DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
36th CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC) MEETING

Summary of Meeting
July 11, 2018

Shady Grove Campus, East Wing
Rockville, MD

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
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The 36th meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was held on Wednesday, July 11, 2018, at 8:30 a.m. The CTAC chair, Dr. Nancy E. Davidson, presided.[1] The meeting was adjourned at 2:36 p.m.

Chair
Nancy E. Davidson

CTAC Members
David F. Arons
Debra L. Barton
Walter J. Curran, Jr.
Janet Ellen Dancey
Timothy J. Eberlein (absent)
Howard J. Fingert
David M. Gershenson
Paul A. Godley
Anne-Marie R. Langevin
Michael L. LeBlanc
Patrick J. Loehrer, Sr.
David A. Mankoff
Lynn M. Matrisian
Neal J. Meropol
Edith P. Mitchell
Nikhil C. Munshi
Augusto C. Ochoa
Roman Perez-Soler
Gloria M. Petersen
Steven T. Rosen
Dan Theodorescu (absent)
Louis M. Weiner

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

Executive Secretary
Sheila A. Prindiville, NCI

Presenters
Michael Carducci, MD, AEGON Professor of Prostate Cancer Research, Professor of Oncology and Urology, Associate Director for Clinical Research, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University
Helen Chen, MD, Associate Chief, Investigational Drug Branch, Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), NCI
Nancy E. Davidson, MD, 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, University of Washington
James H. Doroshow, MD, Deputy Director, Clinical and Translational Research; Director, DCTD, NCI
Percy Ivy, MD, Associate Chief, Investigational Drug Branch, CTEP, DCTD, NCI
Primo Lara, Jr., MD, Director, UC Davis Comprehensive Cancer Center, Professor of Medicine, Executive Associate Dean for Cancer Programs, University of California Davis School of Medicine

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

Holly A. Massett, PhD, Senior Behavioral Science Analyst, Clinical Trials Operations and Informatics Branch, CTEP, DCTD, NCI
Lori Minasian, MD, Deputy Director, Division of Cancer Prevention, NCI
Robert Nordstrom, PhD, Chief, Imaging Guided Intervention Branch, Cancer Imaging Program, DCTD, NCI
MK Holohan, JD, Director, Office of Government and Congressional Relations, Office of the Director, NCI
Geoffrey Shapiro, MD, PhD, Director, Early Drug Development Center, Dana-Farber Cancer Institute
Malcolm Smith, MD, PhD, Associate Branch Chief for Pediatric Oncology, Clinical Investigations Branch, CTEP, DCTD, NCI
Gita Thanarajasingam, MD, Assistant Professor of Medicine, Senior Associate Consultant, Department of Hematology, Mayo Clinic

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I. Call to Order and Opening Remarks

Nancy E. Davidson, MD

Dr. Davidson called the 36th meeting of CTAC to order and welcomed participants.

Dr. Davidson reviewed the confidentiality and conflict-of-interest practices required of CTAC members during their deliberations. She 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 Events Management was videocasting the meeting, and the videocast would be available for viewing following the meeting at http://videocast.nih.gov.

Dr. Davidson introduced Katherine Szarama, PhD, the new Centers for Medicare & Medicaid Services representative on CTAC.

Motion. A motion to accept the minutes of the 35th CTAC meeting held on March 7, 2018, was approved.

II. NCI Deputy Director's Update

James H. Doroshow, MD

NCI Budget. In fiscal year (FY) 2017 and FY 2018, NCI was fortunate to receive an increase in its appropriation and in Cancer Moonshot funding. The overall increase in NCI's appropriation has had a major impact on the number of NCI-funded grants and range of NCI-supported activities. Dr. Doroshow explained that about half of the $275 million increase has gone toward the research project grant pool to ensure that noncompetitive renewal grants receive full funding. Other funding priorities are the Specialized Programs of Research Excellence, the NCI-Designated Cancer Centers, the National Clinical Trials Network, and the NCI Community Oncology Research Program.

Targeted Research Opportunities. NCI has increased funding for the Cancer Imaging Archive, a resource that the imaging community has used extensively. NCI has made an initial commitment to a new glioblastoma research pilot project, and the CTAC glioblastoma working group will develop recommendations on innovative translational research approaches to this devastating disease. Also, NCI will support a new grants program for educational activities that enhance the diversity of the biomedical, behavioral, and clinical research workforce.

Annual Report to the Nation on the Status of Cancer. Most of the news in the latest report, released on May 22, 2018, was good. However, significant progress is still needed in some areas, such as liver and pancreatic cancer.

Cancer Moonshot. NCI has been considering how best to fund Cancer Moonshot projects, given that the program's budget will rise in FY 2019 and then decline until funding ends in 2023. NCI leadership and staff have developed new requests for applications and contract opportunities to address the recommendations of the Blue Ribbon Panel. A list of requests for applications to be awarded by September 30 is available on the Cancer Moonshot website.

Recently Approved Concepts. Dr. Doroshow listed several concepts that the Board of Scientific Advisors recently approved, including some that are part of the Cancer Moonshot. The Experimental Therapeutics Clinical Trials Network, which supports phase I and II clinical trials, is among those that the Board of Scientific Advisors approved.

Frederick National Laboratory for Cancer Research. In addition to the RAS Initiative, the Frederick National Laboratory manages the national Cryo-Electron Microscopy Facility, which collaborates with the extramural community to resolve protein structures. Renovations at the Frederick National Laboratory will create space to assist in the development of T-cell based therapy, initially for NCI's Center for Cancer Research. Plans to extend the resources and expertise to the extramural community for research on solid tumors are being considered.

Workforce Development. NCI now offers Method to Extend Research in Time (MERIT) awards to early-stage investigators who are applying for their first R01 award and whose review score is within the regular payline. These grants provide up to 7 years of grant funding, allowing investigators to establish their careers before seeking to renew their R01 grants. Early-stage investigators with slightly higher scores may be considered for 5-year funding.

Big Data. Dr. Doroshow listed several NCI investments in big data, including Data Commons framework services, new reporting tools for better insight into active clinical trials, and NCI Cloud Resources. A collaboration with the Department of Energy (DOE) will determine how to use the DOE's enormous computing capacity for cancer research in three pilot projects co-funded by DOE and NCI.

Clinical Trials. The accrual for the NCI-Children's Oncology Group Molecular Analysis for Therapy Choice (Pediatric MATCH) trial has exceeded expectations. The rare variant portion of adult MATCH is ongoing, and the number of laboratories helping to find patients for the rare variant and low-penetration mutation arms is expected to increase from five to approximately 30 in the coming months. The Trial Assigning IndividuaLized Options for TReatment (TAILORx) found that most women with early-stage, hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer and an intermediate score on a 21-gene recurrence assay did not benefit from chemotherapy plus hormone therapy compared with hormone therapy alone. The new data, released at the 2018 American Society of Clinical Oncology annual meeting, will help inform treatment decisions for many women with early-stage breast cancer.

NCI and Department of Veterans Affairs (VA) Interagency Group to Accelerate Trials Enrollment (NAVIGATE). NAVIGATE, which facilitates the enrollment of veterans from 12 VA sites into clinical trials of the NCI-funded National Clinical Trials Network and NCI Community Oncology Research Program, has been launched. NAVIGATE is building infrastructure at VA sites to enable more veterans to take part in cutting-edge clinical trials sponsored by NCI. NAVIGATE is anticipated to enhance accrual to NCI clinical trials across a range of diseases and offer veterans access to investigational therapies.

Alan Rabson, MD (1926–2018). Dr. Doroshow gave a tribute to Dr. Rabson, a long-time NCI deputy director who passed away recently.

