DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
19th CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE MEETING

Summary of Meeting
March 13, 2013

Building 31 C, Conference Room 10
National Institutes of Health
Bethesda, Maryland

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
BETHESDA, MARYLAND
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The 19th meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was convened on Wednesday, March 13, 2013, at 9:00 a.m. in Conference Room 10, C-Wing, 6th floor, Building 31 on the National Institutes of Health (NIH) main campus in Bethesda, MD. The CTAC Chair, Dr. James L. Abbruzzese, Chairman, Department of Gastrointestinal Medical Oncology, The University of Texas M.D. Anderson Cancer Center, presided. The meeting was adjourned at 1:36 p.m.

Chair
James L. Abbruzzese

CTAC Members
Peter C. Adamson
Susan G. Arbuck
Monica M. Bertagnolli
Susan G. Braun (absent)
Curt I. Civin
Kevin J. Cullen
Nancy E. Davidson (absent)
Olivera J. Finn (absent)
J. Phillip Kuebler
Scott M. Lippman
Mary S. McCabe (absent)
Edith P. Mitchell
Nikhil C. Munshi
Lisa A. Newman (absent)
Nancy Roach
Daniel J. Sargent
Mitchell D. Schnall (absent)
Peter G. Shields
George W. Sledge, Jr.
Chris H. Takimoto
Joel E. Tepper
Gillian M. Thomas
Frank M. Torti
Miguel A. Villalona-Calero
George J. Weiner

***Ex Officio* Members**
James H. Doroshow, NCI
Paulette S. Gray, NCI
Rosemarie Hakim, CMS
Lee J. Helman, NCI (absent)
Michael J. Kelley, VA
Richard Pazdur, FDA
Alan S. Rabson, NCI (absent)

Executive Secretary
Sheila A. Prindiville, NCI

TABLE OF CONTENTS

WEDNESDAY, MARCH 13, 2013

I. CALL TO ORDER AND OPENING REMARKS—DR. JAMES L. ABBRUZZESE

Dr. Abbruzzese called the 19th meeting of the CTAC to order and then reviewed the confidentiality and conflict-of-interest practices required of Committee members during their deliberations. He asked CTAC members to review their signed conflict-of-interest statements and submit them to Dr. Sheila A. Prindiville, Director, Coordinating Center for Clinical Trials (CCCT), NCI. Members of the public were invited to submit written comments related to items discussed during the meeting to Dr. Prindiville within 10 days of the meeting. Any written statements by members of the public will be given careful consideration and attention. Dr. Abbruzzese reminded members that the meeting was being videocast by NIH Events Management and that the videocast would be available for review following the meeting at: http://videocast.nih.gov/.

Dr. Abbruzzese asked members to review the future CTAC meeting dates and reserve their calendars. He also noted that the CTAC Program Planning Working Group (WG) would convene immediately following the close of the parent CTAC meeting.

Motion. A motion to accept the minutes of the 18th meeting of the CTAC held on November 30, 2012, was approved unanimously.

II. NCI UPDATE—DR. JAMES H. DOROSHOW

Dr. James Doroshow, Deputy Director, Clinical and Translational Research, NCI, reported that five applications have been submitted by academic institutions seeking funds to serve as lead academic participating sites in the National Clinical Trials Network (NCTN). Four applications focus on adult patients and one focuses on pediatric patients. A substantial number of applications also were received for the translational research centers, as well as one Canadian application, as called for in the request for applications (RFA). The applications will be reviewed during the summer.

The budget sequester will result in a reduction in the NCI budget of 4.4 percent, or $219 million. A confidential proposal has been submitted to NIH leadership on how to accomplish this reduction in spending. Every possible effort will be made to sustain the R01 and R21 grant pools, especially for new investigators.

Given that the sequester is for 10 years, it is unlikely that the funds cut from the NIH budget will be replaced. It was suggested that CTAC discuss the implications of these cuts related to training for clinical and translational research personnel. Clarity on where cuts will be made in the NCI budget will need to await an appropriation. The intent is that there not be any furloughs at NIH due to the sequester.

A meeting of the NCI-Frederick Advisory Committee was held recently to discuss ideas for reconstituting Frederick as a national laboratory. A project is under development to create a team to address research questions related to *KRAS* genes at Frederick and other locations around the country. Another new project that is less well defined at this time is to create a library of patient-derived, completely genomically characterized xenografts to be made available to investigators around the country. One challenge for this effort will be creating incentives for cancer centers to provide specimens from patients with recurrent disease. The goal is to put together a library of at least 1,000 tumors so that

there is sufficient inherent heterogeneity to be useful for biological studies or for drug development. It has been very difficult to develop these models for hematologic and pediatric malignancies. Other diseases, such as sarcoma, melanoma, renal cancer, and bladder cancer are very poorly represented in available stocks.

Funding for The Cancer Genome Atlas (TCGA) project ends in 2014. Numerous conversations have taken place about how NCI will make available the enormous data sets generated for use by investigators. It also will be crucial to find a way to provide resources to continue to make available the analytical capabilities of the cancer centers in order to apply the resulting information to the clinical and translational research enterprise.

Questions and Discussion

Ms. Nancy Roach of the C3: Colorectal Cancer Coalition asked whether the proposed tumor bank would include primary tumors, metastatic tumors, or both. Dr. Doroshow replied that it would probably contain both, with an emphasis on recurrent disease in order to study drug resistance and similar questions.

Dr. Abbruzzese asked about the strategy for reviewing Cooperative Group grant applications. Dr. Meg Mooney, Chief of the Clinical Investigations Branch of the Cancer Therapy Evaluation Program, said that the Division of Extramural Activities will convene Special Emphasis Panels to review those applications sometime in the summer and bring the results forward to the National Cancer Advisory Board (NCAB) for approval at their fall meeting.

Dr. Peter Shields, Deputy Director, Comprehensive Cancer Center, The Ohio State University Medical Center, asked whether NCI is considering reducing the number of years for R01s to maintain the number of grants awarded. Dr. Doroshow said that the number of years is awarded on a case-by-case basis, but there currently is no standing policy or consideration for that.

