# DEPARTMENT OF HEALTH AND HUMAN SERVICES
# PUBLIC HEALTH SERVICE
# NATIONAL INSTITUTES OF HEALTH
# NATIONAL CANCER INSTITUTE
# 25th CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC) MEETING

**Summary of Meeting**
**November 12, 2014**

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

**CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE**
**BETHESDA, MARYLAND**
**Summary of Meeting**
**November 12, 2014**

The 25th meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was held on Wednesday, November 12, 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 Abbruzzese presided.[1] The meeting was adjourned at 3:05 p.m.

**Chair**
James L. Abbruzzese

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

***Ad Hoc* Members**
David F. Arons
Susan M. Blaney (absent)
Walter J. Curran (absent)
Michael L. LeBlanc
David A. Mankoff
Louis M. Weiner

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

**Executive Secretary**
Sheila A. Prindiville, NCI

**Presenters**
James L. Abbruzzese, MD, Chief, Division of Medical Oncology and Associate Director for Clinical Research, Department of Medicine, Duke Cancer Institute, Duke University Medical Center
Jeffrey S. Abrams, MD, Associate Director, Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), NCI
James H. Doroshow, MD, Deputy Director for Clinical and Translational Research, NCI
Susan Erickson, Director, Office of Government and Congressional Relations, NCI
Lee J. Helman, MD, Senior Investigator, Pediatric Oncology Branch; Scientific Director for Clinical Research, Center for Cancer Research, NCI

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

Susan L. Holbeck, MD, Biologist, Information Technology Branch, Developmental Therapeutics Program, NCI

S. Percy Ivy, MD, Associate Chief, Investigational Drug Branch, CTEP, DCTD, NCI

J. Philip Kuebler, MD, PhD, Principal Investigator, Columbus Community Clinical Oncology Program, Columbus Oncology and Hematology Associates, Inc.

Holly A. Massett, PhD, Senior Behavioral Science Analyst, Clinical Trials Operations and Informatics Branch, CTEP, DCTD, NCI

Worta J. McCaskill-Stevens, MD, MS, Chief and Head of Breast Cancer Prevention, Community Oncology and Prevention Trials Research Group, Division of Cancer Prevention, NCI

Margaret M. Mooney, MD, Chief, Clinical Investigations Branch, CTEP, DCTD, NCI

Geoffrey I. Shapiro, MD, PhD, Director, Early Drug Development Center, Dana-Farber Cancer Institute

## TABLE OF CONTENTS

## WEDNESDAY, NOVEMBER 12, 2014


I. Call to Order and Opening Remarks ..... 1
II. Deputy Director's Report ..... 1
Questions and Discussion ..... 4
III. Legislative Update ..... 5
Questions and Discussion ..... 6
IV. NCI Intramural Research Program (IRP) Long-Term Planning ..... 6
Questions and Discussion ..... 8
V. NCI's Evolving Late-Phase Clinical Trials System ..... 9
Introduction ..... 9
NCI's Evolving Late-Phase Clinical Trials System: NCTN Overview ..... 10
Prospective Disease-Specific Priority Setting ..... 11
Questions and Discussion ..... 12
Community Oncology Investigator Perspective ..... 15
Questions and Discussion ..... 16
VI. Cell-Based Screens of Drug Combinations at NCI ..... 16
Questions and Discussion ..... 17
VII. Experimental Therapeutics Clinical Trials Network (ETCTN) ..... 17
Overview of ETCTN ..... 17
Questions and Discussion ..... 18
ETCTN: Clinical/Translational Researcher Perspective ..... 19
Insights for the ETCTN: An Analysis of Correction Action Plans (CAPs) for Early-Phase Trials ..... 20
Questions and Discussion ..... 22
VIII. New Business and Announcements ..... 23
IX. Adjournment ..... 23
Appendix ..... 24
Clinical Trials and Translational Research Advisory Committee ..... 24

## I. Call to Order and Opening Remarks

*James L. Abbruzzese, MD*

Dr. Abbruzzese called the 25th meeting of CTAC to order and welcomed participants to the meeting. He also welcomed the new *ad hoc* members—Mr. Arons, Dr. LeBlanc, Dr. Mankoff, and Dr. Louis Weiner—who will join the committee after they complete the clearance process.

Dr. Abbruzzese reviewed the confidentiality and conflict-of-interest practices required of CTAC members during their deliberations. He invited members of the public to send written comments on issues discussed during the meeting to Dr. Sheila A. Prindiville within 10 days of the meeting. An announcement was made that NIH Events Management was videocasting the meeting and that the videocast would be available for viewing following the meeting at http://videocast.nih.gov.

**Motion.** A motion to accept the minutes of the 24th CTAC meeting held on July 16, 2014, was approved unanimously.

## II. Deputy Director's Report

*James H. Doroshow, MD*

Dr. Doroshow provided an update on recent clinical and translational research activities at NCI.

**Recalcitrant Cancer Research Act.** Congress passed the Recalcitrant Cancer Research Act in September 2012. NCI submitted to Congress a report that included scientific frameworks for pancreatic ductal adenocarcinoma (PDAC) in March 2014 and small-cell lung cancer (SCLC) in July 2014. NCI will summarize PDAC and SCLC research activities and awards as well as progress in improving outcomes for individuals diagnosed with these cancers in the NIH biennial reports.

NCI recently created internal action planning groups to track progress for each disease. CTAC will review the progress on the implementation of PDAC and SCLC scientific initiatives over the next few years. Dr. Doroshow asked CTAC to consider creating working groups that would provide external reviews of progress related to the initiatives in the frameworks and identify new scientific opportunities in the two disease sites. Members would include scientific experts, clinicians, and patient advocates.

Progress to date in addressing the recommendations in the reports to Congress is summarized in Tables 1 and 2 below.

**Table 1. Implementation Plans and NCI Activities Related to Pancreatic Ductal Adenocarcinoma (PDAC) Initiatives**

| Initiative | Implementation Plan | NCI Activities to Date |
|---|---|---|
| Understand the biological relationship between PDAC and diabetes | Issue a funding opportunity announcement for expanding research in chronic pancreatitis, diabetes, and pancreatic cancer | Joint National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-NCI Pancreas-Diabetes-Pancreatic Cancer Workshop in June 2013<br><br>Joint NIDDK-NCI request for applications for a consortium for the study of chronic pancreatitis, diabetes, and pancreatic cancer issued in October 2014 |
| Evaluate longitudinal screening protocols for biomarkers for early detection of PDAC and its precursors | Issue a program announcement on the development of novel methods to obtain and interrogate pancreatic tissues containing preneoplastic lesions for early diagnosis in high-risk populations | Development by the Division of Cancer Prevention (DCP) of a funding opportunity announcement |
| Study new therapeutic approaches in immunotherapy | Progress in pancreatic cancer immunotherapy will include:<br>• support of grants on discovery and validation of new immunotherapy targets<br>• rational combination of immune modifiers in preclinical and clinical studies<br>• production of immune-modulatory molecules at NCI Frederick to facilitate initiation of early-phase PDAC immunotherapy trials | Charge to Cancer Immunotherapy Trials Network to design and conduct therapy trials with promising immunotherapy agents for PDAC |
| Develop new treatment approaches that interfere with RAS oncogene-dependent signaling pathways | Identify five high-priority projects for NCI's large-scale program on RAS at the Frederick National Laboratory for Cancer Research | Measurement of PDAC-related progress in the five high-priority RAS projects through periodic reports, publications, and presentations |

