER link its data with genomic data from other sources, such as the Oncology Research Information Exchange Network.

Dr. Kelley asked whether the SEER data could be added to the North American Association of Central Cancer Registries (NAACCR) data to help capture population data from across the country. Dr. Penberthy said that all of the tools that SEER is developing, including the API for data extraction, will be open source and available to all registries. Dr. Kelley said that SEER may be able to encourage NAACCR to begin collecting long-term follow-up data.

IX. External Clinical Data: Opportunities and Challenges For Oncology Trials

Howard J. Fingert, MD, FACP
Rajeshwari Sridhara, PhD
Discussants: Neal J. Meropol, MD; Michael L. LeBlanc, PhD; and Lisa Meier McShane, PhD

External Clinical Data: Opportunities for NCI. Dr. Fingert introduced this session on the use of external clinical data for research and highlighted opportunities for this rapidly expanding field. External clinical data, which includes structured data from past clinical trials and clinical care systems, has many possible applications in oncology. Optimally, external clinical data can help accelerate clinical programs, reduce their costs, and add clinical value. Promising applications include supplementing (or possibly replacing) the control arm of a randomized clinical trial, refining statistical power analyses, supporting clinical monitoring, and trial design. New analytic platforms and practices have been designed to support transparency, quality, and independent audits and analyses. The international regulatory community has proposed to update the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E8 guidelines to advance the quality of external data applications and subsequent review for regulatory decisions. Dr. Fingert outlined several opportunities for leveraging NCI's structured oncology trials data: a) conduct studies designed to replicate outcomes from randomized studies; b) refine standards for clinical trial data capture to increase value and applications; c) gain experience with emerging analytic platforms; and d) build consensus about approaches to data management, statistical designs, and analyses. These efforts will also likely expand opportunities for constructive partnerships with collaborators from the cancer research and data science communities.

External Controls in Cancer Clinical Trials: Challenges and Opportunities. Dr. Sridhara provided examples of where external data can be used as controls. Historical controls or clinical data collected during routine practice can help to understand the natural history of a disease, design future studies by establishing the standard-of-care effect, replace a randomized control arm on a clinical trial, or supplement external data into concurrent controls on a prospective trial.

In the past, FDA has limited the use of historical controls to situations in which the disease has a high mortality rate, the effect of treatment is dramatic, and the usual course of the disease is highly predictable. Historical control data is external control data that is derived from past clinical trials.

The 21st Century Cures Act required FDA to evaluate the potential use of real-world evidence (RWE) to support approval of a new indication for an approved drug or to help satisfy post-approval study requirements. Real-world data (RWD) is data relating to patient health status and the delivery of health care. RWE is the clinical evidence of potential benefits and risks of a medical product that is derived from the analysis of RWD.

Many factors need to be considered when incorporating RWE into overall evidence generation. In 2013, FDA published guidance for industry and FDA staff, "Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data." Among the issues the guidance discusses are the appropriateness of the data source, having a pre-specified study protocol and statistical analysis plan, selection of a study population, exposure and outcome ascertainment, and specifying the inclusion and exclusion criteria. The considerations are similar when using a historical control arm. FDA looks at patient selection, including whether it is a contemporaneous cohort; endpoint ascertainment, including whether the endpoints are pre-specified and objective; whether assessment timing and methods are comparable (e.g., in time to progression); whether the historical control data ensures an adequately sized control group; whether there is pre-specification of the important prognostic and confounding variables; and whether the statistical analysis plan is adequate.

In December 2018, FDA published a framework for the implementation of its RWE program. The framework outlines guidance for this multifaceted program and includes promoting stakeholder engagement, guidance development, and demonstration projects to show when using historic clinical trials data is acceptable. The framework outlines how RWD/RWE is used in regulatory decision making for randomized clinical trials. Guidance for non-randomized single-arm trials and observational studies is under development.

External controls offer opportunities to reduce the number of patients needed and maximize the allocation of patients to the investigational drug in clinical trials. External data may include data from past clinical trials, registry data, case study data, and other RWD. The challenges of using those data include factors such as unmeasured disease and patient characteristics, frequency of assessment and uniformity in the assessment methods, dosing that can change over the course of a trial, and how to define the index date, survivor bias, and follow-up time.

Dr. Sridhara provided examples of challenges and considerations when using RWD. In the first, she showed the limitations of a study using a historical control arm. Among the limitations were that 35 percent of the patients in the original study had to be excluded because they did not match any of the historical controls, there was confounding due to patients' subsequent treatment, and the median follow-

up of the original study was 8.2 months, while the historical controls had a follow-up of 18.2 months. Another example involved a drug where approval was supported by two expanded-access single-arm studies and a retrospective historical case control involving 25 patients. The study found that the two treatment arms had a 96 percent survival rate, versus 16 percent in the historical control group.

In February 2019, FDA provided additional guidance on rare diseases and common issues in drug development, highlighting how RWD could be used in those instances. While not specifically focused on cancer, these documents address the importance of including adequate understanding of the natural history and physiology of the disease, drug mechanisms of action, toxicology considerations, and outcome assessments and endpoints.

Randomized controlled trials (RCTs) continue to be the best way to understand and evaluate treatment effects and account for known and unknown confounding factors. Single-arm studies supported with historical controls should be reserved for special circumstances. FDA requires adequate data based on predetermined patient selection criteria and pre-specified statistical analysis when a historical control arm is used to support a submission. The FDA framework serves as a roadmap for more fully incorporating RWD and RWE into the regulatory paradigm.