Dr. Curt Civin, Director, Center for Stem Cell Biology and Regenerative Medicine, University of Maryland School of Medicine, stressed the need for frequent communication between NCI and the extramural community in order to increase grantees' awareness of funding decisions. This is necessary for institutions in planning their research programs. Dr. Doroshow said that all grantees will be advised as soon as a plan has been approved, but definitive judgments are difficult until an appropriation or Continuing Resolution is in place.

Dr. Peter Adamson, Chair of the Children's Oncology Group and Chief, Division of Clinical Pharmacology and Therapeutics, Children's Hospital of Philadelphia, asked whether programs other than the R01 pool will be made a priority to maintain. Dr. Doroshow stated that NIH guidelines are being considered on grant awards and levels of support for different kinds of grants across mechanisms and those will make clear what NCI will have to do.

Dr. Abbruzzese asked CTAC members who also serve on other NCI advisory boards for comments on their recent meetings.

Dr. Frank Torti, Executive Vice President for Health Affairs, University of Connecticut Health Center, mentioned that at a recent Board of Scientific Advisors (BSA) meeting, a representative from IBM made a presentation on the use of crowd sourcing in science. In 2012, NCI convened a "dream summit" to explore how this concept could be used to address cancer-related research challenges. A number of institutions participated in studies of selected challenges, with varying degrees of success. Even those that were not able to fully solve the challenges were found to have improved their knowledge bases. None of these challenges were taken from the realm of clinical research, but there should be opportunities in that arena. Open access to data will be a key to success. Rather than working prospectively with data from a single trial, NCI should support analysis of raw data from a number of trials.

Dr. Torti added that the BSA conducted an interesting discussion on next steps for supporting genomic research in the post-TCGA era. Many BSA members were skeptical of a proposal to vastly increase the number of samples from multiple tumor sites because of the high cost of collecting and analyzing them and whether those resources might be used in other ways. The discussion also stressed examination of the tumor microenvironment.

Dr. Civin encouraged CTAC members to continue providing input on clinical trial needs to the BSA, which tends to focus on laboratory science. He also stressed the need for CTAC members to communicate to the public that the sequester will result in fewer trials and reduced access to cutting-edge treatments.

Ms. Roach reported on a recent meeting of the NCI Board of Scientific Counselors (BSC), which reviews the Institute's intramural research programs. She noted that the intramural program is working on ways to increase collaboration and innovation across the various intramural programs, which in the past have tended to work in isolation.

Ms. Roach also commented on the difficulty of recruiting the required two advocates to serve on scientific steering committees (SSCs), since many advocates do not feel qualified to review scientific projects. The Patient Advocate Steering Committee (PASC) has been working on bringing in new people and training them effectively. The PASC has been working on accrual feasibility and how to look at that at the concept stage, as well as keeping up with ongoing NCI initiatives, and has developed a tip sheet to help advocates when asking questions about scientific concepts. Ms. Roach offered her assistance to CTAC members in working with advocates.

III. LEGISLATIVE UPDATE— MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations, NCI, reported on the status of appropriations and gave an update on congressional priorities.

Appropriations Status. The government is currently operating under a CR that expires March 27, 2013. The terms of the CR funded NIH at 0.62 percent above fiscal year (FY) 2012 funding levels. However, sequestration took effect on March 1, which reduces each budget line of all discretionary spending programs by 5.1 percent in FY2013; $109 billion will be cut per year through FY2021.

Ms. Erickson highlighted the efforts carried out prior to sequestration to educate Congress on the impact of across-the-board budget cuts. On February 8, Senator Ben Cardin held a town hall meeting with staff on the NIH campus. The White House issued *The President's Plan for a Strong Middle Class and a Strong America* on February 12, which advocated cutting the deficit in a balanced way. On February 13, the House Appropriations Committee Democrats released a report entitled *Discretionary Appropriations Will Reach Historic Lows*; the report provided many examples of the impact of discretionary budget cuts. On February 20, Senator Barbara Mikulski held a press conference on the NIH campus.

Appropriators also initiated early actions to address the impact of sequestration. The full Appropriations Committee held a hearing, "The Impact of Sequestration," on February 14. All of the witnesses were Cabinet Secretaries. Secretary Kathleen Sebelius, Department of Health and Human Services (HHS), was unable to attend the hearing; however, all of the absent secretaries submitted letters to the Committee outlining the impact of sequestration on their Departments. On March 5, the Labor, HHS, Education Subcommittee held a hearing entitled "Public Health Research," during which several division heads within HHS testified. The list of presenters included the Director of the National Institutes of Health.

Both the House and Senate introduced measures to avoid sequestration. The House introduced bill HR933 that calls for a full-year CR with additional appropriations for the Department of Defense and the Department of Veterans Affairs (VA). HR933 adjusts individual funding levels to increase funding for priority programs within Defense and Military Construction-VA bills. All other appropriations maintain current funding levels with subsequent reductions due to sequestration. HR933 was passed by the House on March 6. In the Senate, Senators Barbara Mikulski and Richard Shelby jointly introduced the Compromise CR, which includes the full text of the House bill and adds provisions of three appropriations bills to fund Agriculture, Commerce, Justice, Science and Related Agencies, and Homeland Security. Adding these appropriations bills will help the selected agencies manage spending cuts. Senator Tom Coburn has delayed consideration of the Compromise CR. There are several possible amendments to this CR. Senator Harkin's amendment, modeled on the Labor, HHS, Education bill negotiated with the House in December, would increase NIH funding by $211 million and increase education programs, child care programs, and the Ryan White AIDS program. Senator Ted Cruz proposed delaying funding for the Affordable Care Act; Senators Bill Nelson and Claire McCaskill would reduce salaries of lawmakers; Senator Dean Heller would restore White House tours; and Senator John McCain would remove provisions from the Defense bill.

Congressional Priorities. The Recalcitrant Cancer Research Act (RCRA) originally was introduced as the Pancreatic Cancer Research and Education Act in the House by Representatives Anne Eshoo and Leonard Lance, and in the Senate by Senator Sheldon Whitehouse in February 2011 with strong bipartisan support. In September 2012, the House Energy and Commerce Committee amended the Pancreatic Cancer Research and Education Act—the entire text was replaced and the title was changed to the Recalcitrant Cancer Research Act. The revised bill passed the House on September 19. Senator Tom Harkin introduced the bill in the Senate on September 20 but no further action occurred at that time. On December 18, Senator Whitehouse proposed an amendment to the Defense Authorization Act to include the language from the Recalcitrant Cancer Research Act. Senator Coburn spoke out against the amendment, but did not block the vote. The amendment passed both the House and Senate on December 20. Subsequently, the amended Defense Authorization bill was passed by the Senate and the House and President Obama signed it into law on January 2, 2013.