2018 Cancer Clinical Investigator Team Leadership Recipients. Dr. Prindiville explained that the Cancer Clinical Investigator Team Leadership Awards recognize outstanding clinical investigators at NCI-Designated Cancer Centers who are engaged in NCI-funded collaborative clinical trials. The awards

also encourage the retention of clinical investigators in academic research careers. The clinical investigators who receive these awards, which provide $60,000 per year for 2 years, must devote at least 15 percent of their effort to the activities associated with the award. Dr. Prindiville thanked the reviewers and presented the list of 2018 awardees. CTAC members congratulated them on this accomplishment with a round of applause. The 2018 recipients are:

- Amy DeZern, MD, MHS, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University
- Ryan Gentzler, MD, MS, Cancer Center, University of Virginia
- Ahmad Halwani, MD, Huntsman Cancer Institute, University of Utah
- Caron Jacobson, MD, MMS, Dana-Farber/Harvard Cancer Center
- Michael Liss, MD, MAS, Cancer Therapy & Research Center, University of Texas Health Science Center at San Antonio
- Jason Luke, MD, University of Chicago Comprehensive Cancer Center
- Aaron Mansfield, MD, Mayo Clinic Cancer Center
- Jonathan Riess, MD, MS, UC Davis Comprehensive Cancer Center
- Solmaz Sahebjam, MD, Moffitt Cancer Center
- Robert Wesolowski, MD, The Ohio State University Comprehensive Cancer Center
- Karen Winkfield, MD, PhD, Wake Forest Baptist Comprehensive Cancer Center
- Amer Zeidan, MBBS, MHS, Yale Cancer Center

Questions and Discussion

Dr. Davidson requested an update on the RAS Initiative. Dr. Doroshow explained that the initiative has received many requests for engineered cell lines, antibodies and other tools that have enhanced the RAS field. The initiative's modeling activities have led to the identification of initial therapeutic targets.

III. Legislative Update

MK Holohan, JD

Fiscal Year (FY) 2018 Appropriation. Congress approved the FY 2018 NIH appropriation on March 23 after approving a 2-year budget deal in February. The FY 2018 appropriation provides a $3 billion increase for NIH over FY 2017, including a $275 million increase for NCI and the $300 million authorized by the 21st Century Cures Act for the Cancer Moonshot.

FY 2019 Appropriation Process and Hearings. The President's FY 2019 budget was released on February 12, and it includes $34.8 billion for NIH. This budget does not propose changes to indirect cost policies, even though the prior budget suggested capping indirect cost rates at 10 percent.

Norman E. Sharpless, MD, Director of NCI, accompanied Francis Collins, MD, PhD, Director of NIH, to a budget hearing on April 11, 2018, with the House Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies. Drs. Collins and Sharpless also attended a May 18 hearing of the Senate Labor, Health and Human Services, Education, and Related Agencies Appropriations Subcommittee. Several senators at the hearing praised NCI and NIH, and Senator Dick Durbin (D-IL) commented that those in the room had shown a high level of bipartisan support for sustainable, reliable increases in medical research funding.

The House Appropriations Committee's FY 2019 bill would increase the NIH budget by $1.25 billion, including a $71 million increase for NCI. The Senate's bill would increase NIH funding by $2 million, including an $82 million increase for NCI. Both bills include the full FY 2019 Cancer Moonshot appropriation of $400 million.

Members of Congress visit the NIH campus on a regular basis, and House Appropriations Labor-HHS Subcommittee Chairman Tom Cole (R-OK) brings his subcommittee members every year before the House hearing on the NIH budget. Subcommittee members want to meet researchers, learn about trainees, and hear from patients. These visits help members of Congress understand how NCI uses the funds they appropriate.

New Legislation. The Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act of 2018 was signed into law in June. The provisions directed toward NIH and NCI focus on childhood, adolescent, and young adult biospecimen collection and resources as well as pediatric cancer survivorship research. The Research to Accelerate Cures and Equity for Children (RACE) Act, signed into law in August 2017, permits the Food and Drug Administration to require a pediatric study plan for dosing and activity-seeking studies if a drug's molecular targets are substantially relevant to pediatric patients. The agency is working with NCI to develop a list of targets that are (and are not) relevant to children and adolescents.

Midterm Elections. Midterm elections are volatile, and history has shown that midterms are when majorities flip. In fact, all four of the most recent midterm elections flipped the majority in the House of Representatives, Senate, or both. Ms. Holohan noted some of the "toss-up" seats in the House and Senate that might make the difference to a change in majority in the November 2018 midterm elections.

Questions and Discussion

Dr. Davidson asked for more information on the FY 2019 budget process. Ms. Holohan explained that the House and Senate are unlikely to enact FY 2019 spending bills before the start of the new fiscal year, because this has not occurred in many years. She noted that it is more typical for Congress to pass a series of continuing resolutions, and the final appropriations bills may not be passed until after the new Congress takes office in January 2019.

Dr. Loehrer asked about the impact of the federal deficit on funding for NIH and what NIH can do to prepare for future budget changes. Ms. Holohan replied that she believes that NIH and the broader research community should continue to educate Congress about the importance of basic research and of continued investment in the pipeline to make translational opportunities possible that are meaningful for patients.

Dr. Munshi wondered why NCI's share of the $1.2 billion increase for NIH in the House FY 2019 appropriations bill is only $71 million. Ms. Holohan explained that some of the overall increase goes directly to initiatives that Congress has chosen to fund, and the remainder is distributed to the NIH director's office and to the institutes and centers on a proportional basis. For example, the National Institute of Neurological Disorders and Stroke might receive its proportional share of an overall NIH increase to its base budget as well as funding designated for the NIH Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, which this Institute leads.

IV. The Quantitative Imaging Network

Robert Nordstrom, PhD

Quantitative imaging is the extraction of quantifiable data from medical images to assess disease status or changes. The goal of the Quantitative Imaging Network (QIN) is to translate quantitative imaging methods and algorithms as clinical decision support tools into clinical utility, so that all imaging scanners serve as measuring instruments.

QIN has established a roadmap with the following milestones:

1. Evaluation of imaging hardware performance
2. Creation of harmonization methods through software or protocols to reduce bias and variance during data collection
3. Creation of robust algorithms to extract quantitative information from images
4. Testing and performance validation of algorithms
5. Introduction of candidate algorithms into clinical workflow

QIN uses U01 cooperative agreements to fund research teams. Because awardees begin their programs at different times, their research programs are in different stages of development. Since its founding 10 years ago, QIN has received 276 applications, issued 35 awards, and currently supports 17 research teams. On average, each research team receives $570,500 per year, which is similar to the typical amount for investigator-initiated grants from the Cancer Imaging Program. In addition to the funded members, QIN has associate members from the United States, India, Bulgaria, Denmark, Germany, Sweden, Ireland, and South Korea who contribute to QIN but do not receive NCI funding.

QIN's research has resulted in more than 450 peer-reviewed reports, many written jointly by more than one QIN team. In addition, the editors of four journals have invited QIN to prepare manuscripts for a dedicated QIN issue. QIN's tool catalog has 67 clinical decision tools that will be benchmarked by the fall of 2018 to determine their stages of development. QIN has created 15 challenges to help qualify tool performance.

Dr. Nordstrom reviewed QIN's performance against its roadmap. Although QIN is working on every item in the roadmap, it is experiencing challenges in testing and validating algorithm performance and introducing candidate algorithms into clinical workflows. Quantitative imaging could be useful for identifying patients who are likely to do well with a precision medicine intervention. However, the tools developed for this purpose are not widely used in clinical research, partly because testing for ease of use and compatibility with other clinical data is in progress.

To encourage research teams not yet a part of QIN to focus on clinical validation and translation, the QIN award mechanism is changing from U01 to UG3/UH3. The UG3 phase will focus on algorithm software creation and verification, and the UH3 phase will support clinical validation and translation. For research teams that are experienced in quantitative tools development, the U01 program will be converted to an R01 research grant program. This change will transfer more control of the network from NCI to the research teams and help teams compete successfully for other funding sources.