**Table 2. Implementation Plans and NCI Activities for Small-Cell Lung Cancer (SCLC) Initiatives**

| Initiative | Implementation Plan | NCI Activities to Date |
|---|---|---|
| Build better research tools for the study of SCLC | Support infrastructure via collaborative projects over the next 3 years across NCI's research networks to expand the generation of patient-derived xenografts and conditionally reprogrammed cell lines from SCLC biopsies | Provision of supplemental funding to approximately 12 cancer centers and 12 NCI Community Oncology Research Program sites to collect specimens that can be used to develop patient-derived xenograft models |
| Expand comprehensive genomic profiling studies of clinically annotated SCLC specimens | Characterize the genetic and molecular features of SCLC specimens collected at diagnosis and relapse over the next 3 to 5 years | Receipt of assurance from The Cancer Genome Atlas that resources will be available to conduct the planned genetic and epigenetic analyses once specimens are collected |
| Investigate new diagnostic approaches for populations at high risk of developing SCLC | Issue program announcements for studies to discover early molecular changes in histologically normal lung, blood, and other relevant tissues that could be applied to screening studies in high-risk populations | Development of a program announcement by DCP for publication within the next calendar year |
| Focus therapeutic development efforts on specific molecular vulnerabilities of SCLC | Issue a program announcement in the second half of 2015 for studies focused on understanding how the molecular vulnerabilities of SCLC could be used to develop target agent combinations | Development of a program announcement by the Division of Cancer Therapeutics and Diagnosis for publication within the next calendar year to develop targeted agent combinations *as well as* better understand the rapid development of clinical resistance to drug and radiation therapy |
| Examine the mechanisms underlying both the high initial rate of response to primary SCLC therapy and the rapid emergence of drug and radiation resistance following completion of therapy | Issue a program announcement in the second half of 2015 for studies to better understand the rapid development of clinical resistance to drug and radiation therapy | |

**Motion.** A motion to form a CTAC PDAC Working Group and a CTAC SCLC Working Group to assess progress on the implementation of the Recalcitrant Cancer Research Act initiatives and identify new opportunities was approved unanimously.

**Redesign of the NCI Website.** Mr. Peter Garrett, Acting Director, Office of Communications and Public Liaison, described the first redesign of the NCI website in more than 10 years. The website currently receives four million unique visitors each month. Many are people with a new cancer diagnosis or their family members or friends. The site is also visited by patient advocates, health professionals, researchers, and industry representatives. The new design will provide resources targeted to all of these audiences, be compatible with a range of electronic devices, and be easy to use. The redesigned website will prominently feature clinical research, including clinical trials. The intent is to highlight clinical research and NCI's mission as well as provide information about cancer. NCI is conducting usability testing of the redesigned website with representatives from key audiences.

**2014 Cancer Clinical Investigator Team Leadership Awardees.** The Cancer Clinical Investigator Team Leadership Awards recognize outstanding midlevel clinical investigators at NCI-designated cancer centers whose participation in NCI-funded collaborative clinical trials promotes a culture of clinical research. The awards also encourage the retention of clinical investigators in academic research careers. The clinical oncologists who receive these awards, which provide $50,000 per year for 2 years, must devote at least 15 percent of their effort to the activities associated with the award. The 2014 awardees are:

- Neeraj Agarwal, MD, University of Utah Huntsman Cancer Institute
- Robert Chen, MD, City of Hope Comprehensive Cancer Center
- Michael Gibson, MD, PhD, Case Comprehensive Cancer Center
- Theodore Hong, MD, Dana-Farber/Harvard Cancer Center
- R. Kate Kelley, MD, UCSF Helen Diller Family Comprehensive Cancer Center
- Araz Marachelian, MD, MS, USC Norris Comprehensive Cancer Center
- Stergios Moschos, MD, UNC Lineberger Comprehensive Cancer Center
- Rita Nanda, MD, University of Chicago Comprehensive Cancer Center
- Daniel Persky, MD, University of Arizona Cancer Center
- Erin Reid, MD, MS, UC San Diego Moores Cancer Center
- Teresa Rutledge, MD, University of New Mexico Cancer Center

Dr. Doroshow suggested that a future CTAC meeting include presentations by one or two awardees.

**Recognition of Retiring CTAC Members.** Dr. Doroshow thanked the retiring CTAC members—Dr. Bertagnolli, Dr. Newman, and Dr. Torti—for their service.

**Questions and Discussion**

Dr. Mitchell asked whether NCI had tried to connect the Centers for Medicare and Medicaid Services proposal to cover the costs of annual screening for lung cancer with low-dose computed tomography to NCI's efforts against SCLC. Dr. Doroshow replied that Barnett S. Kramer, MD, MPH, Director, Division of Cancer Prevention, and Paula M. Jacobs, PhD, Associate Director, Cancer Imaging Program, have been actively involved in discussions leading to the announcement about the cancer-screening proposal. It was noted that the data on computed tomography scanning from the National Lung Screening Trial for SCLC were disappointing. Screening led to the detection of early lesions in a few hundred patients; however, early detection had no effect on survival. The program announcement that the

Division of Cancer Prevention is developing will focus primarily on molecular markers in blood rather than imaging correlates for early detection of SCLC.

Dr. Abbruzzese asked about the time frame for launching the redesigned NCI website. Mr. Garrett explained that the new site is scheduled to launch on May 15, 2015. He invited CTAC members to send him any additional suggestions for the revised website.

Dr. Mitchell asked whether the redesigned website would have restricted-access pages with information that is not accessible to the entire public. Mr. Garrett said that NCI does not plan to include this kind of site. But the Office of Communications and Public Liaison does plan to support the development of restricted-access sites for divisions, offices, and centers that want them.

Dr. Davidson asked who reviews the applications for the Cancer Clinical Investigator Team Leadership Awards. Dr. Doroshow replied that leaders of the Office of Cancer Centers, the Cancer Therapy Evaluation Program, the Center for Cancer Research, and the Division of Cancer Prevention participate in these reviews. Dr. Prindiville added that some external reviewers also help review the applications and that a senior leadership group makes the final recommendations to the NCI director.

## III. Legislative Update

*Susan Erickson*

**Appropriations.** The House Labor, Health and Human Services, Education, and Related Agencies Subcommittee has not released an appropriations bill or report this year. The Senate Labor, Health and Human Services, Education, and Related Agencies Subcommittee voted to approve a funding bill and report on June 10, 2014, but the full Committee on Appropriations did not pass this bill. The difference in funding between the House and Senate Subcommittee versions is $1.1 billion, a much smaller difference than in previous years.

The federal government is operating under a continuing resolution that will expire on December 11, 2014. This resolution maintains funding at the fiscal year (FY) 2014 levels of $29.9 billion for NIH and $4.9 billion for NCI. Possible actions on FY 2015 appropriations during the current "lame duck" session of Congress are:

1. pass an omnibus bill that includes funding for NIH
2. extend the continuing resolution for the remainder of FY 2015
3. pass a combination of options 1 and 2 ("cromnibus")—one bill with appropriations for certain departments and a continuing resolution for the rest of the government, including the Department of Health and Human Services

**New (114th) Congress.** The new Congress will have Republican majorities in both the House and the Senate; as a result, the proportions of Republicans on congressional committees will increase. No changes were expected in the leadership of either party. All Senate committees will have new (Republican) chairs, and some House committees will have new chairs or ranking members. Anticipated changes in committee leadership include the following:

- Representative Henry A. Waxman (D-CA), ranking member on the House Energy and Commerce Committee, has retired. His replacement has not yet been chosen. Representative Fred Upton (R-MI) will continue to chair the committee.