The Recalcitrant Cancer Research Act requires NCI to develop a scientific framework to conduct and support research for certain recalcitrant cancers. NCI is directed to convene a working group to provide expertise and assistance in developing the scientific framework for two recalcitrant cancers with a five-year survival rate of less than 20 percent and estimated to cause at least 30,000 deaths per year in the United States. Pancreatic cancer and a group of four types of lung cancer would qualify under this definition. NCI must identify two or more recalcitrant cancers not more than six months after enactment (July 2, 2013). The scientific framework must be developed no later than 18 months after enactment. The framework must be finalized and submitted to Congress and made publicly available on a DHHS website no later than 30 days after that. NCI already has established the PDAC (Pancreatic Ductal Adenocarcinoma) Working Group, whose report is being finalized, and is in the process of forming the Small-Cell Lung Cancer Working Group. Any cancer with a five year survival of less than 50 percent meets the broad definition of recalcitrant cancer outlined in the bill, and the NCI Director may identify that cancer for development of a scientific framework.

Questions and Discussion

Dr. Abbruzzese asked whether any of the CR proposals reverse sequestration. Ms. Erickson clarified that each proposal starts with current funding levels; sequestration will be applied after the current funding levels have been taken into account.

Dr. Civin asked if the Recalcitrant Cancer Research Act will allow NCI to develop a scientific framework for a nontraditional group of cancers, such as hematologic malignancies in the elderly. Ms. Erickson responded that the Act permits NCI to develop a scientific framework for any recalcitrant cancer with a five-year survival rate of less than 50 percent; the language of the Act does not say NCI could further narrow that focus to a particular patient demographic (i.e., the elderly).

Dr. Nikhil Munshi, Associate Professor of Medicine, Hematologic Oncology Treatment Center, Dana Farber Cancer Institute, questioned the financial impact of the Act. Ms. Erickson said that what the Act requires NCI to do—develop a scientific framework—is of very low cost to the Institute, but that the Act does not bring new money to the Institute for this purpose.

Dr. Adamson asked if the Act includes a definition of "scientific framework." Ms. Erickson said that the Act does not define "scientific framework" but prescribes what the framework should look like. She will review the language of the bill and update the CTAC.[i]

Dr. Munshi asked if the framework will result in focused research in the recalcitrant cancers identified by NCI. Ms. Erickson responded that the Act does not require the framework to lead to focused research, but it could guide NCI leadership when planning research activities.

Dr. Doroshow commented that it is within the province of CTAC to identify additional recalcitrant cancers for which to create working groups and develop scientific frameworks.

Dr. Abbruzzese asked how CTAC could generate a list of other recalcitrant cancers that warrant focused attention and communicate that list to NCI leadership. Dr. Prindiville recommended that the Committee first listen to the "Pancreatic Cancer Working Group: Scanning the Horizon for Focused Intervention" presentation later today, decide whether the Small-Cell Lung Cancer Working Group

should be organized and formatted in a similar way, and then have further discussion about other recalcitrant cancers of interest at a future meeting. Dr. Prindiville also told CTAC members to send her any comments on this issue. She will forward them to Drs. Doroshow or Varmus.

Dr. Gillian Thomas, Professor, University of Toronto, Odette Cancer Centre, asked how NCI will evaluate the success of the recalcitrant cancer working groups. Ms. Erickson said that some people would evaluate the success by whether or not funding increases in those research areas. Dr. Thomas added that the most important indicator of success is improved patient outcomes.

Dr. Adamson commented on the language of the Act. Mortality is a useful metric to identify recalcitrant cancers; however, life-years lost would be more useful. Based on the mortality metric included in the Act, there are no pediatric cancers that could be classified as recalcitrant. If the life-years lost metric were used, there would be pediatric cancers that could be evaluated.[ii]

Ms. Roach commented that Research America and the American Association for Cancer Research (AACR) are coordinating the Rally for Medical Research on April 8, 2013, in Washington, DC. She urged cancer center members to get involved with the Rally. Ms. Erickson responded that the Rally could have an impact on the FY2014 appropriations process.

IV. NCI NATIONAL CLINICAL TRIALS NETWORK (NCTN) WORKING GROUP: INTERIM REPORT—DR. GEORGE W. SLEDGE, JR.

Dr. George W. Sledge, Jr., Co-leader of the Breast Cancer Program, Indiana University Cancer Center, presented the NCI National Clinical Trials Network Working Group's interim report and recommendations. The NCTN WG was formed to assess the strength and balance of the active NCTN clinical trials portfolio both within and across diseases. The initial charge of the WG was to recommend new strategic priorities and directions for the NCTN Groups and NCI Scientific Steering Committees, based on the current trial portfolio, evolving clinical needs, and emerging scientific opportunities. The WG later will review and assess the Clinical Trials Working Group (CTWG) evaluation process and results, and provide strategic advice to enhance NCTN clinical trial operations.

The WG developed five criteria for evaluating clinical trial portfolios: feasibility, clinical importance, scientific contribution, relative cost/resources, and appropriateness for the NCTN program. WG members assigned an overall score to each trial based on the scores on the individual criteria listed above. This method of scoring of trials was applied for the review of multiple disease site portfolios (breast, gastrointestinal, genitourinary (GU), and leukemia and lymphoma) at the December 2012 WG meeting. This meeting brought forth a number of cross-disease comments and recommendations. It was noted that some disease portfolios have more scientific opportunities than others, resulting in more highly rated trials. A few common concerns emerged. Tension exists between the selection of more nimble, biology-driven, randomized phase II trials versus larger, more resource-intensive phase III trials. In several of the disease groups, there is a lack of drug availability for a variety of reasons. There is a common lack of ability to predict accrual feasibility in advance.