Leaders of QIN and some of its research teams are discussing collaborative opportunities with NCI's National Clinical Trials Network (NCTN) groups. For example, the ECOG-ACRIN Cancer Research Group is providing data that can be used for QIN challenges, and it is using QIN tools in its

clinical trials. Dr. Nordstrom and members of QIN are visiting all the NCTN adult groups to encourage them to incorporate quantitative imaging tools in their trials. Dr. Nordstrom closed his presentation by asking CTAC what more can be done to encourage the use of QIN imaging tools in clinical trials.

Questions and Discussion

New QIN Funding Mechanisms. Dr. Mankoff said that QIN is going in the right direction by replacing U01 with other grant mechanisms. The new UG3/UH3 awards recognize that some groups are doing first-class, innovative research but are not ready to translate their research into the clinic. He also praised the decision to offer R01 awards to more experienced groups whose applications will receive appropriate reviews by a Center for Scientific Review panel with clinical emphasis. This change will encourage teams with tools that still need to be implemented to pursue the appropriate pathway. Dr. Dancey also supported the plan to replace the U01 awards with R01 awards for experienced teams.

Barriers to QIN Tool Implementation. Dr. Mankoff said that the QIN tools need to be implemented in multicenter clinical trials. The tool developers, who focus primarily on quantitative issues, need to advocate for the use of their tools in trials by reaching out to the clinical component of their team.

Dr. Curran said that the new grant mechanisms will help with the application of QIN tools in clinical trials. The NCTN NRG Oncology group has asked a QIN expert in each of their disease sites to speak about the available tools at the upcoming NRG meeting. He characterized the reason for the gap between tool development and the use of the tools in clinical trials as a cultural issue. Radiologists at academic medical centers may lack the hardware and software to implement the tools, they might not be engaged in clinical trials that could use the tools, and the requirements of the trials may seem insurmountable.

QIN Support for Pediatric Research. Dr. Langevin asked why the plans that Dr. Nordstrom had described did not include the Children's Oncology Group. Dr. Nordstrom explained that QIN is open to pediatric research; however, the pediatric research applications received to date did not score well enough during study section review to receive funding.

QIN Tool Life Cycle. Dr. Petersen wondered whether the tools might become obsolete before they are used in clinical trials. Dr. Nordstrom said that the tools are likely to remain productive for a long time, although QIN has not determined the life cycle of its tools. The main challenge is ensuring that each tool is reliable, trustworthy, and free of biases and errors.

QIN Reimbursement for Image Acquisition. Dr. Langevin asked whether QIN awards include funding for reimbursement. Dr. Nordstrom replied that QIN awards do offer funding for the imaging studies required for its research, but it does not support clinical trials in general.

Dr. Matrisian asked whether a funding mechanism similar to NCI's Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP) supports implementation of the QIN tools in clinical trials. Dr. Mankoff wondered whether a mechanism like BIQSFP would help pay for imaging studies. Typically, the images are analyzed at no cost to clinical trials, and QIN can test imaging studies as part of a clinical trial at very low cost. However, QIN does not fund the acquisition of images that are not part of a trial. Dr. Nordstrom added that the outcome of interest is often prediction of response, which requires a certain amount of time and information.

Dr. Dancey pointed out that when clinical trials incorporate biomarkers, they start with one or a few central laboratories and key investigators to demonstrate their value before these biomarkers can be adopted more widely. She suggested that NCI make funds available from BIQSFP or another mechanism to support the costs of image acquisition. Dr. Nordstrom reported that QIN leaders have considered this idea.

CTAC Recommendations to Promote QIN Tool Use in Clinical Trials. Dr. Mankoff asked Dr. Nordstrom and CTAC to consider ways to encourage oncology investigators to use the QIN tools in their clinical trials on a no-risk basis, given that QIN has already funded these tools. Dr. Nordstrom explained that although QIN does not support clinical trials, it does encourage teams to test the tools they are developing in at least one site.

Dr. Weiner suggested that instead of having QIN investigators create tools and then determine who might use them, the NCTN investigators could identify the tools they need to answer important clinical questions. Clinical trials could then be designed from the start to ask an important question about, for example, the predictive value of a quantitative imaging strategy. Dr. Nordstrom explained that QIN has done this to some extent. Each QIN team has a clinical component, and the clinical team usually generates the research question for the team. The technical team then works with the clinical group to evaluate the tool. QIN is currently evaluating whether this approach is feasible in the broader community.

Dr. Weiner suggested that QIN consider broader tool implementation at an earlier stage and that QIN teams develop partnerships with NCTN groups. Dr. Nordstrom said that this was an excellent idea. Early on, QIN tried to use this approach, but the tools were not ready for implementation in the clinic. Now that a broad range of tools are ready, it is time to try this approach again.

Dr. Dancey recommended that grantees focus on clinical validation and demonstration of their tool's value to the NCTN and clinical trial community. This will require QIN leaders to continue informing NCTN groups and their investigators of the available tools. One way to accomplish this is for QIN leaders to attend NCTN group meetings.

Dr. Loehrer suggested that QIN bring the NCTN group leaders together to identify the provocative questions that could be answered by quantitative imaging. NCI could then issue a request for applications to address these questions. This approach would have built-in commitment from those conducting clinical research.

Dr. Arons reported that NCI recently brought together a group of brain tumor clinical trials leaders with neuroradiology leaders to discuss some of the same issues raised during this CTAC discussion. He suggested that QIN organize a similar intensive small-group meeting to discuss how to optimize QIN because—at least in brain tumors—QIN is invaluable.

V. Retiring CTAC Members Recognition

James H. Doroshow, MD

Dr. Doroshow thanked the retiring CTAC members—Drs. Mitchell, Munshi, and Weiner—for their service and gave each one a plaque.

VI. Cancer Immune Monitoring Analysis Centers (CIMAC) Update

Helen Chen, MD

The CIMAC and Cancer Immunologic Data Commons (CIDC) Immuno-Oncology Biomarker Network consists of CIMACs at four cancer centers and a data commons at the Dana-Farber Cancer Institute. Its immediate goal is to support NCI-funded immunotherapy trials. A longer-term goal is to build a framework that will evolve into a sustainable immuno-oncology data resource to serve the larger research community. This initiative is supported by the Cancer Moonshot and funded through the NCI U24 cooperative grants. The network's total 5-year budget is $55 million. In addition, 12 pharmaceutical company partners pledged matching funds through the Foundation for NIH Partnership for Accelerating Cancer Therapies (PACT). The network website is https://cimac-network.org.

Each CIMAC consists of a multidisciplinary team with expertise in immunology, oncology, pathology, bioassays, bioinformaticians, and statistics. Together with CIDC, CIMAC centers will collaborate with clinical investigators and perform assays and analyses for immune biomarkers in NCI-funded clinical trials involving immunotherapy. Early-phase trials (phase I and phase II) conducted in the Cancer Therapy Evaluation Program's (CTEP's) trial networks or with support from NCI grants will be eligible to use CIMAC resources.

The CIMACs will provide comprehensive tumor and immune profiling for approximately 600 patients per year for 5 years. PACT funding supports the program's infrastructure and some clinical trials (which might be sponsored by industry, nonprofit organizations, or even NCI if they are not otherwise eligible for the program). The CIMACs may work with any trial based on their workload and expertise, but each CIMAC is affiliated with one or two CTEP trial networks.

The CIDC will work with the CIMACs and clinical teams to develop standards for the clinical and biomarker data, serve as an essential repository for biomarker data generated from the CIMACs, and provide an informatics platform to integrate clinical data elements for correlative analyses. Another CIDC function is to provide data access and Web visualization of the data to CIMAC investigators and, ultimately, the external community through the cBioPortal for Cancer Genomics.

The assays used by the network have been categorized as Tier 1 or Tier 2 based on how often they might be used in clinical trials. Tier 1 assays, which are used in most or all CIMAC trials, have higher priority for standardization.