- Senator Barbara Mikulski (D-MD) will become ranking member of the Senate Committee on Appropriations. It is likely that the new chair will be either Senator Richard Shelby (R-AL) or Senator Thad Cochran (R-MS).
- Senator Jerry Moran (R-KS) will probably chair the Senate Labor, Health and Human Services, Education, and Related Agencies Subcommittee. It is not clear who will replace retiring Senator Tom Harkin (D-IA) as ranking member.
- Senator Lamar Alexander (R-TN) or Senator Mike Enzi (R-WY) could become chair of the Senate Committee on Health, Education, Labor, and Pensions. Senator Patty Murray (D-WA) is likely to become ranking member.
- Representative Hal Rogers (R-KY) will be the chair and Representative Nita Lowey (D-NY) will be the ranking member of the House Committee on Appropriations.
- The chair of the House Labor, Health and Human Services, Education, and Related Agencies Subcommittee has yet to be decided. The ranking member will probably be Representative Rosa DeLauro (D-CT).

The leaders of both parties are currently sorting out their priorities for the new Congress. Representative Fred Upton (R-MI) has announced the intention to continue to advance the 21st Century Cures Initiative, which aims to accelerate the pace of cures and medical breakthroughs.

**Questions and Discussion**

Dr. Helman asked whether Congress could simply extend the continuing resolution until the new Congress takes office in January 2015. Ms. Erickson replied that Congress could pass a short-term continuing resolution.

## IV. NCI Intramural Research Program (IRP) Long-Term Planning

*Lee J. Helman, MD*

**Long-Term Plan for the NCI IRP.** In response to a request from Francis S. Collins, MD, PhD, NIH Director, all IRPs at NIH recently developed long-range plans. The NCI IRP's plan has the following goals:

- support the NCI mission by identifying timely projects for broad collaborations across the NCI IRP
- strengthen trans-NCI and trans-NIH collaboration
- expand opportunities for collaboration with extramural investigators and/or industry
- develop new ways to improve the use and fiscal health of the NIH Clinical Center
- identify new organizational elements and cultural features that further enhance the distinctiveness and success of the NIH IRP
- identify barriers to achieving these goals

NIH required all institutes to submit their IRP plans on August 10, 2014. These plans were combined into a single document to be reviewed by the Advisory Committee to the Director of NIH on December 12, 2014.

**Distinctive Features of the NCI IRP.** NCI's intramural investigators are distinguished, with membership in such prestigious groups as the Institute of Medicine and the American Academy of Arts

and Sciences. The NCI IRP is the largest IRP at NIH; its research ranges from basic biology to population science. The program's focus on patient-based science accounts for more than a third of all clinical activity at the NIH Clinical Center. The NCI IRP has a strong commitment to the study of rare diseases and diseases that disproportionately affect underserved patient populations. Other features include support for long-term projects that would be difficult to sustain with standard extramural funding mechanisms and a commitment to address challenging epidemiological questions.

The IRP's achievements include:

- development of multiple drugs approved by the Food and Drug Administration for cancer and HIV
- development of technology to enable the human papillomavirus vaccine
- contributions to the understanding and treatment of rare cancers
- key studies showing the success of adoptive immunotherapy for cancer
- development of new, commercialized technology for prostate cancer imaging

**Competitive Research Funding Opportunities.** The IRP has created several competitive, time-limited funding opportunities to support novel, high-risk, and/or distinctive science. The Major Opportunities Program supports three ongoing projects aimed at accelerating the development of innovative cancer treatment strategies by exploiting the Center for Cancer Research's (CCR's) technological strengths. The Rare Tumor Initiative applies NCI expertise in basic and clinical studies of patients with rare tumors in the Clinical Center to identify and translate new therapies. A pilot project is addressing desmoid tumors and plexiform neurofibromas. The CCR FLEX Program will enable IRP investigators to explore new opportunities that would be difficult to pursue in their regular research programs.

**Recent Changes.** Recent changes in the IRP include a reorganization of laboratories and branches and the creation of a medical oncology clinical service. The IRP has also changed its approach to reviewing protocol concepts and accelerated the time line for opening them. Finally, the IRP created a protocol support office for staff training and administrative support in protocol development

**Future Scientific Opportunities.** The IRP received 30 proposals for new studies, and the CCR Science Board selected five of these for further consideration:

- precision medicine and prevention—develop precision medicine strategies tailored to several pediatric and rare cancers as well as several tumor types that are already part of the IRP portfolio
- cell-based therapies—drive a new wave of cell-based therapies by combining genome engineering, cell engineering, and immunobiology
- the human microbiome—move the field from descriptive biology to mechanistic insight and meta-organism processes affecting cancer initiation, progression, and therapy
- national program for natural products discovery—identify new molecules that target biological processes central to human disease to create a national resource that is fully accessible to extramural investigators
- human RNA project—lead the development of a comprehensive program for the investigation and therapeutic exploitation of RNA

These studies are included in the draft IRP long-term plan that is undergoing review by the Advisory Council to the Director of NCI.

Another opportunity that the IRP would like to exploit is partnering with the extramural program to address rare tumors. NCI leaders have called for increasing interactions between intramural and extramural investigators.

**Questions and Discussion**

Dr. Louis Weiner is co-chair of the NCI IRP Long-Term Planning Committee. He explained that a priority in the IRP long-term plan is funding research that capitalizes on the IRP's distinctive attributes. The five projects currently under consideration target exciting new areas that would be difficult for extramural programs to address. An important consideration is ensuring that the NIH Clinical Center has the flexibility to accommodate changing priorities at the NIH institutes and centers.

Dr. Helman explained that the Opportunities for Collaborative Research at the Clinical Center uses the U01 funding mechanism to encourage collaborations between intramural and extramural investigators using the Clinical Center's unique resources. NCI funded three of these projects during the first round.

Dr. Takimoto commented that the NCI IRP has served as an important incubator for research programs that began at the IRP and moved successfully to the extramural community. This is a valuable accomplishment. Dr. Helman agreed, adding that many IRP investigators have become heads of departments and NCI cooperative groups. The IRP will continue to emphasize training.

Dr. Newman praised the IRP's emphasis on the study of diseases that disproportionately affect minority populations. Dr. Helman said that minority populations have poorer outcomes for many cancers for both genetic and economic reasons. These populations deserve more intensive study. Dr. Helman added that Kevin Gardner, MD, PhD, Senior Investigator in the Genetics Branch of CCR, is studying breast cancer outcomes in African Americans. Dr. Gardner is working with an extramural researcher who plans to apply for a U01 grant to study the clinical versus genetic factors in the outcomes of this population at the Clinical Center.