Recommendations from the meeting focused on how best to advance cutting-edge science in the genomic era in a time of fiscal constraint. Interim cross-disease recommendations include: 1) NCI should conduct an analysis of resource allocation across diseases, taking into account current survival rates and

likely cost/benefit from additional advances; 2) NCTN groups and Disease-specific Steering Committees (DSSCs) should work together to achieve the appropriate balance of innovative, biology-driven randomized phase II trials and larger, more resource-intensive phase III trials in each disease portfolio; 3) NCTN groups and DSSCs should emphasize biology-driven (e.g., molecularly driven, pathway-driven) trials that advance the science by incorporating genomics, biomarker tests, and correlative science into study designs; 4) to empower innovative, biology-driven trials, additional NCI funding should be provided for correlative science studies, biomarker validation, and the development of molecular classification algorithms; 5) accrual challenges should be taken more seriously in proposing and approving trial concepts, and the importance of the clinical question should be balanced with the perceived difficultly of accrual; 6) more consideration should be given to competing European and industry trials in proposing and approving trial concepts, as well as to the potential for collaboration with European and industry partners; 7) DSSCs should increase their involvement in strategic planning and guidance for future trials in collaboration with the NCTN groups; 8) DSSCs should develop standardized guidelines for the level and types of preliminary data required for trial concepts; 9) DSSCs should optimize their use of task forces, WGs, and Clinical Trial Planning Meetings (CTPMs); and 10) greater emphasis should be placed on sharing strategic and tactical best practices across diseases in terms of trial design, accrual, preliminary data requirements, etc.

Dr. Sledge reviewed the conclusions and recommendations for each disease portfolio. The breast cancer portfolio was found to be a relatively strong portfolio that addresses several key, clinically important questions. The portfolio includes multidisciplinary studies with a good balance of systemic and local-regional trials. Based on the review, the WG recommended including smaller, more nimble, randomized phase II trials of newer approaches to balance large adjuvant studies. Priority should be given to molecularly driven trials, marker validation, and correlative science. The portfolio also should incorporate studies on limiting toxicity, improving quality of life, and assessing survivorship. The Breast Cancer Steering Committee could facilitate these changes by providing strategic guidance for concept selection, developing standards for trial design, and optimizing the use of task forces, WGs, and CTPMs.

The WG also found that the leukemia portfolio is relatively strong and includes many innovative, biologically based, and scientifically important trials. The trials address several key, clinically important questions, in particular a chronic lymphocytic leukemia (CLL) trial in older adults. The WG recommended that priority be given to molecularly driven trials, marker validation, correlative science, and imaging techniques. Biospecimen collection needs to be a priority. Additionally, molecular classification algorithms should be developed for patient stratification. The Leukemia Steering Committee should build on its strengths in strategic planning, collaboration, and refinement of trial ideas by working collaboratively with the NCTN groups to make these improvements and work to enhance accrual.

In contrast, the lymphoma portfolio was not felt to be particularly strong. The WG was concerned that the portfolio is far behind European colleagues who have been more successful in putting large numbers of patients on important trials. This has resulted in the best new agents in lymphoma being developed outside of the NCTN. The WG felt that the lymphoma portfolio should focus on innovative, correlative, and translational science. It should incorporate integral biomarkers and molecular characterization into trial concepts, develop a niche in applying molecular science to trial concepts, and work on data standardization and address accrual issues. The Lymphoma Steering Committee should continue its strategic planning and guidance of early concept development and work with the NCTN groups to promote development of phase II trials that inform or lead to phase III trials.

The genitourinary cancer portfolio also was found to be less strong than other disease portfolios looked at by the WG. Recent and ongoing trials are likely to have only moderate scientific and clinical impact. It was noted that some trials are addressing questions that industry would not address. The WG recommended that in addition to the focus on prostate cancer, the GU portfolio should include trials in diseases with poorer outcomes, such as renal and bladder cancers. The portfolio should focus on scientifically important, molecularly driven, multidisciplinary trials with greater clinical impact; leverage new drugs; and move toward smaller phase II studies. The portfolio also should incorporate more molecular correlates and biomarkers, technology assessment, quality of life, and patient-reported outcomes into trial design. The Genitourinary Steering Committee and NCTN groups should develop a strategic plan to guide concept development and decision-making processes, and balance prostate and large phase III studies with other diseases and trial types.

As of the December 2012 meeting, the NCTN WG had completed comprehensive and critical reviews of five disease-specific portfolios. The WG was able to critically assess the strengths and weaknesses of these portfolios and develop interim recommendations to improve clinical cancer research portfolios supported by NCI. The WG will further refine its recommendations based on the review of the remaining disease portfolios. The WG anticipates that two additional meetings will be needed to complete the assessment of the strength and balance of the active phase III and large phase II clinical trials currently being conducted by the NCTN program. In March 2013, the WG will analyze the myeloma, brain, thoracic, and pediatric portfolios. The remainder of the portfolios, including symptom management trials, will be reviewed in summer 2013. A cross-disease portfolio assessment will follow the individual assessments. The WG will communicate with Steering Committee leadership and NCTN group disease committee chairs to implement proposed recommendations. Achieving their recommended goals will require collaboration between NCI, NCTN groups, and SSCs. The WG will begin a series of disease-specific conference calls with NCTN WG chairs, SSC chairs, and NCTN disease committee chairs to facilitate this process.

Questions and Discussion

Dr. Abbruzzese asked if the DSSCs of the weaker disease portfolios are underperforming compared with the DSSCs of the strong disease portfolios. Dr. Sledge responded that the NCTN WG has not reviewed enough disease site portfolios to make that conclusion. There is much variation across the disease sites in how the DSSCs are utilized. Dr. Adamson noted that this variation is due, in part, to the way the DSSCs are structured. The DSSCs are unique in that the peer reviewers also are doing strategic planning. .

Dr. Thomas commented that it is important to understand the causes behind the “less-than-successful” disease portfolios. She noted that in gynecologic cancer, there is much tension between those who develop clinical trials and the Steering Committee regarding whose job it is to develop trials. Dr. Thomas suggested that trial developers view the Steering Committee and task forces as obstructions to trial progress.

Dr. J. Phillip Kuebler, Principal Investigator, Columbus Oncology Associates, Inc., recommended including additional criteria to evaluate the success of disease-specific portfolios. Some trials may not

advance the science but could still have a major clinical impact on the care of patients. For example, trials that result in decreased use of adjuvant therapy would decrease drug toxicity and costs to patients. Criteria that take into account improved clinical care also should be used in evaluating trials.