Updates. Dr. Chen described the activities of two of the network's working groups. The Clinical Trials Working Group identifies scientific opportunities and develops correlative study plans with trial investigators. The group has developed the intake process for new concepts and ongoing trials with biomarker questions that can collaborate with the CIMAC network. The group has identified five pilot projects from CTEP trial networks to demonstrate and optimize the CIMAC process from sample accession to assays and data analysis. The Assay Working Group focuses on analytical validation of the assays, with an emphasis on Tier 1 assays, and also develops tissue-collection protocols for new trials. All assays must be analytically validated for the purpose for which they will be used, and key platforms will be standardized or harmonized across trials to achieve compatible results.

The CIDC has almost finished using public datasets to build the initial version of the CIDC infrastructure and bioinformatics platform. After using one of the pilot projects to create the next version

of this platform, the CIDC will extend this platform to all other pilot clinical trials and ultimately to all trials across all CIMACs.

Questions and Discussion

Dr. Fingert explained that PACT includes Food and Drug Administration (FDA) representatives who give the industry partners confidence that when appropriate, biomarkers developed through the PACT can receive rapid FDA input. He asked whether FDA will have similar involvement in the CIMAC-CIDC Network and whether it will provide independent quality assurance. Dr. Chen replied that the network will follow certain quality control steps. For example, assays will be validated analytically to be fit for purpose for the scientific research questions. However, most of the biomarkers under study by the CIMACs, and by the field in general, are exploratory at the current stage. FDA involvement for approval is premature, although FDA does have representation on the network steering committee.

Dr. Munshi pointed out that the CIMAC-CIDC Network uses clinical trials to establish its tools, instead of developing the tools first and then using them in clinical trials, as in the Quantitative Imaging Network. He asked how the CIMAC-CIDC Network assays will be used in different CTEP networks and studies. Dr. Chen explained that most assays used by individual CIMACs are analytically validated, and the network is ensuring that the different centers using the same platform have compatible data. If the standardization or harmonization process takes too long, the assay might be performed at a single center at first.

Dr. Munshi inquired about making the validated tests available to outside investigators. Dr. Chen explained that investigators with a trial will be able to apply to collaborate with the CIMACs, and these requests will undergo a review process.

Dr. Rosen asked whether investigators submitting an R01 application for a clinical trial involving immunotherapies could use the network as a core. Dr. Chen said that all NCI grant-supported clinical trials, including those that are ongoing, are eligible to use this resource, and requests for collaboration will be prioritized through a review process.

Dr. Dancey asked whether the five pilot projects will assess the network process. Dr. Chen explained that the pilot projects will be used to identify the steps needed to accomplish the goal, and the resulting process can then be spread to all participating trials. The pilot projects might also help the network identify barriers and other issues to resolve.

Dr. Dancey said that in addition to the assays and standard operating procedures for sample acquisition, the network is likely to develop a data platform and definitions of common data elements that can contribute to progress in the cancer immuno-oncology field. Dr. Chen said that a goal is to make these resources—including the analytical tools, pipelines, platforms, and clinical and biomarker data—available to the public through the network's website.

Dr. Perez-Soler asked about the role of the PACT industry partners. Dr. Chen explained that these partners provide $55 million to match the NCI contribution of $55 million. The funding will be used to enhance the infrastructure and capacity of CIMACs and CIDC. In addition, the partners provide technical expertise through representatives in assay and informatics working groups. The PACT will identify high-priority immunotherapy trials that might use the CIMAC network in addition to NCI-funded trials.

VII. The *Lancet Haematology* Commission — "Beyond Maximum Grade: Modernizing the Assessment and Reporting of Adverse Events in Hematological Malignancies"

Gita Thanarajasingam, MD
Lori Minasian, MD

Limitations of Current Approach to Reporting Adverse Events (AEs). Dr. Thanarajasingam explained that the processes for assessing AEs in clinical trials focus on maximum-grade toxicities and do not capture the impact of chronic low-grade toxicities or patient-reported outcomes (PROs). Because AEs affect a patient's willingness and ability to continue the study treatment, the patient's perspective should be included in reports.

Dr. Thanarajasingam gave some examples to show the limitations of the current maximum-grade approach, including a phase III trial that compared two oral agents for relapsed multiple myeloma. Five percent of patients in the carfilzomib arm developed dyspnea (sometimes used as a surrogate marker for heart failure) and five percent in the bortezomib arm had peripheral neuropathy. Investigators would typically give these two types of AEs the same weight based on their incidence. However, the dyspnea peaked quickly and was resolved within days or even hours, whereas the neuropathy was progressive and cumulative, and it could be permanent. From a patient's perspective, these two types of AEs are very different.

New AE Reporting Tools. With colleagues at the Mayo Clinic, Dr. Thanarajasingam developed several tools, including the toxicity over time (ToxT) approach, to improve AE analyses. The ToxT tool combines graphs and AE tables with several longitudinal statistical techniques to study AEs over time. NCI has developed the Web Reporting Tool, which provides a three-dimensional contour map that captures AE grade and frequency and supports aggregate analyses of data from several clinical trials.

***Lancet Haematology* Commission on Improving AE Assessment in Haematology.** This commission, led by Dr. Thanarajasingam, convened 40 experts from around the world. The commission published a call to action (https://www.ncbi.nlm.nih.gov/pubmed/29907552) to define priority areas for improving AE reporting. Dr. Thanarajasingam summarized the challenges in AE analysis outlined in the article and proposed solutions. She noted that some of the solutions are under way, in many cases under NCI's leadership. As this report shows, the conventional maximum-grade approach is insufficient in the modern treatment landscape of most cancers. Novel longitudinal approaches might be able to provide additional complementary information on AE timing and chronic, low-grade events that are relevant to tolerability.

NCI Activities Related to Tolerability of Cancer Treatment. Dr. Minasian distinguished between reporting on individual AEs and analyzing aggregate AEs across a given trial. Individual AE reporting, or safety reporting, is typically based on AEs identified and graded by clinicians. NCI has developed a tool, a PRO version of the Common Terminology Criteria for Adverse Events (CTCAE), that it continues to validate. PRO-CTCAE captures data on patient-reported, symptomatic AEs to complement the clinician-reported CTCAE. Its grading schema is based on patient reports of event frequency, severity, and interference with activities of daily living. Safety is still reported by clinicians in this system, but PRO-CTCAE incorporates the patient experience in some definitions of tolerability.

NCI is testing PRO-CTCAE using the ePRO mobile app, which captures questionnaire responses and patient diaries and transfers these data to the Medidata Clinical Patient Cloud. This app is compatible

with both iPhone and Android devices and is used by the NCTN and NCORP. Three NCI Experimental Therapeutics Clinical Trials Network trials will use ePRO to collect selected PRO-CTCAE items electronically. In addition, NCI's Investigational Drug Branch and the ePRO team are streamlining ways to include PRO-CTCAE items in more early-phase trials.

NCI issued a funding opportunity announcement for sites to analyze and interpret clinician-reported and patient-reported AE data to assess tolerability. Each applicant had to have one or more operational definitions of tolerability using PRO-CTCAE and CTCAE data as well as other PROs and clinically relevant data. The funded sites will form a consortium, which will include representatives of the Food and Drug Administration (FDA) and at least one foreign regulatory agency, to share analytic approaches.

Complementary Activities. The *Lancet Haematology* Commission's report has a section on global regulatory activities related to AE reports, and FDA is working with NCI to develop the PRO-CTCAE. A recent FDA and American Society of Clinical Oncology workshop addressed the collection and analysis of data on symptomatic AEs in cancer clinical trials. A 2017 meeting between FDA, NCI, and the Office for Human Research Protections focused on whether severe AE scores provided by patients constituted safety data and therefore have the same regulatory requirements as clinician-reported AE data. The consensus was that these are not safety data, so regulatory packages do not include PRO-CTCAE data in the safety data, but they can include PRO-CTCAE data in the PRO data. Finally, FDA is developing computational models to understand safety events from real-world data.

