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NATIONAL CANCER INSTITUTE
16th CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE MEETING

Summary of Meeting
March 7, 2012

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

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
BETHESDA, MARYLAND
Summary of Meeting
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The 16th meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was convened on Wednesday, March 7, 2012, 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 2:13 p.m.

Chair
James L. Abbruzzese

CTAC Members
Peter C. Adamson
Susan G. Arbuck
Monica M. Bertagnolli
Susan G. Braun
Curt Civin (absent)
Kenneth H. Cowan
Kevin J. Cullen
Olivera J. Finn
Scott M. Lippman
Lisa A. Newman
Nancy Roach
Daniel J. Sargent (absent)
Mitchell D. Schnall (absent)
Peter G. Shields
Joel E. Tepper
Frank M. Torti

***Ad Hoc* Members**
Nancy E. Davidson
J. Phillip Kuebler
Mary S. McCabe (absent)
George W. Sledge, Jr.
Gillian M. Thomas
Miguel A. Villalona-Calero
George J. Weiner

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

Executive Secretary
Sheila A. Prindiville, NCI

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

Dr. Abbruzzese called the 16th meeting of the CTAC to order. He then introduced new CTAC members who were in attendance for the first time. Dr. Abbruzzese reviewed the confidentiality and conflict-of-interest practices required of Committee members during their deliberations. He asked the 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/. He also noted that today's meeting would focus on the early stages of drug development.

Meeting Dates. The November 2012 CTAC meeting has been rescheduled to take place on Friday, November 30, 2012.

Motion. A motion to accept the minutes of the 15th meeting of the CTAC held on November 9, 2011, was approved unanimously, with acceptance of the correction noted by Dr. Miguel Villalona-Calero, Professor of Medical Oncology, The Ohio State University. On page 3 of the minutes, under Dr. Villalona-Calero's comments, "curative" should be changed to "non-curative."

II. NCI UPDATE—DR. JAMES H. DOROSHOW

Dr. James Doroshow, Deputy Director, Clinical and Translational Research, NCI, gave an update on the current fiscal situation and programmatic activities at NCI.

The fiscal year (FY) 2012 NCI budget has been set at $5.071 billion; a 2-percent increase from the FY2011 NCI budget. NCI expects to be able to fund the same number of new grants in 2012 as were funded in 2011. The grant approval process will be similar to that of last year, with no strict pay line. NCI expects the success rate to be around 15 percent. Now that the budget is official, the process of awarding funds should accelerate.

The President's FY2013 budget, which was released a few weeks ago, includes a $3 million increase over the 2012 budget—essentially the same flat FY2010-level funding. The NCI Director's Bypass Budget will be released soon. The Bypass will focus on six types of cancer and some key initiatives such as genomics, global health, Cancer Centers, provocative questions, and precision medicine. Dr. Doroshow noted that approximately 800 applications have been received in response to the Provocative Questions Request for Applications (RFA). These proposals will undergo a two-phase review.

There is an ongoing search for a new director of NCI's Center for Biomedical Informatics and Information Technology (CBIIT). The former director, Dr. Kenneth H. Buetow, left NCI to take a position with Arizona State University. Dr. George Komatsoulis, former deputy director, has been appointed acting director. A caBIG (cancer Biomedical Informatics Grid) subcommittee of the National Cancer Advisory Board (NCAB) and the Board of Scientific Advisors (BSA) has been assisting the current interim leadership with restructuring NCI's information technology (IT) infrastructure.

There is an active search for a director of the Center for Cancer Genomics (CCG). CCG is currently being led by Dr. Barbara Wold of the California Institute of Technology on an interim basis. The Office of Science Planning and Assessment (OSPA) also is undergoing a search for a new director.

NCI hosted the Team-based Approaches to Scientific Research Workshop, led by Dr. Ed Harlow, Professor, Harvard Medical School, February 7-8, 2012, on the NIH campus. The purpose of the Workshop was to assess strategies that have been used for highly successful intra- and interinstitutional collaborative research, primarily focused on the process and approaches used for building good team research projects. Workshop participants were individuals from various outside organizations and different components of NCI, including: Specialized Programs of Research Excellence (SPOREs), Cancer Centers, Cooperative Groups, P01 and U54 grantees, as well as Stand Up to Cancer, the Department of Defense (DoD), the National Science Foundation (NSF), the Broad Institute, the Howard Hughes Medical Institute, and others.

Key findings of the Workshop highlighted characteristics of successful teams and suggestions for future team science projects. Some of the characteristics identified were: strong leadership; meaningful but difficult goals with built-in incentives; flexibility to redirect funds and alter other parts of projects for team building and timeline management; and sufficient finances to identify key problems, recruit/reward essential people, and help leverage resources from other sources. Some of the suggestions for future team science projects were similar to the recommendations put forward by the Translational Research Working Group (TRWG) a few years ago. The suggestions included developing challenging ideas, using pilot projects to develop teams and refine ideas, enhancing mentoring and training for leadership and team management, considering program managers to manage projects and inform about available resources at NCI and beyond, and creating new methods for project oversight and review.

The Ad hoc Clinical Trials Strategic Planning Subcommittee of the CTAC held its first meeting in November of 2011. The purpose of the Subcommittee is to advise NCI on the development of a fully integrated clinical trials system. The Subcommittee's focus is on trials funded through cooperative agreements and contracts, with an initial focus on trials supported through the NCI National Clinical Trials Network (NCTN). The Subcommittee is in the process of developing the NCI NCTN Working Group, which will be co-chaired by Dr. Robert B. Diasio, Mayo Clinical Cancer Center, and Dr. George W. Sledge, Jr., Professor, Departments of Medicine and Pathology, and Co-Leader, Breast Cancer Program, Indiana University Cancer Center. There will be 25-30 members serving on the Working Group selected from the following categories of stakeholders: Cooperative Group chairs and statisticians, Community Clinical Oncology Program (CCOP) principal investigators (PIs), cancer control research base PIs, Cancer Center directors, Steering Committee chairs, advocates, translational scientists, and NCI leadership. Invitations for membership are being initiated. The goals of the NCTN Working Group are to: assess the balance, coherence, and appropriateness of the NCTN clinical trials portfolio; advise on ways to improve the scientific effectiveness of the NCTN Scientific Steering Committees; recommend new strategies and directions for NCTN clinical trials based on NCI's current portfolio, evolving clinical needs, and emerging scientific opportunities; and provide strategic advice to enhance other aspects of clinical trials operations affecting the NCTN. The aim is for the initial Working Group meeting to occur before the July 2012 CTAC meeting.