Dr. George J. Weiner, C.E. Block Chair of Cancer Research, Holden Comprehensive Cancer Center, noted that the DSSCs have been in place for varying lengths of time—some are more mature, while others are still evolving. This should be taken into consideration when evaluating the performance of the DSSCs and their corresponding disease portfolios.

Dr. Civin asked how the clinician scientist community could become more involved in setting the nonclinical trial priorities of NCI, such as biologic variance of a disease, etc. Dr. Sledge noted that NCI staff have said that different approaches could be considered that would prioritize small, biology-based trials versus larger trials. Dr. Monica M. Bertagnolli, Professor of Surgery, Harvard Medical School, Brigham & Women's Hospital, Dana Farber Cancer Institute, stressed that expensive tumor sequencing work should be based on high-quality clinical data. She also noted that the process of the WG already has been very valuable and that the groups already have acted on some of what has happened in the WG meetings.

Ms. Roach commented that one of the strengths of the NCTN is the collaboration and mutual reward for accruing to one another's trials. She praised the Colon Cancer Task Force for its early review and approval of trial concepts.

Dr. Miguel A. Villalona-Calero, Division Director, Medical Oncology, The Ohio State University, suggested looking to the new Early Therapeutics Network for approaches to improve the NCTN disease portfolios.

Dr. Edith P. Mitchell, Director, Center for the Elimination of Cancer Disparities, Kimmel Cancer Center at Thomas Jefferson University, asked how the WG is evaluating the inclusion of diverse populations within clinical trials. Dr. Sledge responded that the WG is evaluating life-years saved—a criterion that can be applied to specific populations. The WG is not yet evaluating outcomes for specific patient populations.

Dr. Daniel J. Sargent, Director, Cancer Center Statistics, Mayo Clinic College of Medicine, encouraged support for the NCTN WG's cross-disease recommendation to place greater emphasis on sharing of strategic and tactical best practices across diseases in terms of trial design, accrual, preliminary data requirements, etc. He suggested holding state-of-the-science meetings on trial conduct and methodology as a way to facilitate the sharing of best practices.

Dr. Sledge commented that within the last few years, NCI has improved how quickly trials open after concept approval. A shorter time to trial opening has a major impact on trial accrual. However, issues with trial accrual still exist. A systematic evaluation of trial accrual might result in the identification of opportunities for improvement.

Dr. Susan G. Arbuck, President, Susan G. Arbuck, M.D., LLC, stated that industry often has a formalized process to assess trial feasibility. Pretrial, early assessments of feasibility either result in trials that are feasible and accrue, or trials that do not get started. She encouraged NCI to look at industry practices for determining trial feasibility.

Ms. Roach commented that NCI is aware of and doing a great deal of work on issues with trial accrual. For example, NCI has developed the web resource AccrualNet (https://accrualnet.cancer.gov/) in order to provide strategies, tools, and resources to support accrual to clinical trials.

Dr. Torti stated that one of the limitations to asking compelling scientific questions in clinical trials is having compelling drugs with which to ask those questions. He suggested developing a more robust effort led by NCI to provide the research community with compelling, interesting compounds that could be used to address compelling scientific questions. This effort could be done in partnership with NCI-designated Cancer Centers.

Dr. Doroshow responded that part of the challenge of obtaining compelling drugs is that industry is not interested in partnering with a system that does not accrue well. Industry becomes more interested in collaboration when the system is able to provide a service that is not easily replicable, such as using biological information to identify appropriate patient populations for trials. Overall, the more scientifically robust a clinical trials system is, the more likely industry will want to collaborate and provide compelling drugs for study.

Dr. Doroshow also noted that NCI completely revamped its drug development pipeline three years ago, which has resulted in a variety of interesting molecules from sophisticated academic drug discovery groups. NCI also has tested all possible combinations of 100 cancer drugs currently approved by the U.S. Food and Drug Administration (FDA) to see if any previously untested combinations are effective in certain cancers; 5,000 drug pairings have been tested across the NCI-60 assay. These data will be made public in the near future, facilitating new preclinical, phase I, and phase II studies.

Dr. Chris H.M. Takimoto, Translational Medicine Early Development, Oncology Therapeutics Area, Janssen Research and Development, Johnson and Johnson, commented that industry is trying to develop novel drug combinations; however, two drugs from the same company often end up together. He also asked whether the strong disease portfolios have more industry involvement than the weaker portfolios. Dr. Sledge responded that the strength of the portfolios is based more on accrual and that some disease sites accrue better than others.

Dr. Arbuck asked if data from the NCI-60 drug combination testing will be presented to the DSSCs. Dr. Abbruzzese said the discussion of that idea can be brought forward as an agenda item for CTAC. CTAC could look at the data and advise NCI on how to disseminate information to the research community and recommend specific trial ideas.

Dr. Thomas asked if NCI is developing any strategies to incentivize collaboration with industry. Designing a clinical trial with two drugs from two different companies is challenging. Dr. Doroshow responded that in addition to the combination testing with commercially available drugs, NCI also has tested investigational drug combinations. Data from systematic evaluations can provide industry with assurance and eliminate perceived risks.

Motion. A motion to accept the NCTN Working Group Interim Report was approved unanimously.

V. PANCREATIC CANCER WORKING GROUP: SCANNING THE HORIZON FOR FOCUSED INTERVENTIONS—DR. JAMES L. ABBRUZZESE

Dr. Abbruzzese presented the Pancreatic Cancer Working Group's report to the CTAC members. He began by giving an overview of pancreatic cancer. Pancreatic adenocarcinoma is a highly lethal tumor accounting for 2 percent of all cancer cases and 5 percent of all cancer deaths. It is the fourth leading cause of cancer-related death for both men and women. Cigarette smoking, obesity, and diabetes are the greatest risk factors for pancreatic cancer. Combined, these risk factors contribute to about 50 percent of pancreatic cancer cases. In addition to hereditary syndromes that can lead to the disease, pancreatic cancer also can run in families. A subset of patients has been found to have mucinous pancreatic cysts that may put them at risk for invasive disease. Cure of pancreatic cancer is rare and seen only in resected patients. Pancreatic tumors are resistant to chemotherapy and radiation; the mechanisms by which tumors resist therapy are diverse. Survival for most pancreatic cancer patients is measured in months. Prevention of disease and modulation of known risk factors is an extremely important issue that can potentially reduce the risk for developing this disease.