Dr. Civin asked whether the precision medicine project would address screening for drug resistance, which is much more expensive than screening for disease. The IRP has a unique ability to conduct genetic screening on a large scale, perhaps in collaboration with extramural researchers through the U01 program. Dr. Helman explained that a substantial amount of research already focuses on identifying resistance mechanisms, and whether the IRP could make a unique contribution to this field is not clear. Dr. Louis Weiner added that the precision medicine concept could include ways to identify not only the right drug for each patient at the right time but also the right combination of drugs.

Dr. Civin suggested that NCI promote the program by highlighting a relevant success story. Dr. George Weiner suggested that the redesigned NCI website provide detailed information on the IRP. He also suggested planning a session on collaborations between intramural and extramural investigators at the 2015 annual meeting of the Association of American Cancer Institutes.

Dr. Davidson asked about the next steps for the IRP's long-term plan. Dr. Helman said that these steps will become clearer when the Advisory Committee to the Director of NIH discusses the plan on

December 12, 2014. Regardless of what NIH decides, this planning process has given NCI an opportunity to review and prioritize the IRP's activities.

Mr. Arons asked about messages for the patient community from the planning process. Dr. Helman hoped that the patient community learns that the IRP activities are part of NCI's overall effort to improve outcomes for patients with cancer.

Dr. Abbruzzese asked about other ways to foster collaborations between intramural and extramural investigators, which would leverage the "incredible" intellectual and financial resources of the IRP. CTAC members expressed a strong interest in having the committee play a more proactive role in this area. Dr. Helman said that NCI needs CTAC's assistance in addressing this need.

Dr. Gray explained that intramural investigators may collaborate on extramural grants as long as they do not receive funding from the grants. Extramural researchers may also participate in research activities at IRP research laboratories. She added that CTAC could form a working group to brainstorm ways to enhance collaborations between intramural and extramural researchers.

## V. NCI's Evolving Late-Phase Clinical Trials System

**Introduction**
*James H. Doroshow, MD*

Changes in our understanding of cancer biology and the ability to move beyond cytotoxic therapies led to the evolution of NCI's late-phase clinical trial system into an integrated network capable of conducting studies based on precision medicine. Over the last decade, the Institute of Medicine, the Clinical Trials Working Group of the National Cancer Advisory Board, and the Operational Efficiency Working Group of CTAC all evaluated the NCI clinical trials program, endorsed the need for a federally funded clinical trials system, and made recommendations to restructure the system. CTAC was established as a direct result of the Clinical Trials Working Group to ensure that the goals for restructuring were achieved and that the system keeps pace with future opportunities.

In response to the recommendations of these groups, NCI has implemented the following changes:

- created an integrated network that is capable of supporting studies that will modify oncologic practice based on the principles of precision medicine
- enhanced the critical infrastructure for national trials (e.g., through a central institutional review board [CIRB], data management systems, and accrual and regulatory support)
- implemented operational efficiency benchmarks
- supported novel clinical trials despite fiscal constraints

The next four speakers described the changes to the system in more detail. Dr. Mooney provided an overview of the integrated NCI National Clinical Trials Network (NCTN), Dr. Abrams explained the process for setting disease-specific strategic priorities and proposed a process for periodic portfolio assessment, Dr. McCaskill-Stevens provided an overview of the revamped NCI Community Oncology Program (NCORP), and Dr. Kuebler provided his perspective on the impact of the restructured system on clinical trial activities at community sites.

**NCI's Evolving Late-Phase Clinical Trials System: NCTN Overview**
*Margaret M. Mooney, MD*

NCI's development of the NCTN began in May 2010 with an extensive review of the Clinical Trials Cooperative Group Program. After receiving stakeholder input on how to redesign the system, the institute received approval of the concept for the revamped system from the NCI Board of Scientific Advisors in November 2011. NCI issued a request for applications for the NCTN in July 2012 and launched the late-phase clinical trial network on March 1, 2014.

Before the NCTN, the NCI late-phase clinical trials program consisted of 10 decentralized cooperative groups in the United States. This system suffered from duplicative administrative and regulatory activities, which impeded the program's efficiency.

The NCTN structure is designed to optimize scientific opportunities through:

- 5 U.S. network groups (four adult and one pediatric) and one Canadian collaborating network group
- 30 lead academic participating sites to provide leadership in development, accrual, and conduct of clinical trials in association with the adult U.S. trial groups
- 7 integrated translational science awards
- 1 radiation therapy and imaging core for quality assurance/quality control in trials
- centralized functions, including a CIRB, cancer trials support unit, and common data management system

The NCTN focuses on phase III, practice-changing, treatment and advanced imaging trials, especially in research areas that are not well supported in a commercial environment. NCTN studies assess:

- combinations of novel and molecularly targeted agents developed by different sponsors
- integration of new agents and imaging approaches into the standard of care
- evaluation of multimodality regimens
- therapies for pediatric cancers, rare cancers, and uncommon presentations of more common cancers
- treatment and imaging approaches already approved for clinical use

The infrastructure that NCI has built (including the CIRB and a shared roster of trial sites) will serve both the NCTN and NCORP. NCORP conducts cancer prevention and control trials, cancer-care-delivery studies, and comparative effectiveness research.

NCI has developed a national strategy for precision medicine within the NCTN. A portfolio of trials spanning early-stage to advanced disease will identify molecular features of tumors with the aim of predicting responses to drugs with a given mechanism and/or mechanisms of resistance. A public database that links clinical outcomes with tumor characteristics will allow other investigators to build on these results. Four trials have been recently opened or will soon be opened:

1. The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST) is evaluating molecularly targeted therapy in early-stage non-small-cell lung cancer by focusing on drugs with activity in advanced lung cancer whose effectiveness in the adjuvant clinical setting is unknown. This effort has three component trials:

    - Screening trial (A151216)—Resected tumors from approximately 7,000 patients with early-stage lung adenocarcinoma will be tested for epidermal growth factor receptor mutations and anaplastic lymphoma receptor tyrosine kinase (ALK) rearrangements. Patients who test positive for either of these molecular changes will be eligible to participate in one of the following randomized adjuvant studies:
        - Erlotinib treatment trial (A081105)—Patients with activating epidermal growth factor receptor mutations are randomized to receive either erlotinib or a placebo following standard-of-care adjuvant therapy.
        - Crizotinib treatment trial (E4512)—Patients with the ALK fusion protein are randomized to receive either crizotinib or a placebo following standard-of-care adjuvant therapy.
    - Patients without one of these mutations receive standard-of-care adjuvant therapy and are examined every 6 months for 5 years.

2. The Lung Cancer Master Protocol (Lung-MAP) is a biomarker study for second-line treatment of squamous cell lung cancer funded by a public/private partnership. This multi-arm, randomized, controlled phase II/III registration trial is testing the tumors of up to 10,000 patients whose advanced squamous cell lung cancer has progressed after first-line chemotherapy. Genomic features in these tumors are used to match patients to a study arm offering therapy for that target.

3. The Molecular Analysis for Therapy Choice (MATCH) program, which will open in early 2015, will examine the molecular features of tumors in approximately 3,000 patients with a variety of solid tumors or lymphoma who have progressed on standard therapy. The study will match at least 1,000 patients to treatment with a targeted drug or combination with the goal of finding an initial signal of activity to test subsequently in a larger trial. NCI hopes to establish 10 to 20 individual drug arms across a spectrum of molecular mutations in NCTN and NCORP sites.