Questions and Discussion

Ms. Nancy Roach, C3: Colorectal Cancer Coalition, asked whether the findings from the Team-based Approaches to Scientific Research Workshop will be published. Dr. Prindiville explained that there

is no intention to publish an article; however, a two-page summary of the Workshop will be made available on a public Web site.

III. LEGISLATIVE UPDATE— MS. M. K. HOLOHAN

Ms. M. K. Holohan, Deputy Director, Office of Government and Congressional Relations, NCI, reported on the status of appropriations and gave an update on legislative activities.

FY2012 Appropriations. The Omnibus appropriations bill was signed into law on December 23, 2011, appropriating $30.69 billion for NIH with $5.071 billion going to NCI. This is a 0.2-percent increase over the FY2011 budget and a 1-percent cut from the FY2010 budget. NIH received its appropriations on March 5, 2012. Notable programmatic changes included in the FY2012 appropriations bill are a reduction in maximum salary support (from $199,000 to $179,000) for extramural grantees for grants issued on or after December 23, 2011; creation of a pilot study on the viability of third-party reimbursement for Clinical Center patients; and a review of the trans-NIH applicability of the Institute of Medicine's (IOM) recommendations regarding NCI-supported clinical trials.

FY2013 Appropriations. The President's FY2013 budget was announced February 13, 2012. It includes flat funding for NIH and NCI—$5.07 billion ($2.7 billion over the FY2012 enacted level). The House FY2013 Appropriations Hearing will take place on March 20, but more in the format of an oversight hearing about the National Center for Advancing Translational Sciences (NCATS) as opposed to an appropriations hearing for the NIH. There will be two panels of witnesses, the first consisting of NIH Director Dr. Francis Collins and Acting Director of NCATS Dr. Thomas Insel. The second panel will be a group of industry representatives. Subcommittee Chairman Denny Rehberg (R-MT) supported an increase for NIH in FY2012, and visited the campus on November 28 to tour the Clinical Center and meet with a variety of researchers, including a group of NCI researchers and Dr. Doug Lowy. The Senate FY2013 Appropriations Hearing will take place on March 28. Dr. Collins will testify, and several of the Institute/Center Directors; Dr. Harold Varmus, NCI; Dr. Anthony Fauci, National Institute of Allergy and Infectious Diseases (NIAID); and Dr. Griffin Rodgers, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), will accompany Dr. Collins to answer questions. Given the election year, it is unlikely that any FY2013 appropriations bills will pass before the end of the fiscal year, and a series of Continuing Resolutions appears likely.

There are significant looming budget issues. The Budget Control Act of 2011 raised the debt ceiling but required significant deficit cuts over a 10-year period, which the bipartisan "Super Committee" failed to achieve last fall. The consequence, as laid out in the Budget Control Act, is a sequestration, or across-the-board cuts, to bring the spending level down to what is required by the law (a $1.2 trillion savings over 10 years). Calculations from the Center for Budget and Policy Priorities show that a nondefense sequestration of $54.7 billion in 2013 would result in cuts of approximately 9.1 percent in nonexempt, nondefense discretionary programs (e.g., NCI) and 8.2 percent in nonexempt mandatory programs. There are just a few exempted categories (e.g., Pell grants, Veterans Administration (VA) medical care). There is congressional concern about such drastic budget cuts, but at this time it is not clear if Congress will be able to find a way around sequestration.

Legislation of Interest. Three bills have been introduced in an attempt to address the drug shortage issue, which recently was exacerbated by the Ben Venue Laboratories shutdown. Senators Klobuchar and Casey introduced the Preserving Access to Life-Saving Medications Act (S 296) on February 17. Representatives DeGette and Rooney introduced a similar act (HR 2245) in the House on June 21. These acts require manufacturers to notify the Food and Drug Administration (FDA) of

discontinuance, interruption, or disruption that would result in a drug shortage. The Department of Health and Human Services (HHS) must implement evidence-based criteria to identify drugs vulnerable to shortages. The Drug Shortage Prevention Act (HR 3839), introduced by Representatives Carney and Bucshon, seeks to address a number of possible short-term fixes to the drug shortages that can be implemented fairly quickly, including establishing a "national critical drug list"; expediting review of generic applications by FDA; and conducting a feasibility study of a "national contingency plan." Each of the bills requires FDA notification when manufacturers anticipate a shortage. Being notified that a shortage is coming is helpful, but FDA may not be able to do anything about the shortage. For clinical trials that use drugs that are in shortage as control treatments, there either need to be changes in the treatment or the trials must be suspended. The drug shortage bills that have been introduced represent congressional interest in fixing the problem but not the tools or solutions for resolving it.

There are three "must pass" bills related to FDA—the Prescription Drug User Fee Act (PDUFA), the Medical Devices User Fee Act (MDUFA), and the Generic Drug User Fee Act (GDUFA)—currently pending. These bills must pass in the fall; otherwise, FDA is not legally permitted to collect user fees, which comprise a significant portion of FDA's budget.

The House Energy and Commerce Committee held a hearing on the drug shortage issue on September 23, 2011. Representatives from HHS and FDA testified at the hearing. On March 6, 2012, Secretary Sebelius testified on the issue for the House Appropriations Subcommittee. One of the appropriators, Representative Kay Granger, asked about shortages of pediatric cancer drugs. The issue of drug shortages has refocused congressional attention on cancer treatment and research and presents NCI and FDA with a united opportunity to educate Congress about the connection between the supply of drugs for clinical trials and the entire pharmaceutical industry.

Questions and Discussion

Dr. Abbruzzese asked NCI staff whether there is a contingency plan in place should the Institute have to take a 9.1-percent funding cut as a result of sequestration. Dr. Doroshow responded that NCI is preparing for the consequences of sequestration. At the 2011 NCI Leadership Retreat, all of the Division Directors were asked to prepare budgets that would deal with major funding cuts. Ms. Holohan added that should sequestration occur, there could be protection for some Federal programs, in which case there may be some congressional requests for information from NIH and/or NCI.

Dr. Richard Pazdur, Director, Division of Oncology Drug Products, FDA, commented that given current commitments, the 9.1-percent cut may leave few options for new funding opportunities.

Ms. Roach asked how NCI is reaching out to the advocacy community regarding the congressional appropriations hearings. Ms. Holohan replied that NCI's Office of Advocacy Relations is in a constant dialogue with the advocacy community about congressional activities affecting NIH. For example, Representatives Carolyn Maloney and Darrell Issa introduced the Research Works Act that would essentially destroy public access to research papers. There was a substantial response from the advocacy and research communities, and the sponsors ultimately withdrew the bill.