The purpose of the Pancreatic Cancer WG is to develop strategies and recommendations that will advise CTAC on ways to reduce the incidence and mortality rates of pancreatic adenocarcinoma. The WG was charged with assessing recent advances in PDAC research, including epidemiology, risk assessment, screening, early detection, molecular pathology, and therapy, and developing a set of tractable, near-term strategies to improve outcomes for people at risk for and with PDAC.

Dr. Abbruzzese highlighted recent translational and clinical progress in pancreatic cancer. Pancreatic cancer researchers have a better understanding of the initial histologic and molecular characterization of precursor lesions, as well as an understanding of the sequence of genetic alterations that contribute to development of the disease. Genetically engineered mouse models (GEMMs) and patient-derived xenografts (PDX) have been developed to study novel therapeutic agents. The importance of tumor-related stroma in the disease is now known. Researchers also now are recognizing the role of diabetes and obesity in pancreatic cancer risk and survival. In the clinic, there are initial screening efforts for patients with familial pancreatic cancer or known germline mutations conferring risk. The natural history of mucinous cystic neoplasms is understood and criteria have been developed for surgical resection. It is recognized that the development of targeted agents will require understanding of pancreatic cancer cellular heterogeneity. There also is an effective integration of currently available treatment modalities (surgery, radiation, chemotherapy).

The first meeting of the Pancreatic Cancer WG was held October 23-24, 2012. The specific goals of the meeting were to identify unsolved problems in PDAC research, develop strategies to increase the extent of collaboration between centers studying pancreatic cancer, develop recommendations to capitalize on opportunities, and provide advice on the NCI plan to implement these recommendations. The WG focused on addressing three critical questions: 1) Can we identify cohorts of individuals at high risk? 2) Can we screen patients deemed to be at high risk and identify preinvasive pathologic precursors or very early cancers? 3) Can we develop more effective systemic therapies? The WG also discussed some other provocative questions, including the reasons why pancreatic cancer occurs in some patients with no known risk factors or genetic abnormalities. Why do identical mutations (e.g., *CDKN$_2$A*) result in pancreatic cancers in some patients and melanoma in others? The WG discussed whether aspirin and/or metformin could prevent or control pancreatic cancer. Lastly, they addressed the reasons why some pancreatic cancer patients respond remarkably to treatment while most others do not. The meeting was organized around three breakout sessions: Epidemiology and Risk Assessment Research; Pathology, Screening, and Early Detection Research; and Therapeutic Research.

Breakout session discussions resulted in the identification of tractable, near-term goals for NCI to improve pancreatic cancer research. Biomarkers can be developed and tested to risk-stratify patients deemed at moderate risk based on clinical criteria (e.g., those patients with new-onset diabetes, obesity/metabolic syndrome, and mucinous cystic neoplasms). The screening of patients with high-risk germline mutations or pancreatic mucinous cysts that are precursors to invasive pancreatic tumors can be improved. It would be useful to develop greater consensus on criteria that should be generated in preclinical testing of novel therapeutic approaches before testing in patients with pancreatic cancer.

Available model systems may need to be used to better identify the molecular or biochemical characteristics of the pancreatic cancer patient population likely to respond to a targeted intervention in the clinic. Minimally invasive biopsy strategies and noninvasive imaging technology can be developed to more effectively study pancreatic cancer in patients. The WG identified four high-level recommendations from their proceedings, which include: (1) developing a means to identify the approximately 1/125 patients with new-onset diabetes who have early pancreatic cancer; (2) developing screening methods to identify those patients with heritable pancreatic cancer (specific germline mutations or pancreatic cancer families) or mucinous pancreatic cysts who will progress to invasive pancreatic cancer and require surgical intervention; (3) developing strategies that neutralize the driver oncogene *KRAS*; and (4) accelerating clinical and preclinical therapeutic approaches that target the immune and nonimmune components in pancreatic tumors.

Dr. Abbruzzese concluded by asking CTAC members for their comments on the pancreatic cancer initiative. NCI would like to know whether the approach used would be appropriate for other "recalcitrant" cancers such as small-cell lung cancer.

Questions and Discussion

Dr. Munshi commented that there does not seem to be any emphasis on the identification of newer targets, drugs, and treatments, but a lot of emphasis on preidentification epidemiology. He said that to find a successful cure for pancreatic cancer, new therapeutic options are needed. Dr. Abbruzzese agreed and said there is ongoing work to identify new treatments and treatment targets, and that the WG endorses continuing those efforts but does not necessarily want to put the emphasis there.

Dr. Villalona-Calero suggested there be an emphasis on drug development for pancreatic cancer through the combinatory programs. Data from the NCI-60 combination testing could be used to identify new combinatorial treatment approaches for pancreatic cancer. Those data also could be used in concert with GEMMs and PDXs.

Dr. Kuebler noted that the process used for pancreatic cancer also could be used for small-cell lung cancer but will result in different types of recommendations.

Dr. Arbuck agreed that the process has worked well. She also asked whether it will fall under the purview of the WG to develop educational materials on pancreatic cancer prevention, especially with regard to cigarette smoking, obesity, and diabetes. Dr. Scott M. Lippman, Director, University of California, San Diego, Moores Cancer Center, encouraged collaboration across NIH to address this issue.

Dr. Doroshow responded that the WG's report recommends working more closely with the National Institute of Diabetes and Digestive and Kidney Diseases.

Dr. Takimoto commented that the most important aspect of this process will be implementation of the WG's recommendations.

Dr. Torti said that further refining the definition of high-risk patient populations will be integral to successful screening strategies. Dr. Abbruzzese agreed and said that work is being done utilizing magnetic resonance (MR) technology to define pancreatic steatosis. The hope is to be able to identify an additional subset of high-risk patients based on the degree of fat infiltration within the pancreas, which may contribute to pancreatic carcinogenesis.

Dr. Villalona-Calero suggested that the emphasis for small-cell lung cancer be on acquired treatment resistance.