Questions and Discussion

Dr. Dancey said that from the perspective of a clinician trialist, the biggest challenge to improving AE reporting is publishing the AE data. Clinical trial investigators collect data on the grade of each toxicity in each cycle, but they do not typically report all the toxicity data they collect because of the rules about what they can include in primary publications. Dr. Dancey asked whether journal editors have developed a standard approach for publishing AE data in response to the *Lancet Haematology* report or whether they have expressed an interest in publishing more detailed toxicity assessments.

Dr. Thanarajasingam explained that when *Lancet Oncology* published her first paper on the ToxT approach in 2016, *Lancet Haematology* invited her to lead the AE commission. The journal plans to support the recommendations in the commission's report with a range of follow-up initiatives. Investigators might already be collecting PROs data, but a cultural change is required to determine which of these data to include in reports. Regulators, patient advocates, and medical journals are paying more attention to this issue. The AE data might not yet be published in primary publications from clinical trials, but the number of publications focused on toxicity or health outcomes is increasing.

Dr. Fingert thanked Drs. Thanarajasingam and Minasian for the work they described. Serious, unexpected, and suspected adverse reactions (SUSARs) are a major cost burden. Dr. Fingert asked whether NCI is considering the broad scope of data management, including SUSARs. Dr. Thanarajasingam said that the commission's recommendations and NCI's activities are not intended to replace existing safety assessments, which need to continue. The commission is also considering how to overcome some of the challenges of SUSARs, including the cumbersome reporting requirements. The regulatory section of the commission's report addresses this issue.

Jeffrey S. Abrams, MD, Acting Director for Clinical Research and Associate Director of the Cancer Therapy Evaluation Program, agreed that reporting SUSARs to meet the FDA requirements within the established timeframe is laborious and time consuming. NCI recently updated the CTCAE criteria to address side effects seen for the first time in oncology with immunologic agents, and NCI is always looking for ways to improve SUSAR reporting on the Web. NCI now has much greater ability to assess cumulative toxicity data across trials and identify the frequency of severe AEs.

Dr. Meropol distinguished between clinical and regulatory decision making. Clinical practice decisions often require long-term data on mild-to-moderate AEs. Aggregating data on very severe toxicities from electronic medical records could be very useful and could perhaps be done using machine learning or artificial intelligence tools or using diagnosis codes that could identify rare serious events with reasonable accuracy. More common, chronic, low-grade AEs might be more difficult to identify with a high degree of fidelity using electronic methods. Entering PROs data into medical records would be useful, and large numbers of patients will probably not be required to collect sufficient real-world data on new agents or combinations to develop a clear picture of their toxicity and tolerability profile in the real world. Dr. Meropol believes that patients would probably be very willing to assist with this type of effort, and Dr. Minasian agreed.

Dr. Loehrer gave examples of drugs that caused serious AEs in very small numbers of patients: Oraflex, which caused hepatotoxicity, and chloramphenicol, which led to aplastic anemia. These drugs are no longer on the market, but if the patients who will develop these rare, serious AEs could be identified in advance, these drugs could still be on the market. Dr. Loehrer proposed that every patient contribute a blood sample that could be used to identify the genomic characteristics of patients who experience a serious AE, and these data could be linked to PROs.

Dr. Rosen stated that when he was conducting interferon studies, a patient reported erectile dysfunction. When Dr. Rosen asked his male patients about this AE, all of them reported similar issues. Similarly, patients in chat rooms often report an AE that is not included in the trial report, and Dr. Rosen sometimes finds out from chat rooms that many patients developed that AE.

Several thousand patients have signed up for a Leukemia and Lymphoma Society community website that asks a question every week, and these data can be used for research. These patients could be asked whether, for example, those undergoing a certain treatment have developed neuropathy.

Dr. Rosen explained that the Research on Adverse Drug Events and Reports team, led by Charles Bennett, MD, Northwestern University, investigated early signs of toxicity well before FDA was aware of them. The efforts of this group led to 18 black box warnings. Dr. Rosen recommended that Drs. Thanarajasingam and Minasian consult Dr. Bennett about his experience, including ways to identify cohorts that might be at greater risk of AEs. Chat rooms for patients on clinical trials could also gather important information.

Dr. Thanarajasingam agreed that a great deal of AE information is not collected, but it is important to avoid asking clinical investigators to collect yet more data. It is up to those who are interested in this issue to find ways to facilitate the collection of these data in clinical trials.

Dr. Mitchell pointed out the importance of collecting AEs from a diverse patient population. For example, women tend to report toxicity differently than men, and members of different racial and ethnic

minority populations might describe the same toxicities differently. It is important to be cognizant of who is reporting the information to ensure equity across all populations.

VIII. Adult Experimental Therapeutics Topics

Experimental Therapeutics Clinical Trials Network (ETCTN): Evaluation and Concept Renewal Plans
Percy Ivy, MD
Holly A. Massett, PhD

Dr. Davidson explained that the Board of Scientific Advisors recently approved the ETCTN renewal, and NCI is preparing the new request for applications (RFA) and would appreciate CTAC's input.

Accomplishments to Date. Dr. Ivy described ETCTN, which consists of 12 lead academic organizations (LAOs) and 29 affiliated organizations. As of the fourth quarter of 2017, ETCTN had activated 82 trials, enrolled 2,120 patients, and closed and completed 37 trials. During this initial grant period, ETCTN also established a biorepository and centralized reporting services, and it awarded funding for non-ETCTN cancer centers to enroll patients in ETCTN trials. The ETCTN uses the UM1 grant mechanism, which supports complex projects with significant NCI staff input.

An initial ETCTN goal was to transform a set of silos into a network that uses a collaborative approach to clinical trial development and implementation. During the ETCTN planning phase, NCI stopped issuing mass solicitations and instead formed extramural drug development project teams which drew on disease-specific clinical expertise. ETCTN also transformed its approach to biomarkers from laboratory-developed tests to analytically validated bioassays that are fit for purpose. In addition, infrastructure supporting good clinical practice principles was enhanced.

ETCTN Evaluation. Dr. Massett described the 3-year process evaluation that began in 2015, just prior to the first year of the ETCTN. The goals were to document the ETCTN's implementation, and ensure it was being adopted as planned, to identify any course corrections that might be needed for the new program, and to provide data to guide decision making for the subsequent funding cycle. The evaluation included an annual online survey, in depth interviews, and analysis of CTEP's centralized systems.

An online survey assessed satisfaction with ETCTN's processes, resources, and portfolio as well as team interactions and approaches. The survey was distributed to LAO grant principal investigators (PIs) and other investigators who participated in ETCTN. Investigators' satisfaction with the number of trials grew substantially between years 1 and 3, as did their satisfaction with therapeutic classes in the portfolio, the portfolio's scientific balance, and opportunities for junior PIs. However, satisfaction remained stable with the number of drugs available for letters of intent (LOIs) and with the ETCTN portfolio overall.

Dr. Massett showed density maps that indicated that although ETCTN investigators were highly connected professionally (through papers, grants, or committees) from the start, they were not well connected with respect to accrual to other LAOs' trials. Accruals to clinical trials of other LAOs increased substantially each year, and the accrual network now has similar connectivity to the professional network. These results show that ETCTN is in a strong position to move into a second funding cycle.

As a follow-up to the survey, NCI interviewed the PIs of each LAO grant to identify the greatest challenges to trial activation and accrual and to obtain recommendations to improve the network. In response, NCI now provides accrual incentives to investigators to lead new ETCTN studies and activate studies from other LAOs. To promote awareness about trials in the ETCTN pipeline, CTEP created an easy-to-access newsletter with a list of trials in all stages of development. A flow chart of trials for each disease by stage and a fact sheet for each trial made it easy for sites to identify trials of interest to their investigators. CTEP seeks site champions for challenging trials, and it has targeted key barriers to reduce activation timelines; for example, with a centralized protocol authoring service.