IV. CHANGING THE FACE OF NCI-SUPPORTED EARLY-PHASE THERAPEUTIC TRIALS—DRS. JAMES H. DOROSHOW, S. PERCY IVY, PATRICIA M. LORUSSO, AND BARBARA A. CONLEY

Dr. Doroshow described NCI's approach to early-phase therapeutics and some of the proposed restructuring activities. Clinical trials data from 2008-2010 reveal that the issue with early-phase therapeutics, and even with the progression of drugs into later-stage development, is that most of the molecules that are tested preclinically are ineffective. Issues that were major problems 10 to 20 years ago—namely, bioavailability and pharmacokinetic instability—are no longer the reasons why drugs fail. The barrier to cancer drug development is making the effective transition from early-phase therapeutics (Phase I to mid-Phase II) to larger studies.

One outlet through which NCI has been engaged in early-phase drug development is the Phase I (U01) program. NCI has associations with outstanding academic investigators, almost all of whom are located at one of the NCI-designated Cancer Centers, to conduct either first-in-human trials or trials of novel combinations. The U01 program is relatively modest but accrues a substantial number of patients (898 to 1,290 per year) across the 14 U01 sites. There are 80 active Investigational New Drugs (INDs) held in support of the program. This program has been very successful and has led to the development of many important drugs entering the clinic. However, the field of targeted therapeutics has changed significantly over the past 10 years and the U01 program needs to be restructured to reflect those changes in drug development. Challenges that need to be addressed moving forward include the fact that while new agents may be very active in tumors with specific mutations or other defined genotypes, smaller patient populations with the specific molecular characteristics must be identified. Biomarker-driven studies will require multisite participation. A program of sufficient breadth and flexibility that is capable of rapidly adapting to variable accrual needs is required across multiple sites. Additionally, resources need to be developed that can support scientific requirements and Internal Review Board (IRB) review in early-phase trials across sites.

In transitioning to the future, NCI must choose agents for early trials only if the timeframe allows for development of an appropriately qualified molecular marker. Agents to be developed must be able to be brought into the clinic under conditions that could demonstrate proof of mechanism in early studies. The transfer of the full range of tumor biology expertise that exists uniquely in NCI's major translational programs should be facilitated into the NCI Experimental Therapeutics Program (NExT) pipeline through development of a new Early Phase Network. An essential part of this new Network will be to provide core laboratory resources to ensure that for every clinical trial supported by the Division of Cancer Treatment and Diagnosis (DCTD), there will be an understanding at its conclusion of why the trial succeeded or failed. Most of the U01 sites that NCI currently funds, and is likely to fund in the future, are located at NCI-designated Cancer Centers.

The new Early Phase Network will seek to make their interactions among collaborators more effective. The Network will serve as a nexus for enhanced collaboration across NCI-sponsored programs by providing broader access to critical pharmacodynamic and clinical genomic core resources for early-phase clinical trials utilizing facilities in Frederick, Maryland, and/or extramural core laboratories. It also will ensure standardization of clinical genomic and molecular marker testing, as well as data handling, storage, and analysis in concert with NCI's overall clinical genomics program. The reprogramming of current resources to a smaller number of early-phase clinical sites performing fewer trials should support critical imaging studies, repetitive biopsies for molecular characterization, core tissue handling and storage resources specifically for early-phase trials (which are not currently available), as well as

utilization of translational cores now funded by NCI Cancer Center, P01, and SPORE grants by early-phase trialists.

Dr. Doroshow stated that the purpose of today's discussion on the early-phase program is to glean input from the CTAC members on how to redefine NCI's early-phase clinical trials model. In addition to gaining input from the CTAC, NCI needs to develop a national consensus around a redefined early-phase model. NCI also needs to enhance the capacity of the new NCI-Frederick Molecular Characterization Laboratory and the clinical assay development network initiated with American Recovery and Reinvestment Act (ARRA) funds in the area of specific multi-analyte assays (i.e., next-generation sequencing panels of targeted mutations or exome-capture sequencing). NCI needs to develop the additional data acquisition, storage, and analysis capabilities in concert with the extramural community to support a modern early-phase network that will conduct trials at multiple sites based on the availability of an expanding range of molecular information (that must ultimately be placed in a confidential but widely accessible database). Lastly, NCI needs to work with industry partners to establish a process by which molecular characterization data will be developed, utilized, and shared over multiple, sequential clinical trials that involve a variety of agents (from different companies) and that a single patient may enter.

Some major concerns moving forward are that fewer, but better-resourced sites will be required to perform substantially more sophisticated clinical investigations; however, Network sites will have to interact with a much larger group of academic/industry collaborators than currently is the case. There will be many more, and more complicated, components to the new Network. A database sufficient to hold new clinical genomic information will need to be established that is quantitatively and qualitatively different than those currently available. In addition, a molecular analysis and reporting pipeline will need to be developed and validated. Other concerns are that a new core of (likely extramural) bioinformaticians will need to be recruited to participate in this effort, and pharmaceutical collaborators will have to agree to the sharing of patient response data and permit NCI and affiliates to use these data for future clinical research studies.

Questions and Discussion

Dr. Nancy E. Davidson, Director, University of Pittsburgh Cancer Institute, asked whether the new Early Phase Network will incorporate only Phase I sites or Phase I and Phase II. Dr. Doroshow said that NCI is envisioning that the Early Phase Network will continue to focus on Phase I sites for now. Ultimately, Phase I and Phase II sites will be merged into one program.

Dr. Villalona-Calero commented that bringing investigators together from different institutions is often difficult due to institutional bureaucracy; bringing together investigators from the same institution is easier.

Dr. George J. Weiner, Director, Holden Comprehensive Cancer Center, asked whether the new Early Phase Network will be able to utilize the NCATS infrastructure. Dr. Doroshow responded that he is not sure how much funding NCATS has available to be able to support NCI's early-phase therapeutics.

Dr. Frank M. Torti, Director, Comprehensive Cancer Center, Wake Forest University School of Medicine, commented that some of the barriers to acquiring an IND for a drug at Cancer Centers include formulation; chemistry, manufacturing, and control (CMC); and toxicology—aspects of drug development that the NExT program, and the Rapid Access to Intervention Development (RAID) program before it, supported. Dr. Torti asked where support of these aspects will fit into the new Early Phase Program. Dr. Doroshow stated that in the two years that the NExT program has existed, over 350

applications have been received and a series of novel, high-risk targets have moved into high-throughput screens. The NExT program has the resources to move from target validation through formulation into the Early Phase Network. Before the Early Phase Therapeutics Network RFA is released a year from now, additional core resources in genomics will be built.

Dr. Peter C. Adamson, Chair, Children's Oncology Group, and Chief of the Division of Clinical Pharmacology and Therapeutics, The Children's Hospital of Philadelphia, commented that conducting early-phase trials exclusively within networks requires infrastructure support. In developing the Early Phase Therapeutics Network, infrastructure that can support multi-institutional trials needs to be built as opposed to leveraging of existing infrastructures. Dr. Adamson added that there should be a graded approach to bringing drugs into the clinic. Because not everything is known about a drug for a disease until it is brought into the clinic, a graded introduction could preserve resources.