Ms. Roach suggested that the DSSCs discuss how NCI and the extramural community can decrease mortality quickly and effectively, in addition to holding clinical trials planning meetings.

Motion. A motion to establish a CTAC Working Group on small-cell lung cancer was approved unanimously.

Motion. A motion was made to accept the Pancreatic Cancer Working Group's report with the modification noted by Dr. Villalona-Calero to include more emphasis on drug development and combinatorial efforts to identify new treatment options. The motion was seconded and approved unanimously.

VI. SYMPTOM MANAGEMENT AND QUALITY-OF-LIFE STEERING COMMITTEE (SXQOL SC) PLANNING MEETING REPORT: RECOMMENDED CORE SET OF PATIENT-REPORTED OUTCOMES (PROs) FOR PHASE III CLNICAL TRIALS—DR. LORI M. MINASIAN

Dr. Lori Minasian, Deputy Director, Division of Cancer Prevention (DCP), NCI, presented an overview of recommendations on patient-reported outcomes developed at the November 2011 Symptom Management and Quality of Life Steering Committee clinical trials planning meeting, "Building Bridges: Identification of Core Symptom and Health-Related Quality of Life Domains for Use in Cancer Clinical Trials." The purpose of the meeting was to identify core symptom and health-related quality-of-life (HRQOL) domains for use in cancer clinical trials.

Measures of HRQOL have been incorporated into treatment, prevention, and cancer control for more than 30 years. However, findings of these studies have been published inconsistently— PRO-related data seldom are included in treatment-related articles. HRQOL measures are not fully integrated into analyses of toxicity and efficacy in phase III trials.

Patient-reported outcomes include any information reported by a patient, usually in response to questions from health care providers. Overall quality of life can relate to any aspect of life, including

family and work. HRQOL studies collect PRO data to determine the impact of illness or treatment on physical, emotional, and social aspects of QOL.

The FDA has begun developing guidelines for use of PROs as endpoints in clinical research. In addition, the Center for Medical Technology Policy recently issued PRO effectiveness guidance. The National Quality Forum has identified methodological issues related to collecting PROs.

Within NCI, DCP is the lead Division for primary review of PRO/HRQOL endpoints in trials, but other NCI Divisions and organizations are involved in PRO/HRQOL research. For example, the Division of Cancer Control and Population Sciences (DCCPS) is guiding development and validation of the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). The NCI Center for Biomedical Informatics and Information Technology (CBIIT) is supporting development of common data elements for measuring PROs.

Challenges in incorporating PRO endpoints in cancer trials include ensuring that inclusion of PROs is hypothesis driven, optimizing study efficiency, and keeping the burden for patients and physicians low. Opportunities for collecting PROs include conducting cross-trial comparisons of PROs and providing support for improved patient-physician decision-making.

The objectives for the November 2011 meeting were to identify a core set of PRO domains to be used in cancer clinical trials across cancer types and a second set of PRO domains designed for application to three specific cancer types.

Criteria for selection of core domains were listed among the top 10 symptoms of at least two large clinical data sets, present across diverse cancer populations, measurable from the patient perspective, and endorsed by participants in the planning meeting. Criteria for cancer-specific domains were multiple treatment modalities, significant treatment-related morbidities, and some crossover or similarities between the disease sites for the treatment-related morbidities. The types of cancers selected for the clinical data sets were head and neck, prostate, and ovarian.

The domains are sets of symptoms that should be considered for all phase III trials. For the core domain, these include nausea, vomiting, anorexia, diarrhea, sensory neuropathy, dyspnea, fatigue, pain, impaired mental concentration, insomnia, depressed mood, anxiety, and fatigue. For ovarian cancer, the domains include abdominal core, neuropathy, fear of recurrence, sexual dysfunction, and poor overall HRQOL. For prostate cancer, the domains are urinary incontinence, urinary obstruction, bowel dysfunction, sexual dysfunction, and hormonal symptoms. For head and neck cancers, the domains are difficulty swallowing, oral pain, dry mouth, poor dental health, impaired taste, difficulty opening the mouth, shoulder dysfunction, and social dysfunction. The Committee developed a matrix indication where major data collection tools address each of the domains, but is not recommending any specific tool, since the tools have different features that make them good choices in specific situations.

The Committee is recommending the adoption of three domains and will continue to emphasize the importance of using these domains in hypothesis-driven trials. Next steps include publishing the results of the Committee's work and collaborating with CTAC, DSSCs, and Cooperative Groups to implement the recommendation to adopt the sets of PRO domains. One question CTAC may be able to help answer is whether these recommendations should be disseminated to organizations outside the NCTN.

Questions and Discussion

Dr. Takimoto asked whether any interaction with industry is planned. Dr. Minasian replied that there is no active industry engagement in this discussion, primarily because FDA guidance on PROs sets the framework for industry. There may be some indirect engagement through the FDA/NCI PRO consortium.

Dr. Adamson noted that toxicities are graded differently by physicians and patients. Dr. Minasian said this issue has not yet been addressed but will play a part in planned discussions that are pending about PRO-CTCAE.

Dr. Sledge asked whether the Committee has addressed the question of how to determine acceptable toxicity in terms of the proposed endpoints. Dr. Minasian noted that advances in therapeutics have resulted in a reduction in life-threatening toxicities. As combinations of therapies increase, there is a much greater understanding of combinations of non-life-threatening toxicities and their effects on quality of life. Retrospective studies of symptomatic toxicities may help develop algorithms for determining whether dose modifications can be made earlier in treatment.

Dr. Villalona-Calero asked whether the Committee anticipates addressing the wide variation in methods used by physicians to treat symptoms associated with exposure to toxins. Dr. Minasian stated that symptom management studies are under way. One complicating factor is that some agents for treating symptomatic toxicities may interfere with the treatment being evaluated in the trial.

Dr. Shields asked whether institutions incorporating these domains into trials also are incorporating them into routine clinical data systems. Dr. Minasian noted that some health systems have begun to collect data on PROs.

Dr. Shields asked whether there is a repository or inventory of tools that can be used to measure PROs. Dr. Minasian replied that the developers of the ProQOL system have a list of available quality-of-life assessment tools. She will send information on accessing this list to Dr. Prindiville for distribution to CTAC members.