4. The Exceptional Responders Initiative, which is open now, takes the reverse approach to that of the first three trials. It is studying patients who have responded unexpectedly to a drug and looks for molecular mutations or gene expression changes that could explain why that particular patient responded when the drug did not work for others with the same disease. This program is open to NCTN sites, cancer centers, and other research groups.

NCI is planning two additional precision medicine trials for the NCTN. Pediatric MATCH is an umbrella protocol that is similar to the adult NCI MATCH program. The ALK master protocol will compare second-generation ALK inhibitors to crizotinib as first-line therapy in advanced lung cancer.

**Prospective Disease-Specific Priority Setting**
*Jeffrey S. Abrams, MD*

The following principles were recommended by the CTAC NCTN Working Group for the prioritization of NCTN clinical trials:

- establishment of strategic priorities for NCTN trials in advance
- expectation that most concepts will align with strategic priorities
- potential need for additional justification of trial concepts outside strategic priorities
- responsibility of the NCTN groups for concept development
- rigorous evaluation of all concepts for scientific and clinical quality by steering committees, regardless of their alignment with strategic priorities

The planned process for setting disease-specific strategic priorities begins with an assessment of the clinical trials landscape within a given disease to identify gaps and provide context. The NCTN groups propose strategic priorities and discuss the priorities for each disease under the aegis of the steering committees. A few major priorities for each disease are selected by the steering committees. It is envisioned that the steering committees will review and revise these priorities annually in response to new advances. The process is flexible, allowing slightly different approaches for different diseases. The steering committees are currently identifying their priorities and will finalize a strategic priority-setting document by June 15, 2015.

At its July 2014 meeting, CTAC discussed whether a portfolio assessment similar to that performed by the NCTN Working Group over the past 2 years should be performed in the future. Members commented that some form of periodic assessment of clinical trial portfolios was needed to provide feedback to the steering committees and groups and to ensure that trials address the strategic priorities established for each portfolio. Committee members also noted that assessments would benefit from involvement of portfolio-specific experts and, perhaps, a self-assessment by the steering committees, augmented by input from outside experts as needed. CTAC discussed the appropriate time to begin another strategic assessment and concluded that about 3 to 5 years after the initial NCTN Working Group review was reasonable. There was little enthusiasm for convening a cross-portfolio assessment group as large as the NCTN Working Group to conduct the detailed assessments of trials in each disease portfolio. NCI is currently seeking extramural input on the design of such a periodic portfolio assessment process, and a proposed plan should be ready for discussion by CTAC at its next meeting.

**Questions and Discussion**

Dr. Sledge questioned the effectiveness of self-assessments by the steering committees and advocated for external reviews. Dr. Abrams explained that the self-assessments would only be the first step. A CTAC oversight group would review the results of the self-assessments to determine whether the strategic priorities within each disease and across diseases were being met.

Dr. Sledge asked whether NCI plans to use a standardized format for the assessments. Dr. Abrams said that the self-assessments should use a standardized format to provide the CTAC oversight group with a common measure.

Dr. Arbuck reminded everyone of the amount of work involved in the NCTN Working Group portfolio evaluations. She suggested that the reviews be conducted annually but be as simple as possible, without necessarily separating strategy from assessment. They could be operational in nature by describing the committee's portfolio, how it fits with the stated priorities, what the challenges are, and how the steering committee plans to address these challenges. These reviews could include some external

input and be summarized in annual reports that would enable other committees to learn from each other's experiences and avoid problems. Annual reviews would immediately detect and address major issues.

Dr. Abrams explained that the steering committees have until June 2015 to develop their priorities, and they will need another year to begin implementing those priorities. The CTAC oversight group will then assess the steering committees on a rolling basis, reviewing every steering committee over a 3-year period. NCI needs to strike a balance between a comprehensive assessment process and the need to conduct high-quality trials.

Dr. Louis Weiner warned about the need to ensure the rapid advance of novel concepts in areas that might not have been anticipated by the steering committees in their priority setting process. Dr. Abrams responded that the steering committees are composed of senior leaders in a given disease; all committees have translational scientists who will be aware of cutting-edge research; and the committees will be instructed to rigorously review concepts based on their merits, whether or not they address the strategic priorities.

Dr. Munshi asked about the plans for centralization and quality control in the precision medicine studies. Dr. Mooney replied that centralization and quality control are major features of these trials. The extent of centralization for each trial will depend on the state of the science at that time.

Dr. Munshi asked about the amount of money that NCI is saving by replacing the 10 cooperative groups with 5 U.S. network groups and eliminating redundancies and inefficiencies. Dr. Mooney explained that the total budget for the clinical trials enterprise is about the same. NCI plans to fund accrual and the lead academic sites at a higher rate than in the past.

Dr. Mankoff commented that the precision medicine studies focus on targets that are likely to cut across diseases. He asked how NCI could use the new clinical trials infrastructure to address precision medicine. Dr. Abrams said that several precision medicine programs, such as NCI MATCH, are "histology agnostic" and were easily accommodated by the NCTN structure. If pathways increasingly supersede histology, NCI might alter its steering committee structure. However, the tissue of origin still has an impact on outcomes for many tumor types. Dr. Mankoff suggested that NCI periodically revisit this issue as the process evolves.

Dr. Sledge asked when NCI MATCH would end and how NCI would evaluate its success and failure over the long term. Dr. Mooney responded that NCI MATCH will screen 3,000 patients and assign 1,000 to single-arm trials. If insufficient patients with molecular alterations of interest enroll in the single-arm trials, NCI MATCH will end early. Dr. Sledge asked whether NCI would continue the program if it generates a few successes because the program probably will be popular. Dr. Abrams said that NCI would evaluate the program and, if it leads to subsequent randomized phase II trials, the study likely would continue beyond the initial cohort.

Mr. Arons asked whether the steering committees would consult the Food and Drug Administration (FDA) about its strategic priorities. Dr. Abrams said that NCI has no formal plan for such consultations, but the steering committees have FDA observers and their input is welcome. Dr. Pazdur added that his staff provided input on each of the trials discussed during this session as part of FDA's review process.

**NCORP**
*Worta J. McCaskill-Stevens, MD, MS*

NCI began planning NCORP in April 2012. After the institute solicited input from the public and scientific communities, NCI's scientific leadership and Board of Scientific Advisors approved the NCORP concept. NCI released the NCORP funding opportunity announcement in November 2013 and launched the program on August 1, 2014.

NCORP is a community-based national network that builds on the strengths of the NCI Community Clinical Oncology Program (CCOP/Minority-Based CCOP network and the NCI Community Cancer Centers Program). NCORP clinical trials address prevention, cancer control, health-related quality of life, comparative effectiveness, and screening. NCORP also sponsors cancer care delivery research (CCDR) to identify the influences of patients, providers, and organizations on cancer outcomes. All types of NCORP research incorporate cancer disparities research. Finally, NCORP sites enroll patients into NCTN treatment and imaging trials.