Dr. Kevin J. Cullen, Director, University of Maryland Greenebaum Cancer Center, expressed concern over using up resources quickly by conducting full-exome sequencing and molecular imaging on every patient.

Dr. Gillian M. Thomas, Professor, University of Toronto Odette Cancer Center, recommended supporting infrastructure that will link the large patient bases available through the Cooperative Groups with early drug development. Dr. Monica Bertagnolli, Professor of Surgery, Harvard Medical School, Brigham & Women's Hospital, Dana Farber Cancer Institute, echoed Dr. Thomas' comments. As the Cooperative Groups are reorganized and redesigned, they need to take on a dual role of being an operations center and a facilitator of science.

One CTAC member asked whether this is the first presentation of NCI's redesigned early-phase therapeutics program. Dr. Doroshow responded that NCI has had conference calls and face-to-face meetings with Phase I and II investigators; Dr. S. Percy Ivy, Associate Branch Chief, Investigational Drug Branch, Cancer Therapy Evaluation Program, DCTD, has made presentations to the SPORE PIs, and there will be multiple teleconferences or Webinars with the Cancer Center directors. DCTD is seeking input from every venue possible.

Redesign of the DCTD Early Experimental Therapeutic Program. Dr. Ivy continued the presentation on the redesign of the early experimental therapeutics program, which is still in the input-gathering phase of the redesign process.

The Early Phase Therapeutics Network faces three major challenges: (1) accrual; (2) development of biomarkers; and (3) translation. As early-phase trials focus on smaller patient populations that have been identified via a highly specific molecular fashion, the number of patients that can be accrued to these studies will diminish. For example, if a biomarker is expressed in 10 percent of patients, 100 patients will have to be screened to identify 10 to enroll on a trial. Studies will require multisite/multidisciplinary participation, and the Early Phase Therapeutics Network will have to be a flexible program that can rapidly adapt to accrual needs. Additionally, resources will have to be developed that address scientific and IRB review issues. Moving forward, validated integral biomarkers will be needed for patient selection and tumor characterization. A strong translational component also will be needed in the Network. Technology expertise and an understanding of mechanism of action and resistance, proof of concept and mechanism, and molecular characterization will help build this translational component.

DCTD/CTEP (Cancer Therapy Evaluation Program) has two primary goals for the Early Phase Therapeutics Network. The first is to optimize the integration of the experimental therapeutics program with NCI/DCTD-funded assets and programs. Achieving this goal will entail development of

interdisciplinary teams and promotion of collaboration between preclinical and clinical investigators. The second goal is molecular characterization of patient tumors to enable evaluation of proof of concept, proof of mechanism, combinations, and resistance. This will require resources for collection (with biopsies), tumor banking, and analyses.

New agents are identified for development within DCTD through the Special Emphasis Panel (SEP). The SEP reviews a large number of agents and prioritizes them for NCI development. There is a great deal of internal action within NCI in defining the agent development plan, determining funding allocation, and allocating the resources. Input is also received from external committees such as the Investigational Drug Steering Committee (IDSC). The IDSC provides extensive input directly and through its task forces on optimization of NCI's development of new agents. The new agents enter clinical trials through the activation of studies at U01/N01 sites. The number of INDs in NCI's early experimental therapeutics program is around 95. DCTD actively is working to identify agents and pathways so that agents can optimally be combined.

The early experimental therapeutics program is evolving in three aspects. The first is that DCTD wants to take a more team-science-focused approach. Secondly, DCTD wants to molecularly profile every patient enrolled on an early experimental therapeutics clinical trial. Lastly, there will be enhanced collaboration both within NCI/DCTD and with other NCI-sponsored programs, including SPOREs, Cancer Centers, mouse models consortia, grantees (P01s), etc. The ideal translational clinical research process will be to identify patients eligible for early-phase clinical trials; analyze tumor and other tissues for pathway activation or resistance; assign patients to trials based on the molecular characterization of their tumors; monitor patients during the course of the study, which will involve obtaining additional tumor biopsies; and, at conclusion of the trial, conduct posttreatment molecular reanalysis of the patients. Molecular characterizations obtained from patients will enter back into basic cancer biology laboratories to enhance NCI's understanding of the science of cancer biology. The new team-science-based approach of the Early Phase Therapeutics Network will be investigational agent specific. The drug development team will consist of clinical scientists, translational scientists, and cancer biology scientists.

Dr. Ivy summarized the changing early experimental therapeutics program. The redesigned program should learn from every clinical trial performed. Each patient's tumor should be molecularly characterized to inform current and future drug development. The focus of the Early Phase Network primarily should be on defining proof of mechanism; proof of concept; target engagement; and comprehensive, multiphase tumor evaluation. NCI funds many translational and cancer biological grants and Cancer Centers that could be leveraged in this effort. Lastly, NCI's early drug development should be scientifically focused and complement the pharmaceutical industry, whose primary goal is drug approval.

Questions and Discussion

Dr. Abbruzzese commented that it seems that NCI is looking at the same target agents that the pharmaceutical industry is covering. With the pharmaceutical industry's motive for profit, they are not necessarily interested in taking on high-risk agents. Dr. Abbruzzese asked whether NCI's early drug development program will focus on agents for which the pharmaceutical industry has no interest or where the targets are not yet well characterized. Dr. Doroshow responded that one of the review criteria of the Special Emphasis Panel is novelty in high-risk target development. Additionally, if one looks at NCI's partners in the early drug development process, one could note a substantial increase in the number of small biotechnology companies, many of which have novel targets. In the most recent round of NExT applications, 40 percent of the applications were from small biotechnology firms. Dr. Doroshow noted that almost all of the applications that are successful are then purchased by large pharmaceutical

companies. Dr. Ivy added that from NCI's discussions with the pharmaceutical industry, pharma's focus is on identifying drugs that hit driver mutations; these are usually single targets. One of the goals of NCI's early-phase program is to complement pharma by focusing on other targets.

Dr. Villalona-Calero added that the IDSC looks carefully at drugs brought in for partnership with pharma so as to not overlap efforts. For example, a drug may be developed by pharma for lung or breast cancer because those are large markets, but it may not be developed for a thyroid cancer or a pediatric tumor.

Dr. Ivy commented that at last year's American Society of Clinical Oncology (ASCO) meeting, NCI representatives met with a number of NCI's industry partners; these partners expressed that they are not currently prepared to undertake the depth of molecular characterization toward which clinical studies are moving. NCI can complement this aspect of early-phase clinical studies.