Dr. Mitchell asked whether the plan for these domains includes validation of their use in multicenter trials. Dr. Minasian noted that the instruments that have been identified for measuring the PRO domains are validated and have been used in multicenter trials for more than 30 years.

Ms. Roach recommended that the Committee prepare written materials on this effort that can be distributed to the many task forces involved in clinical research planning. She also asked how these plans can address the problem of lack of publication of PRO-related data. Dr. Minasian acknowledged that this will be a slow process. One need is better coordination and integration of the analysis of treatment data and PRO data. Another need is recognition of the importance of PRO research on the part of journal editorial boards.

Dr. Lippman suggested partnering with the NCTN to encourage incorporation of PROs into electronic medical records.

Dr. Abbruzzese suggested that publication of PRO data would increase if the FDA would accept PROs as an integral component of its decision-making.

Motion. A motion to support the recommended core set of patient-reported outcomes was unanimously approved.

VII. POTENTIAL CHANGE IN NCI POLICY REGARDING THE SUBMISSION OF GRANT APPLICATIONS THAT REQUEST SUPPORT FOR PHASE III CLINICAL TRIALS—DR. ROY S. WU

Dr. Roy S. Wu, Chief, Clinical Grants and Contracts Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis (DCTD), NCI, explained that NCI currently follows an unwritten policy regarding the inclusion of phase III clinical trials in investigator-initiated research applications using the R01 and P01 funding mechanisms. Acceptance of applications for phase III clinical trials is regulated indirectly by the requested direct costs of these applications. Applications with requested direct costs exceeding $500,000 in any of the requested funding years require special approval, whereas applications costing less than $500,000 direct costs per year are accepted automatically.

A proposal has been made to create a policy removing phase III therapeutic trials from the R01/P01 portfolio. The rationale for revising this policy is based on the fact that most phase III trials are multicenter studies that cost more than $500,000 per year and usually take longer than the standard five-year grant period. A second reason for reconsidering the policy is the recent trend in grants that result in duplication of infrastructure already in place through the NCTN and the Community Clinical Oncology Program (CCOP).

The policy revision process began with discussions with NCI Division-level stakeholders and a portfolio analysis. A draft revision was presented to senior NCI leadership and Scientific Program Leaders (SPL). A Request for Information (RFI) was issued to extramural investigators. The final step in the process is presentation of the proposed revision to CTAC.

The portfolio analysis showed that the majority of extramural investigators do not propose therapeutic or imaging phase III trials in the grants portfolio. In the past 10 years, only 150 investigators would have been affected by a policy change.

Only 19 responses were received in response to the RFI. There was no consensus on the proposal, even among investigators working in the same institutions. The responses showed significant support for excluding behavioral research from the revised policy.

Concern was also evident about how phase II trials addressing rare diseases can be supported. NCI's response to this concern is that phase II trials in rare diseases have been incentivized through NCTN via revised review criteria and the development of a common menu for the entire Network.

The proposed policy states that "NCI will no longer accept R01 or P01 applications…for phase III (efficacy) trials that test therapeutic or imaging modalities in clinical trials. NCI will continue to accept R01 or P01 applications for trials that are limited to public health interventions, comparative effectiveness

research (nontherapeutic, behavioral or health systems research), and other psychosocial, behavioral, and related interventions to address consequences of cancer provided they can be completed entirely within the five-year grant cycle. Ongoing phase III efficacy clinical trials/studies currently supported by NCI in the grant portfolio are permitted to be supported as part of a competitive renewal grant."

Questions and Discussion

Dr. Sledge asked about the net change in dollars spent on clinical trials that would result from this new policy. Dr. Wu said that the change would be minimal. If investigators are not allowed to propose phase III therapeutic trials, they likely will conduct multicenter phase II trials and then move into phase III studies within the NCTN. Examples of this type of collaboration include bone marrow transplantation and reduced-intensity regimens in the Blood and Marrow Transplant Clinical Trials Network.

Dr. Bertagnolli noted that relationships between U01 investigators and Cooperative Groups, which have grown out of the need to downsize the costs of the U01 grants, have been successful.

Dr. Weiner asked about mechanisms for exceptions to this policy for important, promising concepts. Dr. Wu replied that NCI would consider such requests, although investigators would be encouraged to work through the NCTN.

Dr. Adamson suggested that in addition to therapeutic and imaging interventions for which phase III applications will not be accepted, the policy should include immunotherapy and cellular therapies. He also suggested that it would have been preferable to have the proposed policy presented to CTAC before issuance of the RFI.

Dr. Shields suggested that the issues of cost limits and accrual time could be addressed through the review process.

Dr. Jeffrey Abrams, Associate Director, Cancer Therapy Evaluation Program, DCTD, NCI, noted that for a large, multicenter trial that is expected to have practice-changing significance, achieving regulatory approval, accrual, and data analysis within five years is very difficult.

Dr. Abbruzzese asked whether worthwhile proposals can be funded through more than one process. Dr. Doroshow said that examples exist of studies in which correlative science is funded by NCI and the actual clinical trial is funded by a separate source.

Dr. Adamson expressed concern that ending awards to phase III therapeutic trials would reduce the clinical research portfolio. Dr. Doroshow stated that the funds would remain in the Research Project Grant pool.

Ms. Roach expressed support for bringing all multisite phase III treatment studies under the NCTN, noting that this will expedite the review process and provide better resources for long-term follow-up and data sharing for studies of secondary concepts.

Dr. Shields expressed support for avoiding infrastructure duplication.

Motion. A motion to support the recommended policy revision was made with the modification to indicate that the definition of "medical interventions" includes immunotherapy and cellular therapies. The motion was seconded and approved unanimously.

VIII. NEW BUSINESS AND ANNOUNCEMENTS—DR. JAMES L. ABBRUZZESE

Dr. Abbruzzese announced that the CTAC Program Planning Working Group is having its first meeting today. He also announced that some replacement members are needed for CTAC and that current members can submit their nominations to Dr. Prindiville. Also, there is an additional opening on the CTAC Clinical Trials Strategic Planning Subcommittee. CTAC members should contact Dr. Prindiville if they are interested in serving on the Subcommittee.

IX. ADJOURNMENT—DR. JAMES L. ABBRUZZESE

There being no further business, the 19th meeting of the CTAC was adjourned at 1:36 p.m. on Wednesday, March 13, 2013.