NCORP consists of the following components:

- 7 research bases—research hubs that design and conduct multicenter cancer prevention, control and screening/posttreatment surveillance clinical trials, and CCDR studies and that provide an infrastructure (including administration, data management, scientific and statistical leadership, study operational processes and personnel, and regulatory compliance for clinical trials and CCDR)
- 34 community sites—sites that accrue participants to clinical trials conducted by NCORP research bases and to NCI NCTN treatment, imaging, and quality-of-life trials; engage community partners; and support CCDR studies
- 12 minority/underserved community sites—sites with a patient population comprising at least 30 percent racial/ethnic minorities or rural residents that accrue participants to trials conducted by NCORP research bases and to NCI NCTN treatment, imaging, and quality-of-life trials; engage community partners; and support CCDR studies

NCORP conducts research in several broad areas. Research bases can choose the activities that best fit their interests and areas of expertise.

NCORP cancer-prevention studies identify and evaluate interventions to reduce cancer risk and incidence. NCORP cancer control research is designed to reduce the incidence and comorbidity of cancer and its treatments and enhance patients' quality of life. Cancer screening studies evaluate early diagnosis interventions and identify cancer recurrence. Studies in these three areas focus on mechanisms of cancer-related symptoms, biomarkers of risk for treatment-related toxicities, molecularly targeted agents, posttreatment surveillance, management of precancerous lesions, enhancement of accrual of racial/ethnic and other underrepresented populations, and over- and underdiagnosis. NCORP also sponsors research on health-related quality of life or patient-reported outcomes in NCTN treatment trials.

NCORP investigators are working to advance the agenda for treatment- or cancer-related toxicities. For example, a task force is prioritizing research in cardio-oncology. The Division of Cancer Prevention offers a series of webinars on such topics as integrating patient-reported outcomes into clinical trials and standardizing end points.

The CCDR activities are a new component of NCI's community-based clinical research program. Three major categories of CCDR studies are envisioned:

- descriptive observational studies—to document the prevalence and variability of specific cancer care delivery models, approaches, and/or processes
- analytical observational studies—to understand how the multilevel characteristics of care delivery models, approaches, and processes influence quality, outcomes, and access
- interventional studies (including randomized controlled trials)—to test new models, approaches, and/or processes of care delivery to improve quality, outcomes, and access

The CCDR Coordinating Committee will promote and coordinate cross-NCORP scientific collaboration and develop operational procedures for the development, review, and implementation of CCDR within NCORP. The committee will standardize various aspects of CCDR within NCORP, such as data definitions, data collection tools and procedures, and the data infrastructure. The CCDR Steering Committee will set strategic scientific priorities for CCDR in the community setting, provide rigorous scientific reviews for CCDR concepts, and facilitate uptake of evidence-based clinical outcomes from clinical trials.

NCORP will collaborate with the NCI Center to Reduce Cancer Health Disparities in its cancer disparities research. Many opportunities are available for integrating research questions in health disparities into clinical trials and CCDR studies.

The FY 2014 budget for NCORP totaled $97 million. An additional $5.2 million (in the form of one-time supplemental funding) to enhance clinical trial accrual was awarded to community sites. NCORP has more than 50 active or approved clinical trials, including some that began under the CCOP network and transitioned into NCORP.

**Community Oncology Investigator Perspective**
*J. Philip Kuebler, MD, PhD*

Dr. Kuebler highlighted five challenges for NCORP community sites:

1. Uncertainty about the need to restrict accrual to trials for budgetary reasons

2. The nature of the trials themselves—Simple trials comparing one treatment to another, which were common in CCOP, will become less frequent in NCORP. Explaining targeted therapy to patients is time consuming; some patients might not want to wait for their genetic analysis results before enrolling in a trial. Demands on physicians' time that are unrelated to clinical care continue to increase at a time when their funding for clinical trials activity is declining. As a result, community physicians need to accrue patients to trials more efficiently, which is challenging given the amount of funding available.

3. "New initiatives," including CCDR and health disparities research—Community sites have just a year to develop the infrastructure needed to conduct CCDR (which is new for them) even though the CCDR protocols have not yet been developed. Another concern is whether hospitals will support CCDR if they must wait a long time after a grant becomes active to start the trials. Minority recruitment is not a new challenge for community sites, although these sites typically have little experience in health disparities research.

4. Changes in the NCTN—The NCTN minimum recruitment numbers might be difficult for small institutions to meet and are hard to integrate with the restrictions on accrual for budgetary reasons. If these institutions are eliminated from trials, the NCORP community sites could lose access to these institutions' patients, and the sites would lose access to the trials. Research groups want to increase community physician participation, which requires education on how to participate in research networks. In contrast, NCTN standardization of protocols and audits are welcome changes.

5. Regulatory issue—CIRBs are new to some community site investigators. Administrative issues related to names of sites delayed patient enrollment. New reimbursement procedures for study-specific tests are complex and could result in payment delays.

**Questions and Discussion**

Dr. Takimoto asked about competition between NCORP and industry trials in community sites. Dr. Kuebler replied that some community sites use trials sponsored by pharmaceutical companies to bridge funding gaps. He noted that some practices within his NCORP community site are heavily involved in industry-sponsored trials that compete with NCORP trials to accrue patients.

Dr. Mankoff asked whether the NCORP screening and surveillance studies, especially those involving imaging, can be conducted in collaboration with payers. Some of these approaches might be costly. Dr. McCaskill-Stevens replied that payers are involved in NCORP screening trials.

## VI. Cell-Based Screens of Drug Combinations at NCI

*Susan L. Holbeck, MD*

New combination treatments are needed because single agents are rarely curative and patients often relapse after an initial response. NCI has conducted two parallel combination in vitro drug-screening programs.

The first of these, a Large Matrix of Antineoplastic Agent Combinations (ALMANAC), focused on the more than 100 small-molecule oncology drugs that have Food and Drug Administration approval. A search of clinicaltrials.gov showed that trials had been initiated on only 25 percent of these pairs, indicating an untapped potential for active anticancer therapy. NCI combined the approved agents into approximately 5,000 pairs and tested them on each of the cell lines in the NCI-60 human tumor panel. Promising data from these experiments led to a new phase I clinical trial in solid tumors (NCT02211755) that is testing the combination of clofarabine and bortezomib (agents individually used primarily for hematologic cancer). Another combination that showed activity in triple-negative breast cancer lines is also being investigated. NCI will be able to pursue other positive results and more potential leads. The data will be posted on the Developmental Therapeutics Program website after the manuscript has been submitted. NCI ALMANAC included approximately 300,000 experiments at a total cost of $4 million over 2 years.

The second screening study focuses on combinations of 130 investigational agents tested against 70 approved and investigational agents representing known target classes. Each pair of agents is tested in three to five cell lines. To date, NCI has tested 9,000 pairs of these drugs. The experiments generated a fingerprint of activity against various targets and confirmed that, in many cases, test agents with the same

molecular target have similar activity patterns. These agents could be studied in a combination trial similar to NCI's Molecular Analysis for Therapy Choice, where agents are chosen based on the presence of the target. In contrast, in another example, patterns of benefit for three compounds revealed a potential new mechanism for one investigational agent. The data from the second screening study will be made available to the public as allowed by the agreements with the manufacturers.

**Questions and Discussion**

Dr. Abbruzzese asked whether NCI considered additional validation steps for bortezomib and clofarabine, such as using cell lines from patient-derived xenografts, before advancing this combination to a phase I clinical trial. Dr. Holbeck said that patient-derived models have been developed only recently. NCI is assessing pharmacodynamic markers in patients in parallel with the clinical trial. Dr. Doroshow added that decades of data show that if three cell lines show significant activity, a clinical trial is warranted.