Ms. Roach asked what the timeline is for seeing some of these novel agents enter the clinic. Dr. Doroshow replied that the earliest projects started receiving support two years ago and are likely another two years away from first-in-human trials.

Ms. Roach also asked Dr. Doroshow to expand on the pilot program being initiated at the Clinical Center to test some of the new approaches to early-phase drug development. Dr. Doroshow said that NCI is still in the developmental phase of trying to understand in a randomized manner whether or not genomic characterization along a specific set of genes not known to predict for response or resistance are actually predictive. The idea of the pilot program is to understand prospectively whether this approach is useful. This effort will begin in the fall at the Clinical Center and eventually will be expanded to the entire Phase I and II program nationally.

Dr. Susan G. Arbuck, President, Susan G. Arbuck, M.D., LLC, urged identifying specific objectives in different settings (i.e., pharmaceutical company versus small biotechnology company) before trying to redesign the program.

Dr. Abbruzzese commented that one of the practical areas in which substantial work needs to be done is the acquisition of biospecimens with appropriate handling, characterization, and quality control. This is central to the early-phase initiative. Dr. Abbruzzese asked whether there are concerns about being able to achieve DCTD's outlined goals because of biospecimen issues. Dr. Ivy responded that this is a very complex issue, but there has been a lot of work done in the area of biospecimen sample acquisition. All of the early-phase studies will require a well-detailed tissue acquisition and handling protocol. The nature of the clinical study will determine how intensive the tissue sampling must be.

Investigational Drug Steering Committee. Dr. Patricia M. LoRusso, Director, Phase I Clinical Trials Program, Barbara Ann Karmanos Cancer Institute, gave a presentation on the IDSC. The IDSC was created in response to recommendations of the Clinical Trials Working Group (CTWG) in 2005. CTWG recommended the involvement of all stakeholders in the design and prioritization of clinical trials that address the most important questions using the tools of modern cancer biology. This led to the formation of the IDSC, which makes recommendations to NCI regarding agents for early-phase trials, and to the formation of the Disease-specific Steering Committees (DSSCs), which develop later-phase trials.

The goals of the IDSC are to provide external strategic input into prioritization of Phase I and II trials for new agents with CTEP at the NCI. The Steering Committee increases transparency of the process and gives input to NCI's Investigational Drug Branch on drug development plans. The IDSC also optimizes clinical trial designs to improve the effectiveness of early-phase therapeutics; increase the

predictive value of early-phase trials, resulting in the design of more successful Phase III trials; and develop a new forum for interaction among grant and contract holders with CTEP. IDSC membership includes the PIs of all NCI Phase I U01 grants and Phase II N01 contracts. Dr. LoRusso currently co-chairs the Committee, representing U01 grantees, with Dr. Villalona-Calero representing N01 contracts. The Committee also includes representatives from Cooperative Groups and liaisons with other Steering Committees, in addition to content/subject experts. The IDSC has nine specific task forces to help accomplish its goals. These task forces focus on: angiogenesis, biomarkers, cancer stem cells, clinical trial design, DNA repair, immunotherapy, PI3K/Akt/mTOR (PAM), pharmacology, and signal transduction.

Dr. LoRusso reviewed the IDSC's accomplishments to date. The IDSC has achieved transparency and enhanced scientific input into NCI's drug development process and has been integrally involved in the review of 24 Clinical Development Plans, 20 of which have moved forward. The Steering Committee reassessed the Letter of Intent (LOI) review process by formulating an LOI Review Working Group to assist in the presolicitation efforts for U01 and N01 investigators. A Career Development LOI (CrDL) program also has been developed for new investigators, resulting in dozens of junior investigators becoming PIs through this mechanism. The IDSC also has identified niches for NCI involvement that are complementary to industry. Additionally, communication between the IDSC and the Disease-Specific Steering Committees is facilitated by designated liaisons. The IDSC is actively working to enhance this process by inviting DSSC members to present to the IDSC during in-person meetings. Targeted DSSC members also will be invited to attend IDSC CTEP agent reviews when specific diseases are being discussed for trials.

The IDSC has published 23 manuscripts during the last several years. The manuscripts focus on Phase I and II clinical trial design, management of drug-related toxicities, and management of common cardiovascular toxicities, as well as hyperglycemia and hyperlipidemia.

The IDSC convened interdisciplinary expert panels to review the pathophysiologies of hyperlipidemia and hyperglycemia induced by mTOR pathway inhibitors and cardiac toxicities such as hypertension, left ventricular dysfunction, heart failure, and myocardial ischemia and infarction associated with antiangiogenic therapies. These expert panels summarized the incidences of these toxicities in the current literature, provided recommendations for clinical trial screening and monitoring criteria, and provided management guidance and therapeutic goals upon occurrence of these toxicities. The Cardiovascular Toxicities Panel published guidelines for management of cardiac toxicity in patients receiving vascular endothelial growth factor signaling pathway inhibitors in the *American Heart Journal,* and the PAM Task Force published guidelines on management of metabolic effects (hyperlipidemia and hyperglycemia) associated with anticancer agents targeting the PAM pathway in the *Journal of Clinical Oncology* in 2012. These publications raise awareness of these adverse events to enable their early recognition and regular monitoring and timely intervention in clinical trials.

In looking at novel clinical trial designs, a Phase I Workshop was held in 2008 that covered optimal planning, design, and conduct of Phase I studies of new therapeutics; approaches to Phase I design focusing on safety, efficiency, and selected patient populations; and guidelines for the development and incorporation of biomarker studies in early clinical trials of novel agents. The findings of this Workshop led to several opinion publications in 2010 in *Clinical Cancer Research (CCR)*. In addition, a series of Phase II opinion papers was published in *CCR* in 2009. Lastly, a manuscript on Phase I agent combinations and recommendations currently is being developed; a draft summary of these recommendations was presented to the IDSC during the March 2012 face-to-face meeting.

The Immunotherapy Task Force has put together an Adoptive Immunotherapy White Paper on the adoptive transfer of immune effector cells against metastatic melanoma, which is a clinically promising and complex procedure. The Task Force put together recommendations on adoptive therapy

and developed a multi-institution Phase II trial, which was adequately powered, randomized, and controlled, with a central facility for cell growth. Pharma is currently conducting a study based on the Immunotherapy Task Force subcommittee white paper. A white paper titled "White Paper on Adoptive Cell Therapy for Cancer with Tumor-Infiltrating Lymphocytes: A Report of the NCI CCCT Subcommittee on Adoptive Cell Therapy" was published in *CCR* in 2011.