An external ETCTN review in January 2018 found that phase I/II ETCTN trials have opened at an adequate rate, ETCTN trials are answering important questions and are optimally designed, and the program promotes team science and provides adequate clinical research opportunities for early-career investigators. The reviewers agreed that ETCTN had met its initial goals and objectives.

ETCTN Objectives and Process. The network's goals and objectives have become more comprehensive over time. ETCTN aims to advance the clinical development of CTEP's investigational new drug (IND) agents in early-phase trials. These trials, especially those of combination treatments, establish the dosing schedule and sequence for these agents. ETCTN gives priority to cancers that are not addressed by industry-sponsored trials.

ETCTN has enhanced its biomarker and cancer biology studies using patient specimens. The network plans to acquire high-quality patient tumor specimens for correlative studies and incorporate pharmacokinetic/pharmacodynamic biomarker assays into its trials. In addition, ETCTN gives early-career investigators experience leading clinical trials, and they play a major role in drug development project teams.

When a new agent comes to ETCTN through the NCI Experimental Therapeutics (NExT) Program, within a month, NCI assembles a team of investigators to help plan the first stages of the development process, including the initial clinical trials. In addition to their clinical and translational components, these drug development project teams include extramural researchers and emphasize early-career investigator development. The Investigational Drug Steering Committee (IDSC) then reviews the trials proposed by the teams.

ETCTN Accomplishments. ETCTN has conducted several high-impact clinical trials of IND agents that have led to FDA approval, for example dinutuximab for treatment of neuroblastoma and orphan drug designation for triapine in ovarian cancer and selumetinib in neurofibromatosis type 1. ETCTN is working toward fast-track or breakthrough designation for triapine. Accrual rates are increasing consistently each quarter, and 90 percent of LOIs from project teams were led by early-career investigators. Young investigators also had high rates of submission of unsolicited LOIs and of activated or transitioned ETCTN protocols.

ETCTN Transformation in 2020–2025. Plans for the next award cycle include addressing the need to find rare or uncommon, molecularly defined subsets of patients; enhancing requirements for high-quality biopsy material for correlative studies; and improving the ability to perform validated biomarker assays to characterize and monitor molecularly defined subsets of common or uncommon tumors. Additional goals for 2020–2025 are to use Cancer Moonshot networks and centers for preclinical studies in support of clinical trials, broaden classes of agents under NCI development, use the ePRO patient-

reported outcomes smartphone app in early-phase ETCTN studies to determine safety and tolerability, and further develop risk-based monitoring approaches.

NCI Drug Development Project Teams
Geoffrey Shapiro, MD, PhD

When CTEP procures an agent, it solicits applications to join a drug development project team. Membership on these teams is open to basic, translational, and clinical investigators from ETCTN sites, NCTN sites, and Cancer Immunotherapy Network sites. Applications from junior investigators with experienced mentors are strongly encouraged. These teams develop a preclinical and translational research plan that addresses questions that are critical to the drug's development and include innovative disease-based or biomarker-based clinical trials that incorporate safety, pharmacokinetic, pharmacodynamic, and efficacy endpoints.

The teams typically propose four to six phase I combination or phase II clinical trials for the IDSC's consideration. The phase I trials might involve just a few ETCTN sites, but the phase II trials are usually open throughout the network. CTEP asks knowledgeable IDSC members to identify all the agents that address a given target and any ongoing industry-sponsored trials, which prevents overlap. The IDSC reviews the drug development plan prior to the submission of the team's LOIs. Each team is expected to submit career development LOIs, which provides opportunities for junior investigators to lead the studies.

The resources available to project teams include centralized, specialized preclinical and biomarker resources, such as the CIMACs for immuno-oncology endpoints, Molecular Characterization Laboratory for sequencing, and Drug Resistance and Sensitivity Network for drug resistance studies. Each project team evaluates available preclinical data and identifies gaps, and team members can complete preclinical studies with supplements to their UM1 awards. This approach provides invaluable scientific insight to the design of the clinical studies.

As an example, one project team focused on M3814, a DNA-dependent protein kinase (DNA-PK) inhibitor. The call for project team member applications suggested several possible studies, such as a combination of this agent with radiation for patients with liver metastases and gastrointestinal malignancies. Dr. Shapiro, who has experience with DNA repair inhibitors, ultimately led this project team with Eileen O'Reilly, MD, of Memorial Sloan Kettering Cancer Center, who has expertise in gastrointestinal malignancies. The team had 28 teleconferences within 12 weeks. The initial discussions included reviews of the basic biology of DNA-PK inhibition, M3814 pharmacology and potential drug-drug interactions, and early versions of clinical trial proposals. After the first eight teleconferences, the team split into subgroups, and the remaining teleconferences focused on acute myeloid leukemia (AML), ovarian cancer, gastrointestinal cancers, or molecular subsets. From these deliberations, the team proposed six trials in the drug development plan, and the IDSC approved all of them. Six career-development LOIs are currently being submitted by junior clinical investigators. Thus, within 3 months, six trials were developed that would not have been done by industry.

Dr. Shapiro described several potential problems with the project team approach and potential solutions. For example, the project teams may be quite large; however, some believe that the teams are too selective. The solution is careful selection of members based on prior experience, publications, and peer-reviewed grants in the field.

He concluded by stating that the project teams are a compelling innovation by CTEP. This approach has increased extramural community engagement in drug development plans, added support for important preclinical studies, and provided a rich training ground for junior investigators in clinical trial development and leadership.

Investigational Drug Steering Committee (IDSC) Update
Michael Carducci, MD
Primo Lara, Jr., MD

Drs. Carducci and Lara are co-chairs of the IDSC, which is made up of the 33 PIs of CTEP early phase grants, representatives of the Cancer Immunotherapy Trials Network and Adult Brain Tumor Consortium, six subject matter experts, two biostatisticians, two patient advocates, one FDA representative, and NCI staff. The IDSC provides input into drug and clinical development plans prepared by the project teams, fosters a team approach, and creates task forces to evaluate scientific issues that are important to NCI and the broader early-phase clinical trial community. The IDSC has task forces focused on immunotherapies, biomarkers, pharmacology, and clinical trial design. IDSC activities have led to more than 40 publications since its inception in 2005.

After pharmaceutical and biotechnology applications are submitted to the NExT Program, they are reviewed by the program's special emphasis panel, which includes some IDSC members. Meritorious applications move forward, and an initial clinical development plan is put together by NCI. The IDSC recommended adding extramural researchers to this initial NCI step, and CTEP agreed. With a tentative drug development plan in place, NCI solicits drug development project team members. Once the project teams complete their work, they present their drug development plan to the IDSC during one of its four annual meetings. The IDSC then holds a closed session to vote on the recommended trials. The IDSC makes recommendations for the clinical trials it approves, applicants are informed of the IDSC's recommendations, and project team LOIs are solicited. The IDSC recently created and has used an appeals process for unsolicited LOIs.

One of the valuable contributions of CTEP and the ETCTN is putting two drugs together from different companies, building on preclinical data from R01 grants and SPORES. A junior faculty member, who completed a rotation at CTEP as an oncology fellow, worked with UM1 investigators and CTEP to identify factors that affect agent combination trial success. The study surveyed IDSC members on phase I combination therapies to (1) assess rates of advancement and regulatory approval, (2) identify factors associated with these rates, and (3) assess the degree to which phase I trials were concordant with IDSC Clinical Trial Design Task Force guidelines. The results showed that 18.7 percent of combination trials progressed to phase III or FDA approval, largely because of the thoughtful preclinical studies that contributed to trial design. These results were recently presented at an American Society of Clinical Oncology meeting.