Panel Discussion. Dr. Meropol said that there are opportunities to advance the science of RWD as a source of evidence through partnerships between RWD sources and entities that produce clinical trial data, such as the National Clinical Trials Network (NCTN). Such collaborations could provide an opportunity to define and explore the relationship of real-world outcomes, such as real-world time to disease progression, time to next treatment, and treatment response to standard clinical trial outcomes. There is also an opportunity to advance the science of endpoints and the understanding of differences between patients treated in a clinical trial receiving frequent follow-up testing and the real world, where the population is more diverse and follow-up may not be as frequent or comprehensive as in a clinical trial.

Dr. LeBlanc said that RCTs are the gold standard, because they produce convincing data. The task is to figure out how RWD can add value to make the RCT even more convincing. Also, clinical trial patients usually do better than patients who are not in a clinical trial. It is necessary to learn what factors lead to those differential results. He added that while RWD adds value it also complicates the trial.

Dr. McShane said that it would be a "very high bar" to supplement a control arm of a trial of investigational agents that uses external data. It is more realistic to use external data for comparable effectiveness trials or for post-trial ancillary investigations. Dr. McShane listed a variety of cautions in using external data in trials for investigational agents. For example, with more targeted therapies being used, patients in the historical database may not be representative of the patient population today. Dr. McShane suggested using pilot exercises as a way to learn about the practicality of external datasets and how best to make use of them. One example would be replicating a control arm from a trial for which the outcome has not been reported, because of the importance of having blinding in place. As for the idea of augmenting the control group with external data, it is difficult to combine the external and internal controls because they are likely to be different.

Dr. Sridhara agreed that it is harder to compare data from the newer, more targeted therapies with historical data in which the treatment was not as targeted. The standard of care changes so rapidly that it

becomes difficult to compare using a historical control. Contemporaneous external controls would provide better data, but even then, the controls would need to receive clinical trial standards of care. She went on to say that external controls would be useful in pragmatic trials to determine dosage.

Questions and Discussion

Dr. Dahut said that external controls may be useful for diseases such as prostate cancer, in which there is sequential approval of drugs against a control that is no longer a control. For example, there will never be a randomized trial of enzalutamide versus apalutamide versus abiraterone. It would be useful to have RWD about survival and sequence activity.

Dr. Dancey agreed that RWD is useful when the disease is predictable, and the data is convincing. She did not think that it is possible to match the patients in trials with RWD or RWE. Dr. Fingert agreed but noted an instance in which RWD was useful: He recounted a situation in which researchers were told that their control arm was unconvincing because it was underperforming. The sponsor used RWD to show that the control arm was not underperforming.

Dr. Dancey said that she can see the value of RWD when the experimental effect is large. Dr. Fingert said that he prioritizes using RWD to augment or supplement the control group. External data can be used to accelerate trials, particularly for rare diseases.

Dr. Meropol said that there are situations in which it is possible to match real-world patients to clinical trial patients and that for some contexts, matching is more difficult. Dr. McShane agreed that being able to match clinical trial patients to RWD is context dependent, and she said it would be necessary to do pilot studies to determine where matching would be possible.

X. Ongoing and New Business

Patrick J. Loehrer, Sr., MD

Dr. Loehrer said that the November 6 CTAC meeting will be cancelled. Members were asked to send topics for future CTAC meetings to Drs. Loehrer and Prindiville.

XI. Adjourn

Patrick J. Loehrer, Sr., MD

There being no further business, the 39th meeting of CTAC was adjourned at 2:52 p.m. on Wednesday, July 17, 2019.

11/27/19
Date

Patrick J. Loehrer, Sr., MD, Chair

11/27/2019
Date

Sheila A. Prindiville, MD, MPH, Executive Secretary

Appendix

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Clinical Trials and Translational Research Advisory Committee

CHAIR

Patrick J. Loehrer, Sr., MD **2020**
Director
Indiana University Melvin and
Bren Simon Cancer Center
Associate Dean for Cancer Research
Indiana University School of Medicine
Indianapolis, Indiana

MEMBERS

Debra L. Barton, PhD, RN, FAAN **2021**
Associate Dean for Research and Rackham Graduate Studies
Mary Lou Willard French Endowed Chair
Department of Systems, Populations and Leadership
Professor of Nursing
Professor of Psychiatry
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Ann Arbor, Michigan

Walter J. Curran, Jr., MD, FACR **2019**
Executive Director
Winship Cancer Institute of Emory University
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Janet Ellen Dancey, MD, FRCPC **2021**
Professor
Department of Oncology
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Director, Canadian Cancer Trials Group
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Nancy E. Davidson, MD (BSC) **2022**
Senior Vice President, Director and Full Member, Clinical Research Division
Fred Hutchinson Cancer Research Center
President & Executive Director
Seattle Cancer Care Alliance Head, Division of Medical Oncology, Department of Medicine
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Anne-Marie R. Langevin, MD **2021**
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Department of Pediatrics Hematology/Oncology
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Michael L. LeBlanc, PhD **2019**
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University of Washington
Seattle, Washington

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Gerd Muehllehner Professor of Radiology
Vice-Chair for Research
Department of Radiology
Perelman School of Medicine
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Lynn M. Matrisian, PhD, MBA **2021**
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Professor
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