The Biomarker Task Force developed guidelines for incorporation of biomarkers into early-phase clinical trials. The Task Force reviewed biomarker trials, peer-reviewed literature, and NCI and FDA guidance documents, and conducted a survey of investigators to determine practices and challenges to executing biomarker studies in clinical trials of new drugs in early development. Based on these efforts, the Task Force published a paper in *CCR* in 2010 that provides standard definitions and categories of biomarkers, and lists recommendations to sponsors and investigators for biomarker incorporation into such trials.

Another of the IDSC's accomplishments is the focused educational sessions at CTEP Early Drug Development meetings, which occur twice a year. Many of the educational sessions have focused on drugs that were either in the CTEP portfolio or about to enter the portfolio to help educate investigators prior to solicitation of LOIs for these agents. The first educational session was on cancer stem cells and focused on the CTEP agent GDC-0449, which is now an FDA-approved agent. The Phase II recommendations led to a Phase II LOI benchmarking project. Biomarker Task Force recommendations led to biomarker assay templates for CTEP/DCTD. There were also educational sessions on JAK-STAT, c-Met, ALK, PIM kinase, and PI3 kinase.

The future directions of the IDSC are to continue to assist CTEP with the Phase I redesign effort and increase expertise on IDSC agent-based Task Forces and ad hoc groups to better assist CTEP with Drug Development Plan reviews. The IDSC will increase trial opportunities with agents already in the CTEP portfolio and continue to develop an effective communication effort in collaboration with DSSCs to inform them of early drug development.

Questions and Discussion

Dr. Abbruzzese asked whether the IDSC will change based on NCI's recommendations for further development (i.e., a smaller number of agents that are better characterized). Dr. LoRusso affirmed that the Steering Committee will evolve as the needs of CTEP and early drug development change. The IDSC brings in many external experts to help meet those needs.

Dr. Olivera J. Finn, Distinguished Professor and Chair, University of Pittsburgh School of Medicine, asked what the Steering Committee's efforts are in terms of recommending sequential, combined use of interesting agents. Dr. LoRusso responded that CTEP and the IDSC are aware of the importance of combination therapy and have worked to bring forward novel-novel combinations. It is currently easier to conduct novel-novel combination studies through CTEP than through almost any other mechanism because CTEP's portfolio cross-fertilizes with different companies. Dr. Villalona-Calero added that the IDSC incorporates basic science and translational science expertise to advise on the combined use of agents.

Dr. Joel E. Tepper, Hector MacLean Distinguished Professor of Cancer Research, Lineberger Comprehensive Cancer Center, commented that direct interaction between the IDSC and the Gastrointestinal (GI) Steering Committee has been difficult. This may be due to the fact that the GI Steering Committee has seven different task forces and a large number of personnel would be required to

get involved with each of the task forces on an ongoing monthly basis. This issue needs to be addressed. Dr. Villalona-Calero responded that interaction with the DSSCs is something the IDSC is working on. Dr. LoRusso added that liaisons from the DSSCs with disease site-specific expertise will be asked to attend the reviews during the IDSC's review of NCI's agent Clinical Development Plans, which will further improve interactions between the IDSC and the DSSCs.

Dr. Lisa A. Newman, Professor of Surgery and Director, Breast Care Center and Multidisciplinary Breast Fellowship Program, University of Michigan Comprehensive Cancer Center, asked whether there are any opportunities for Phase III Cooperative Group investigators to extrapolate on what the IDSC has accomplished in hyperglycemia and hyperlipidemia. Dr. LoRusso answered that the recommendations developed by the PAM Task Force will enhance recruitment to clinical trials. The manuscript was recently published; it may be helpful to present the data at the Cooperative Group meeting.

Cancer Diagnosis Program's Resources to Enhance Biomarker Inclusion in Early-Phase Trials. Dr. Barbara Conley, Associate Director, Cancer Diagnosis Program (CDP), DCTD, presented on the Clinical Assay Development Program (CADP), which is currently in its pilot phase. CADP was implemented because clinical trial protocols often include markers for determining eligibility, stratification, or treatment assignment (integral markers). However, the assays used to determine these markers usually do not meet standards that are required for clinical decision making. Predictive markers and robust means to measure them are urgently needed in the clinic. The analytical performance (analytical validity) indicates how accurately the assay test detects the analyte(s) of interest. Clinical validity refers to how well the test relates to the clinical outcome of interest (e.g., response to therapy or survival). The clinical utility refers to whether the results of the test provide information that can contribute to and improve current management of a patient's disease. Assay qualification is the process of linking a biomarker with biological processes and clinical endpoints to show it is "fit for purpose." Validation of clinical utility and qualification usually require clinical trials.

CADP provides resources but is not a grant. It provides a process and services to efficiently develop diagnostic tests that address clinical needs, including codevelopment of targeted agents and predictive markers. The clinical assays that are developed will meet rigorous performance standards and should speed evaluation of molecularly guided therapy. The components of this Program consist of contracts and program resources. The Clinical Assay Development Network (CADN), the Specimen Retrieval System, and project management are contracted. CADP has in-house statistical and program expertise. The CADN was competitively awarded in 2010; the function of these Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories is assay optimization and analytical validation. The CADN includes the Molecular Characterization Laboratory at NCI-Frederick and eight contracts with outside institutions (three are companies; five are academic institutions). The Specimen Retrieval System (SRS) provides paraffin-embedded and annotated specimens that closely reflect the types of cancers diagnosed and managed in the community setting. The contract for the SRS is with Kaiser Permanente Northwest; this is a large health plan with stable membership and electronic medical records. A natural language processing tool from Harvard was used to scrub identifiable data from these samples.

CADP has three receipt dates yearly. Submission deadlines for 2012 are February 15, June 15, and October 15. The earliest point of entry for utilizing CADP resources is a prototype assay that works in human tissue; the intended clinical use is clearly defined and prevalence data and preliminary clinical validation data are available. Assays that have progressed further but need additional validation also are eligible. Assays that have progressed further may need optimization, transfer to a CLIA-certified laboratory, platform migration, validation of analytic performance, statistical consultation, help with appropriate specimens to refine cutpoints, and assistance with transportability. Applications submitted to

CADP are reviewed by a Special Emphasis Panel of external experts, followed by internal review. Applications finally are reviewed by a Senior Advisory Group. Each review round has different SEP members. There are typically two members from industry, representation from several fields of clinical research, one to two patient advocates, pathologists, and statisticians. Once the assay is accepted into the Program, the necessary contracts are arranged (e.g., with CADN) and tissues are obtained. The project management team overseeing the assay consists of the submitter, the clinical assay development laboratory from CADN, and NCI personnel. Timelines, milestones, and go/no-go decisions are implemented. After CADP, the assay is returned to the submitter to proceed with the planned use.