In 2017, CTEP began including IDSC members in its initial individual drug development planning meetings and in developing project team member application announcements. The IDSC also updated the LOI arbitration process and tasked the Clinical Trials Design Task Force with reviewing the feasibility of alternative trial designs in ETCTN. In 2018, the IDSC began including ad hoc experts in its drug development plan review process.

Questions and Discussion

Availability of Drugs for ETCTN Studies. Dr. Davidson praised ETCTN for building evaluation in from the beginning. Given that the biggest concern was the availability of drugs, Dr. Davidson wondered about efforts to expand this portfolio. Dr. Ivy said that NCI often meets with drug companies to discuss their portfolios and pipelines, with a focus on gaps in the NCI portfolio or steps needed to develop a new drug or drug combination. In addition, the portfolio is quite broad, and work is ongoing to develop biopharmaceuticals or radiopharmaceuticals as well as combination trials. Dr. Carducci added that use of the NeXT by pharmaceutical companies is increasing, and he believes that more drugs are likely to be added to this portfolio soon, particularly with efforts to allow sponsors to bring in multiple agents for combination studies.

ETCTN Timeline. Dr. Munshi asked about the timeline for the development of a new agent. Dr. Ivy said that the entire process typically takes a year and a half. NExT accepts applications three times a year, and it evaluates them within a month or two. ETCTN has been doing fewer phase I clinical or first-in-humans trials because pharmaceutical companies are increasingly doing those studies themselves. ETCTN's expertise is in phase I combination studies, which are quite complex. Several ETCTN trials have used agents from two different companies through agreements in which NCI served as an honest broker and all parties (including the academic partner) agreed to the same data-sharing requirements.

Dr. Loehrer wondered if the interval between an agent's entry into the NExT portfolio and initiation of a trial could be cut from one and a half years to 6 months. Dr. Ivy said that the Operational Efficiency Working Group meets weekly to review trial activation timelines and consider ways to shorten them. The network has implemented some new processes, including offering protocol writing support, that might help achieve this goal. Dr. Massett added that the biospecimen review process is being revised. Overall, these new processes could shorten the timeline by 150 days.

Dr. Lara pointed out that concerns about protocol authoring and the laborious consistency checks were communicated to CTEP a year ago, and NCI took action almost immediately. Dr. Lara worked on a protocol that used the new protocol authoring process, which helped him quickly make the transition from an LOI to a finished protocol. This is an example of how NCI can help overcome administrative barriers.

Imaging Studies. Dr. Mankoff praised the decision to add radiopharmaceuticals to CTEP's portfolio and asked about incorporating novel imaging approaches in ETCTN trials. For example, the ECOG-ACRIN Experimental Imaging Science Committee works with centers that make their own imaging probes and study imaging techniques. Even a few imaging studies using these markers would provide proof of mechanism for ETCTN trials. Dr. Mankoff suggested that NCI take advantage of its investments in these centers in ETCTN. Dr. Ivy said that this is an option, and the grant mechanism allows these linkages.

Transition Between ETCTN and NCTN Trials. Dr. Curran wondered whether agreements with pharmaceutical companies up front could speed the transition from an ETCTN trial to an NCTN trial. Perhaps rewards for investigators whose trials move to an NCTN group could assist with this transition. Dr. Ivy reported that the Clinical Trial Design Task Force recently completed a project to design seamless phase I/II clinical trials, and ETCTN works with NCTN groups to conduct phase II/III clinical trials more seamlessly. For example, an ETCTN phase I clinical trial evaluated the cediranib/olaparib combination in triple-negative breast cancer and ovarian cancer. The strong signal in ovarian cancer led to a small randomized phase II trial, and that trial's results led to phase III and phase II/III NCTN studies in

different kinds of ovarian cancer. The phase III study completed its accrual 2.5 years early. The phase II/III study has completed its phase II portion and will use the results to choose arms for the phase III component.

Dr. Lara added that the IDSC has several NCTN investigators, and ETCTN and NCTN share the vision of linking ETCTN with NCTN in a more seamless way. Dr. Shapiro reported that one ovarian cancer project team did not believe that patients could be enrolled quickly enough within ETCTN, so the team decided early on to move the study to NCTN. Dr. Ivy concluded that seamless transitions between ETCTN and NCTN are a work in progress. Examples of successful transitions do exist, but the process probably goes less smoothly in some cases.

Addressing Disparities. Dr. Mitchell asked about the demographic characteristics of patients in ETCTN trials and whether any of these trials address biological differences among different racial and ethnic populations. Dr. Ivy said that NCI reviews trial enrollment reports and assesses accrual based on gender, race, and ethnicity. In some cases, individual sites are asked to take corrective actions to reach their targets for certain patient subgroups. Dr. Gray added that new clinical trial guidelines require RFAs to have review criteria that address the inclusion of minorities and children.

Dr. Lara reported that ten years earlier he had received a grant as part of an NCI program to address barriers to accrual to early-phase clinical trials, but this was pre-ETCTN. The results showed that the physician/patient relationship was the determining factor in accrual to those trials. Dr. Lara added that ETCTN is poised to study molecular phenotypes associated with disparities or other defined populations. For example, ETCTN conducts studies on rare lung cancer phenotypes, including mutations that tend to be more common in certain racial and ethnic groups. However, ETCTN does not have studies designed to address disparities *per se*, and the trials might not have sufficient statistical power to answer broad disparities questions. Dr. Ivy pointed out that the NCI Community Oncology Research Program addresses many disparities questions.

Dr. Mitchell stated that numbers of minorities are increasing, and minority groups will make up a majority of the U.S. population by 2050. Therefore, disparities seem to be an ideal area to study to reduce cancer death rates and increase knowledge of the molecular underpinnings of cancer. Not aiming to understand cancer disparities would miss an important opportunity to move the field forward. Dr. Mitchell also emphasized the importance of addressing disparities in early phase trials. Otherwise, drug mechanisms of action, cellular receptors and the causes of effectiveness or non-effectiveness will not be fully understood. She recommended that those developing the RFA consider how best to include representatives of different populations to better understand cancers and make treatments more effective for all patients. Dr. Massett said that which patients are recruited to ETCTN trials depends on cancer center catchment areas, but efforts are under way to revise the process for reaching out to potential trial participants.

Dr. Fingert commented that barriers to accrual should be revisited because the landscape has changed since NCI issued the grants that Dr. Lara had mentioned. Dr. Massett explained that NCTN has an accrual core team with representatives from all groups, patient advocates, and experts in communication. Now that NCTN has applied the recommendations of this team to its trials, the next step is to implement the lessons learned in ETCTN trials. Dr. Shapiro added that the move from a siloed system to a network has helped tremendously. For example, a phase I combination study of topotecan and veliparib had very slow accrual because it was developed in the initial, siloed system and open at few

sites. This study was brought into ETCTN for an expansion cohort study, and more than 30 patients enrolled within the first few months. This example shows that the network approach is effective.

Dr. Doroshow explained that ETCTN has undergone tremendous change, and its second iteration will focus on several improvements. The biggest challenges are to obtain access to compounds of interest to clinicians and patients and make sure that the studies are both feasible and of high scientific quality. Dr. Ivy added that CTEP has been working with FDA, the American Society of Clinical Oncology, and Friends of Cancer Research to make eligibility criteria for early-phase clinical trials less restrictive.

IX. Pediatric Early Phase Clinical Trials Network

Malcolm Smith, MD, PhD

The Pediatric Early Phase Clinical Trials Network (PEP-CTN), which was to begin soon after this meeting, will continue the clinical trial activities of the Children's Oncology Group (COG) Phase 1/Pilot Consortium. In the last 5 years, the COG Consortium activated 15 new trials, evaluated a range of novel therapies (e.g., checkpoint inhibitors and molecularly targeted agents), and incorporated pharmacokinetics and imaging studies.