Dr. Abbruzzese said that because of the large amount of molecular data available for the NCI-60 cell lines, it is possible to identify a molecular fingerprint for the type of patient that is likely to benefit from a given combination once that combination has been shown to be safe. Dr. Holbeck agreed and added that for bortezomib and clofarabine, NCI determined that three of five cell lines that responded *in vitro* also were responsive *in vivo.* Researchers are now trying to find genes that are similar in the three responding cell lines and could identify patients who are more likely to respond to the combination.

Dr. Civin asked whether a pharmacokinetic or dosing issue was what kept the two xenografts from responding when the same cell lines were sensitive to the bortezomib and clofarabine combination in *in vitro* studies. Dr. Holbeck suggested that the gene expression might have changed when the cell line was transferred into mice. NCI is looking for additional examples of this issue in the data mining.

Dr. Helman asked whether more than one drug with the same mechanism of action was tested in the bortezomib and clofarabine studies. Dr. Holbeck said that bortezomib was the only approved drug with that mechanism of action when the analysis in ALMANAC was done. In the second screening program, NCI used multiple investigational agents for each mechanism of action, and the results show similarities. For example, most kinase inhibitors inhibit the expected target as well as two or three other targets. These targets might be different from those of another kinase inhibitor.

## VII. Experimental Therapeutics Clinical Trials Network (ETCTN)

**Overview of ETCTN**
*S. Percy Ivy, MD*

The goals and objectives of the ETCTN are:

- research and development for new treatments
- tumor characterization in biomarker-driven studies
- enhanced understanding of cancer biology
- education and training for young investigators

As populations of patients decline with the advent of molecularly defined diseases, it is becoming difficult for a single institution to accrue enough patients for a study. At the same time, NCI wants the

ETCTN to be scalable and flexible so that it can adapt rapidly to accrual needs. Developing biomarkers often requires multiple biopsies or functional imaging, which can be challenging in clinical settings.

The steps for clinical translational research and cancer biology in the ETCTN are to identify patients who are eligible for early-phase clinical trials, analyze tumor and other tissues for pathway activation or biomarker evaluation, assign patients to trials based on their tumor's molecular characterization, and monitor patients during and after treatment for response or resistance. Once researchers determine why patients responded or became resistant to a treatment, they can choose the next agent or combination of agents for that patient. The studies include a range of clinical observations (e.g., pharmacokinetics, functional imaging, and tumor and normal tissue pharmacodynamic markers) and molecular characterizations (e.g., sequencing, methylation, and expression arrays).

NCI is using drug project teams comprising experts in clinical and translational sciences and cancer biology. NCI uses the drug project teams to develop preliminary drug development plans and regulatory agreements. NCI then issues an announcement inviting applications from extramural researchers to join the drug project team. NCI selects the final members based on their skills and abilities in desired areas, such as early clinical trials or biomarker evaluation for the agent.

For example, the NCI Experimental Therapeutics Program (NExT) approved AZD9291, an epidermal growth factor receptor inhibitor that targets treatment resistance in non-small-cell lung cancer, on January 17, 2014. The NExT Senior Advisory Committee approved the formation of an AZD9291 drug project team on April 3. NCI issued a call for applications to join the AZD9291 project team on May 20, and the protocol review committee selected the final team on July 9. The entire team or one of its subgroups met 17 times over 10 weeks. NCI signed a cooperative research and development agreement in September 2014, followed by unanimous Investigational Drug Steering Committee approval to develop AZD9291 on October 22. Thus, the time from NExT approval to final steering committee approval was about 9 months. The program's goal had been to decrease this interval from 21 to 15 months.

NCI has redesigned its clinical trials infrastructure to support ETCTN trials. Investigators can now use the Cancer Trials Support Unit website to locate clinical trials in which they can enroll patients. Once NCI approves a trial, a single institutional review board reviews and approves the trial, and NCI can open each trial throughout the network. The Cancer Therapy Evaluation Program (CTEP) now uses a Web-based reporting system for early clinical trials, and the data can be viewed in tabular and graphic format.

The ETCTN began on March 1, 2014, and has approximately 15 protocols. Two drugs have now completed the project team process. NCI plans to evaluate four key domains of the ETCTN: adoption/implementation, team science approach, clinical trial performance, and network synergy.

**Questions and Discussion**

Dr. Mankoff commented that the AZD9291drug project team did not include imaging experts. Dr. Ivy explained that the team had no external imaging experts because the protocol uses a standard imaging technique. However, the group did receive input from the Cancer Imaging Program. If a study involved an imaging technique that is not widely used, NCI would consult an expert in that technique.

Dr. Takimoto said that this pathway to developing new drugs rapidly is marshalling impressive resources. Doing these types of studies in industry is difficult. He wondered how to synergize the ETCTN with industry activities. Dr. Ivy replied that NCI hopes to work closely with industry in the ETCTN.

Dr. Lou Weiner said that the ETCTN approach of assembling teams by selecting excellent representatives with unique areas of expertise is less commonly used than asking preexisting teams to describe what they can offer. Preexisting teams have a history of working together that facilitates effective collaboration. Dr. Weiner wondered whether NCI plans to compare its approach to forming teams to this traditional model. Dr. Ivy explained that NCI does plan to evaluate its project teams by determining, for example, whether this approach leads to rapid initiation of clinical trials. Currently, this model appears to be working well.

Dr. LeBlanc asked about the number of compounds evaluated in the ETCTN. Dr. Ivy replied that in addition to the three drugs that are on track for a project team or project team member application or for a solicitation, NExT continues to review new agents that come to NCI for development. The "bandwidth" for the program is quite broad, and the main limitation on the number of agents in the program will be its budget.

**ETCTN: Clinical/Translational Researcher Perspective**
*Geoffrey I. Shapiro, MD, PhD*

The creation of the drug project teams in the ETCTN gives researchers opportunities to participate in a collaborative network that makes substantial contributions to drug development plans. These teams include junior investigators. CTEP fosters the development of novel drug combinations that might not otherwise be tested in clinical trials.

Before creating the ETCTN, CTEP solicited for predefined trials of agents in its portfolio that complemented company plans. Investigators submitted detailed letters of intent that included extensive preclinical data and details on the proposed trials and biostatistical plan. The process had a high failure rate because NCI approved only a small number of letters of intent, resulting in substantial investigator frustration.

In the ETCTN, investigators apply to join a project team as basic, translational, or clinical scientists. CTEP assembles a project team to assess the preclinical package and determine whether other work is needed to inform the agent's clinical development. The team also proposes innovative disease- or biomarker-based clinical trials incorporating appropriate safety, pharmacokinetic, and efficacy end points. Investigators submit full letters of intent only after the Investigational Drug Steering Committee reviews the drug development plan.

Dr. Shapiro was a member of the first ETCTN drug project team for the heat shock protein (HSP) 90 inhibitor AT13387. The company's development plan focused on non-small-cell lung cancer (NSCLC), gastrointestinal stromal tumor, and castrate-resistant prostate cancer. The NCI internal team suggested evaluating HSP90 inhibitors in areas in which they had not been well studied, such as certain lymphomas, triple-negative breast cancer, and epidermal growth factor receptor-mutated NSCLC. The team also proposed assessing the ability of HSP90 inhibition to modulate DNA damage responses. These ideas were listed in the solicitation for drug project team member applications.