After three application rounds, there have been 16 applications and 15 applicants. One application was submitted for a companion diagnostic and is currently in project management. One assay ready for task order is intended to be predictive for ALK expression. Another assay under consideration is intended as a predictive and/or prognostic assay for the effectiveness of radiation therapy. Two applicants plan to resubmit their assays after consultation. Through this process, it has become clear that there is an ongoing educational need in the community. When assays are submitted, whether from academia or small biotechnology companies, the intended clinical use usually is not clearly stated. Most can make a reasonable case for the clinical need/impact, but many do not have prevalence data for their markers nor a biologic rationale. The need for specimens is great, and the available formalin-fixed paraffin-embedded specimens from SRS are not adequate. There also is a great need for statistical expertise in the development plan. Because of these educational needs, CADP works with many of the applicants prior to evaluation by the SEP. Statistical consultations have increased and CADP is working to acquire additional tissue resources.

CADP's current activities involve publicizing the Program to NCI-supported clinical trialists. CADP has presented to the IDSC, the National Comprehensive Cancer Network, the American Association for Cancer Research, and ASCO, and conducts conference calls with the SPOREs. A Cancer Centers Webinar will be conducted in March. The Program advertises in journals and individually offers participation in CADP via networking.

Questions and Discussion

Dr. Sledge asked how CADP handles intellectual property (IP) rights. Dr. Conley responded that Program developers were aware that IP would be an issue; IP that is brought in remains with the submitter. Dr. Sledge also asked whether CADP looks at NCI's Phase I and II portfolios when making decisions on which diagnostics to develop. Dr. Conley replied that it is the responsibility of the Senior Advisory Group to take into account NCI's portfolio. At this point, CADP does not encourage the development of specific diagnostics.

Dr. Finn asked whether cellular assays that have not yet been tested in human tissue but potentially could act as an effective substitute for an existing assay will be accepted in CADP. Dr. Conley said that CADP, as currently designed, requires that assays work in human samples before being brought into the Program.

Dr. Cullen asked how the Program will be evaluated and monitored over the next few years to improve or reallocate resources. Dr. Conley responded that CADP is ARRA-funded and has an endpoint. The Program is being evaluated for the possibility of continuing funding once the ARRA funding has ended. As far as evaluation, if a diagnostic enters a clinical trial, that can be considered a success.

Dr. Arbuck asked whether the assay has to be accepted into one of NCI's programs or if it can simply enter CADP for diagnostic support. Dr. Conley said that CADP is interested in predictive and prognostic diagnostics that are not necessarily the subject of Investigational New Drug applications. An assay does not need to be accepted into an NCI program. Dr. Arbuck also asked for clarification on CADP timelines. Dr. Conley clarified that the targeted timeline from submission to project start for accepted projects is four months.

Dr. Villalona-Calero commented that some drugs have been approved with accompanying diagnostic tests. He asked how CADP incorporates development of new assays for drugs that have been approved based on one particular assay. Dr. Conley responded that they do not believe that one approved assay is appropriate for all patient populations and that FDA has procedures for other assays to come in and be approved for such use.

Dr. Adamson asked whether CADP provides regulatory support for Investigational Device Exemption filings. Dr. Conley said that CADP has a working relationship with FDA's Center for Devices and Radiological Health. CADP does not provide funded support but facilitates conversations as to what is needed.

Dr. Davidson asked whether CADP will continue to be funded after ARRA funds are depleted. Dr. Doroshow replied that it depends on the intended use of the Program and whether there is a real demand for the resources. ARRA funds will continue to support CADP for another one to two years.

Dr. Torti commented that CADP is an extraordinarily important program and that it brings a value to the clinical trials equation that currently is lacking.

Dr. Abbruzzese asked whether there are any plans for a broader educational effort, particularly with FDA. Dr. Conley replied that CADP and FDA are in discussion about partnering on this effort.

Ms. Susan G. Braun, Executive Director, Commonwealth, asked how CADP plans to acquire additional specimen samples. Dr. Conley said that CADP has partnered with an institution in Arizona that has a biobank of brain tumors, which CADP has tapped into. Similarly, leukemia centers have leukemia samples that can be utilized by CADP. Statisticians are needed in the Program to determine how few tissue samples are needed to validate the diagnostic. The Resources Development Branch and specimen resource locator help determine where to locate the necessary tissue samples.

V. NCI'S CONSORTIA FOR EARLY PHASE PREVENTION TRIALS—DR. EVA SZABO

Dr. Eva Szabo, Chief of the Lung and Upper Aerodigestive Cancer Research Group, Division of Cancer Prevention (DCP), NCI, gave a presentation on NCI's Consortia for Early Phase Prevention Trials, which supports both Phase I and Phase II clinical trials. Early-phase prevention trials focus on the beginning phases of the carcinogenesis process and, consequently, face a set of unique scientific and logistical challenges. Logistical drug development challenges include the expense and difficulty of biomarker trials requiring tissue acquisition, limited funding opportunities to conduct early-phase clinical trials, and the magnitude and duration of definitive Phase III trials. The unique scientific challenges include target/agent selection, risk-benefit balance, cohort selection, and recognition of efficacy during early clinical development. The risk-benefit balance and efficacy calculation are particularly important at the early stages of research. Benefit is defined as efficacy in preventing cancer and associated morbidity/mortality. Risk is related to adverse side effects that increase morbidity/mortality from other diseases and the tolerability of the intervention (i.e., minor side effects affecting compliance). Indications

of efficacy are obtained from knowledge of the mechanism (e.g., the human papillomavirus vaccine and cervical cancer), preclinical (*in vitro* and animal) models reflective of the complexity of human disease, and observational epidemiology (cohort and case-control studies). An area of investment on which DCP has been focusing aggressively is secondary endpoint analysis from other clinical trials, which is how tamoxifen/raloxifene entered the prevention realm for breast cancer. In order to optimize the risk-benefit balance, researchers must identify subjects who are most likely to develop cancer in a short timeframe and minimize toxicities from the drug. Barriers to optimizing this balance include a lack of adequate risk assessment models for most cancers and an incomplete understanding of carcinogenesis in different target organs.

The objective of the Consortia for Early Phase Clinical Trials is to qualify cancer preventive agents for further clinical development via the conduct of Phase 0, I, and II clinical trials that assess preliminary efficacy and safety. The majority of supported trials are Phase II trials. Secondary goals of the Consortia are to optimize clinical trial designs and investigate intermediate endpoint biomarkers. The Consortia program has six main contractors who then subcontract to additional sites to complete the early-phase studies. The program is currently in the process of recompetition. In its upcoming iteration, there will be Steering Committees comprising the lead PIs from each of the six main contractors (or lead organizations) and select DCP staff. There also will be an External Advisory Committee. Structuring the Consortia in this manner allows DCP to conduct multiple studies in multiple organ systems simultaneously. A study may be open at one site, or multiple sites, depending on the needs.