PEP-CTN, which focuses on early-phase clinical trials, is a key element of NCI's pediatric drug development program. Unlike phase III clinical trials, these early-phase trials involve a limited number of institutions, more intensive data collection, close study monitoring, detailed pharmacokinetic and pharmacodynamic sampling, and rapid development and activation of protocols using standard templates.

The new Research to Accelerate Cures and Equity for Children Act directs the Food and Drug Administration (FDA) to create a list of molecular targets that are substantially relevant to the growth and/or progression of pediatric cancers. If a pharmaceutical company is developing an agent aimed at one of those targets, FDA may require that company to conduct a molecularly targeted pediatric cancer investigation to yield clinically meaningful pediatric clinical data. PEP-CTN will be well positioned to do studies of these agents, including targeted agents developed primarily for adult cancers that might be effective for pediatric cancers, pediatric-specific target agents, agents that modify the DNA damage response, and immuno-oncology drugs.

PEP-CTN is designed to address some limitations in previous early-phase pediatric consortia, such as the slow and complex prioritization process for moving agents to clinical evaluations. Other enhancements will, for example, help the program better meet regulatory requirements and expand the ability to use genomic characterization for eligibility determinations and other purposes.

The network will fund approximately 20 core institutions to conduct early-phase clinical trials with pharmacokinetic evaluations and monitoring. These institutions will include those in the existing COG Phase 1/Pilot Consortium as well as others that will be selected and will be credentialed for participation in phase II studies. The network will allow seamless phase I to phase II expansion by adding sites for selected trials that require additional accrual. It will apply central monitoring to supplement onsite auditing, integrate genomics into study designs, and provide a single portal for agent prioritization.

The PEP Agent Prioritization Committee will include network leaders and representatives of COG, NCI, and FDA, as well as independent researchers and patient advocates. The committee will review applications from pharmaceutical companies, academic research teams, and PEP-CTN members to pursue agents that might be relevant to one or more pediatric cancers. Once the committee decides that an

agent is ready for pediatric evaluation, protocol development will start quickly. The protocol that is developed will be reviewed by the Cancer Therapy Evaluation Program (CTEP) to ensure that it addresses all relevant regulatory and safety issues. Every PEP-CTN protocol will be required to include a monitoring plan.

The PEP-CTN Operations and Data/Statistics Center will be responsible for clinical protocol development, data management and analysis, and regulatory affairs and compliance. The PEP-CTN Translational Research Program will guide the incorporation of genomics, translational biology, pharmacokinetics, and imaging for PEP-CTN clinical trials. The Pharmaceutical-Biotechnology Advisory Committee will provide feedback on collaborations with industry and help make the network's capabilities more visible to industry.

Dr. Smith commented that the PEP-CTN, which builds on the accomplishments and lessons from the preceding Phase I Consortium, is well placed for timely agent prioritization, protocol development, and seamless phase I to phase II clinical trials of promising agents. It will be able to incorporate genomic and pharmacokinetic studies, meet regulatory requirements, and collaborate with pharmaceutical companies and the COG disease committees to greatly accelerate the discovery of new, more effective treatments for children with cancer.

Questions and Discussion

Dr. Weiner noted that most institutions in PEP-CTN are on the two coasts, and he asked whether children in states without a PEP-CTN institution will have access to its resources. Dr. Smith said that most PEP-CTN institutions can accommodate children outside their immediate catchment area. Furthermore, the 20 or so phase II expansion sites can serve children in some areas that lack a PEP-CTN core institution.

Dr. LeBlanc asked about the relationship between the network and COG and how the network will provide statistics and data management. Dr. Smith said that PEP-CTN leaders—Brenda Weigel, MD, MSc, University of Minnesota, and Elizabeth Fox, MD, Children's Hospital of Pennsylvania—also lead the COG Developmental Therapeutics Committee, and they will interact with all other disease committees. The COG Operations Center will provide statistics and data management support.

Dr. Loehrer asked about ways to ensure that those who study adult cancers collaborate with pediatric researchers. Dr. Smith said that CTEP brings important drug development findings from the Experimental Therapeutics Clinical Trials Network (ETCTN) into the pediatric setting, and it facilitates interactions between COG and other NCTN groups. The adolescent and young adult population would benefit from such collaborations, and Dr. Smith believes that these collaborations are becoming more common. Dr. Davidson suggested a joint meeting or retreat for PEP-CTN and ETCTN, given that both networks are being revised and restarted now.

Dr. Fingert asked whether PEP-CTN can address drug shortages in clinical trials. Dr. Smith said that CTEP works with COG and FDA when these situations arise. Dr. Fingert noted that Janet Woodcock, MD, Director of the Center for Drug Evaluation and Research at FDA, is keenly interested in this topic, and she helps sponsors arrange backup manufacturing.

Dr. Gershenson stated that some adult research groups outside NCTN are collaborating with COG. For example, a COG investigator has organized an international malignant germ cell tumor group that developed a phase III NCTN trial. It would be helpful for NCTN to coordinate this type of activity.

Dr. Langevin pointed out that many pediatric hospitals do not accept anyone older than 18, so older patients must be transferred elsewhere. There is also a cultural barrier because pediatric and adult researchers operate differently, so they need to reach a common ground.

Dr. Mankoff noted that PEP-CTN has an imaging committee, and he asked whether it will build on the COG infrastructure. Dr. Smith responded that the Phase 1 Consortium's imaging center worked well and added that outside experts also will be available to support studies with imaging questions.

Dr. Shapiro said that his pediatric colleagues have expressed frustration with the difficulty of moving adult agents into early-phase trials in pediatric populations. Some companies do not want to conduct separate pediatric trials, but they might be amenable to lowering the cutoff age in their adult trials to 12 years. He recommended that the network interact with ETCTN, and he supported the suggestion of a joint retreat.

X. Ongoing and New Business

Sheila A. Prindiville, MD, MPH

Working Group Updates. CTAC formed the Progress in Pancreatic Adenocarcinoma Research Working Group and Progress in Small-Cell Lung Cancer Research Working Group in response to the Recalcitrant Cancer Research Act, and they submitted their scientific frameworks for these diseases to Congress 5 years ago. It is time to update the frameworks, so these working groups will start meeting again in the fall, and they will present their findings to CTAC in November 2018 or March 2019. The pancreatic cancer report is due to Congress in March 2019, and the small-cell lung cancer report is due in June 2019.

Although Dr. Weiner is rotating off CTAC, he has agreed to continue to lead the Clinical Trials Informatics Working Group with Warren Kibbe, PhD, Duke University School of Medicine. This working group will review NCI's implementation plan and make recommendations within the next 6 months.

Now that the NCTN program has been renewed, it is time to review the network's clinical trials portfolio. CTAC's Clinical Trials Strategic Assessment Working Group will be formed in the next 6 months or so.

The Translational Research Strategy Subcommittee of CTAC, the National Cancer Advisory Board, and the Board of Scientific Advisors will provide recommendations for enhancing and broadening NCI's translational research portfolio. The subcommittee will focus initially on glioblastoma and radiation oncology. Its two chairs will be Chi Dang, MD, PhD, Wistar Institute, and Dr. Davidson. Drs. Dang and Curran will chair the Glioblastoma Working Group, which will have its first call later in the summer. The Radiation Oncology Working Group is being formed.

Agenda for Next CTAC Meeting. Several members of CTAC had volunteered to work with Drs. Doroshow and Davidson to plan the agenda for the next CTAC meeting. This group would gather

immediately after this meeting. Potential future agenda items mentioned during this meeting include a working group focused on QIN and research on cancer health disparities.

CTAC's next meeting will be on Wednesday, November 7, 2018.

XI. Adjournment

Nancy E. Davidson, MD

There being no further business, the 36th meeting of CTAC was adjourned at 2:36 p.m. on Wednesday, July 11, 2018.

Appendix

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

CHAIR

Nancy E. Davidson, M.D. 2018
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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