Dr. Szabo provided two examples of early-phase prevention studies conducted by the Consortia. The first focuses on the drug *myo*-inositol. *Myo*-inositol is a glucose isomer derived from dietary sources (e.g., grains, beans, fruits, rice). It is the source of several second messengers and signaling molecules and has been studied in several small trials of various health conditions. In a variety of animal model systems, *myo*-inositol has been shown to inhibit carcinogen-induced tumors under different settings, including in the setting of mainstream and sidestream smoke exposure. By FDA terminology, *myo*-inositol is classified as Generally Regarded as Safe (GRAS). In 2006, Dr. Stephen Lam performed a Phase I trial looking at maximum tolerated dose of *myo*-inositol in bronchial dysplasia. Patients (10 participants) experienced a very marked reduction in dysplasia. There was also an approximate 14mmHg reduction in blood pressure. Subsequent gene expression pattern studies revealed that the PI3 kinase pathway is activated in smokers with bronchial dysplasia and in lung cancer patients but not in healthy smokers without dysplasia. *Myo*-inositol inhibited PI3 kinase activation in normal bronchial airways in smokers, with resulting regression of dysplasia. This study is a potential new clinical trial model—pathway analysis is performed pre- and posttreatment using a smaller number of participants and shorter interventions. The goal of the next phase of the study is to identify mechanisms of interventions that may have the potential for personalized chemoprevention. A Phase IIb *myo*-inositol chemoprevention trial currently is ongoing. The participants on this trial are 30 pack-year smokers with dysplasia; 110 patients are slated to enroll. Bronchoscopy and spiral computed tomography (CT) will be conducted on participants; they then will be treated with *myo*-inositol or a placebo for six months. The primary endpoint is regression of bronchial dysplasia, while secondary endpoints include gene expression analysis from normal bronchial epithelium to confirm the results of the prior Phase I *myo*-inositol study.

Dr. Szabo presented a second area of emphasis, focusing on the use of agonists of peroxisome proliferator-activated receptorγ (PPARγ) for prevention of aerodigestive cancers. Pioglitazone is a PPARγ agonist approved for type II diabetes mellitus. In cell line studies, PPARγ activation induces growth arrest; in animal carcinogenesis models, agonists reduce incidence and multiplicity in the rat tongue model. Epidemiologic studies of pioglitazone show decreases in lung cancer or head and neck cancer in diabetics treated with pioglitazone. A small Phase IIa study of pioglitazone in 22 oral leukoplakia (precursor to oral cancer) patients was conducted. There was an 81-percent clinical response rate and an average reduction of 79 percent in the size of the lesions. Two pioglitazone trials currently are being

conducted by the Consortia. One is a Phase IIb oral leukoplakia trial. One hundred patients at 11 sites are expected to be enrolled on the trial; they will be given pioglitazone or placebo for six months; the primary trial endpoint is clinical and pathologic response. A pilot presurgical non-small-cell lung cancer (NSCLC) trial also is being conducted. Twenty patients who are awaiting surgery will receive a short (two to six weeks) treatment of pioglitazone prior to definitive surgery. Gene expression analyses in addition to standard immunohistochemical analyses will be conducted on the tumor samples pre- and posttreatment, as well as on the normal bronchial epithelium.

Dr. Szabo summarized areas of emphasis for the new iteration of the Consortia program. Emphasis will be placed on understanding the biology of carcinogenesis. Pilot studies integrating high-throughput technologies to understand mechanisms of carcinogenesis and drug action will be conducted. The Consortia also will expand to new scientific areas such as immunoprevention. Old drugs will be repurposed for prevention, with an emphasis on drugs affecting multiple chronic diseases (e.g., aspirin, antidiabetic agents). Intermediate endpoint biomarkers as surrogates for cancer incidence will remain a critical goal of the Consortia; collaborations with the Early Detection Research Network (EDRN) will be key. The Consortia will continue to focus on integration of risk assessment strategies into trials to identify the highest-risk populations. Minimizing toxicity through combination therapies, alternative delivery schedules, and regional drug delivery is also a goal of the Consortia. Finally, emphasis will be placed on developing a centralized biorepository.

Questions and Discussion

Dr. Peter G. Shields, Deputy Director, The Ohio State University Comprehensive Cancer Center, asked for clarification on how the drug dosing is chosen for the trials. Dr. Szabo explained that the maximum tolerated dose (highest approved dose in use) is often used for the first study; subsequent studies may focus on dose de-escalation before use in larger trials.

Dr. J. Phillip Kuebler, Principal Investigator, Columbus Oncology Associates, Inc., asked whether there is a clear mechanism for moving potential prevention agents that show adequate efficacy and safety into Phase III trials. Dr. Szabo responded that the DSSCs will facilitate that process; however, this mechanism will need to be polished when the Consortia is ready to move on to a Phase III study.

Dr. Kenneth H. Cowan, Director, Eppley Cancer Center, commented that the risk-benefit and toxicity profiles change dramatically in increasingly high-risk patient populations. Dr. Cowan asked whether there will be integration with other programs to facilitate the conduct of prevention trials in high-risk patient populations. Dr. Szabo responded that EDRN is a natural partner for this effort.

Dr. Scott M. Lippman, Professor and Chair, Department of Thoracic/Head and Neck Medical Oncology, M.D. Anderson Cancer Center, commented that early-phase cancer drug development is a difficult field but is critical to support of personalized cancer prevention therapies.

Dr. Adamson commented that oncology drug development is different from drug development in any other field of medicine. He suggested learning from other drug development models in building the early-phase prevention drug development program.

Dr. Abbruzzese asked how many trials and discrete agents are currently in development through the Consortia mechanism. Dr. Szabo reported that since 2003, there have been about 60 completed and ongoing trials on approximately 40 different agents.

VI. NEW BUSINESS—DR. JAMES L. ABBRUZZESE

Dr. Abbruzzese thanked the presenters for their participation in today's meeting and the CTAC members for their active discussion. He then encouraged CTAC members to participate in the meeting agenda planning process. Topics to be covered at future meetings include a detailed portfolio analysis of NCI expenditures on clinical trials and overall and minority accrual to clinical trials.

It was noted that many of the members are new to the CTAC and that Dr. Prindiville's office is working on an orientation book for new and existing members. Additionally, the first session of the July meeting, which will be closed to the public, will focus on Committee operations and issues.

VII. ADJOURNMENT—DR. JAMES L. ABBRUZZESE

There being no further business, the 16th meeting of the CTAC was adjourned at 2:13 p.m. on Wednesday, March 7, 2012.