The drug project team that NCI ultimately assembled included experts in head and neck cancers, lymphoma, NSCLC, and triple-negative breast cancer as well as basic scientists who are national leaders in the HSP90 field. Several team members evaluated biomarkers for all of the trials. The team also included experts in imaging and biostatistics, CTEP staff, experienced Specialized Programs of Research

Excellence translational researchers, and junior investigators. Each junior investigator was paired with a senior investigator on the team.

The team met by telephone approximately 12 times within a month. One call focused on the lymphoma and breast cancer trials, while another addressed the lung and the head and neck cancer trials. The team also spoke to people not on the team who had relevant expertise and might participate in the trials. At the end of the month, the team developed four proposals for presentation to the Investigational Drug Steering Committee for the following clinical trials of AT13387 with pharmacodynamic and genomic components:

- non-Hodgkin lymphoma—monotherapy phase II study in anaplastic lymphoma receptor tyrosine kinase-positive anaplastic large-cell lymphoma, mantle cell lymphoma, and BCL6-positive diffuse large B-cell lymphoma
- triple-negative breast cancer—phase 1I/Ib monotherapy followed by taxane combination
- NSCLC—phase Ib erlotinib/AT13387 following erlotinib run-in, including patients with tumors harboring exon 20 insertion mutations
- squamous cell carcinoma of the head and neck—phase I study of AT13387 with standard-dose chemoradiation

The project team model has several potential problems, all of which can be resolved. For example, the project teams must be large to be inclusive. To prevent teams from being unwieldy, CTEP carefully chooses members based on their experience and focuses each call on a specific topic. Some investigators who apply to join the team are not selected; the project team can engage them by giving them opportunities to participate in calls to learn about the team's activities and generate excitement about the plans. Developing the concepts is time consuming and might not lead to a trial. However, the benefits of engaging junior investigators and interacting with basic and translational researchers to crystallize experiments that inform drug development can outweigh this time commitment. Not every idea can be developed, so project team leaders and CTEP must provide strong leadership, and investigators may submit unsolicited letters of intent after the project team plan is approved.

The project team model facilitates a highly collaborative process for proposing a drug development plan that is superior to the legacy system, which had far less engagement of sites in trial prioritization and design. The ETCTN draws on a multidisciplinary team of senior leaders and junior investigators early in the process. The CTEP portfolio is poised to promote the development of innovative combinations of agents from different pharmaceutical companies based on a strong preclinical rationale. CTEP operational improvements (central institutional review board, patient registration, and data management) will speed up study activation and network engagement when required for robust accrual.

**Insights for the ETCTN: An Analysis of Correction Action Plans (CAPs) for Early-Phase Trials**
*Holly A. Massett, PhD*

NCI obtained funding from the NIH Evaluation Set-Aside Program for a 3-year process evaluation of the ETCTN's first 3 years of implementation. The evaluation will assess four key domains: adoption/implementation, team science approach, clinical trial performance, and network synergy. The six components of the process evaluation are quarterly data reviews, establishment of archival baselines, annual field surveys, annual network analyses, annual in-depth interviews, and drug development plan milestone reviews. The Institute of Medicine's consensus goals for a transformed clinical trials system,

especially the goals designed to improve the speed and efficiency of trial development and conduct, will inform the evaluation.

Starting in 2010, in response to the Operational Efficiency Working Group report, CTEP began tracking postactivation activities of early-phase trials. CTEP also began requesting a CAP from the study principal investigator (PI) for each phase I trial with an accrual rate of less than 50 percent of the projected rate during active enrollment after quarter 2 and for each phase II trial with an accrual rate of less than 50 percent of the projected rate (for the last two quarters) after three quarters. PIs must complete and return the CAPs within 2 weeks to identify reasons for the slow accrual and possible actions to increase accrual.

CTEP analyzed data on the CAPs to identify accrual challenges for early-phase trials and provide guidance for the ETCTN. The sample consisted of 327 studies that were active between August 2011 and February 2013. For these 327 studies, CTEP sent 150 CAP requests (46 percent of all studies), and 135 CAPs (90 percent) were eligible for analysis. Approximately half of the trials in the evaluation were phase I and half were phase II. Most (88 percent) were adult trials.

Results from the analysis include the following:

- CAP trials that met their minimum accrual goals took about three times longer to close than projected.
- Of closed trials, over two-thirds met their primary scientific objectives. But trials meeting their objectives took three times longer than projected to close, and those not meeting their objectives took six times longer before being closed due to slow accrual.
- More than one-quarter (27 percent) of all closed trials had an accrual rate increase associated with a greater likelihood of meeting their primary scientific objectives.
- The most common reason for slow accrual in phase I trials was safety, and 74 percent of these trials had at least one other reason for the slow accrual other than safety.
- Among phase II trials, institutional/administrative barriers were the main reason for slow accrual.
- Slightly more than half (54 percent) of actionable reasons matched the proposed corrective actions.

Recommendations for ETCTN trials based on this analysis are:

- provide more realistic accrual projections
- define and implement an accrual plan early in a trial's development (i.e., decrease the need for a CAP)
- match corrective actions more closely to slow-accrual reasons, when feasible

The ETCTN is well positioned to address many of these accrual challenges. The CIRB will reduce IRB delays and accelerate site activation. Because ETCTN trials are accessible to the entire network, more sites will be able to accrue patients to ETCTN trials. Finally, the team approach will improve the quality of the science and commitment of sites to complete trials.

CTEP is developing a CAP coding sheet to standardize the collection of reasons and actions for slow accrual and develop statistical algorithms for evidence-based decision making for trial closure due to slow accrual. CTEP is continuing the CAPs analysis as part of the 3-year ETCTN process evaluation.

**Questions and Discussion**

Dr. Abbruzzese asked whether the CAPs are an effective tool or whether CTEP needs a different strategy to increase accrual in some trials. Dr. Massett said that the CAPs have led to improved accrual rates by bringing the accrual problems to PIs' attention. Systematizing the CAPs process through the data that CTEP collects might be helpful.

Dr. George Weiner asked about the reasons why some trials achieved their accrual targets more quickly than others. Dr. Massett explained that CTEP is now collecting and will evaluate these data.

Dr. Munshi speculated that accrual rates are likely to be better in trials of drugs that are effective because their investigators will be more enthusiastic about these studies. Dr. Massett said that CTEP is collecting these data as part of the 3-year evaluation.

Dr. Arbuck noted that the evaluation results suggest that investigators should conduct more feasibility studies in advance instead of trying to increase their accrual rates after starting a trial. Many of the problems in the CTEP trials could probably be identified in advance. If these problems cannot be resolved, then these trials should not be conducted. Dr. Massett said that CTEP is using this approach for late-phase trials and plans a similar approach for the ETCTN.

Dr. Mitchell asked whether CTEP has demographic data that can be used to determine whether the trial populations reflect the U.S. population. Dr. Massett said that CTEP did not have these data for this analysis; the ETCTN system can collect demographic data.

Dr. Mankoff asked about cross-fertilization between the ETCTN and National Clinical Trials Network, such as the use of accrual tools or biomarkers that might help trials in both networks. Dr. Massett said that CTEP is collaborating with the NCTN to build a repertoire of tools for use in both networks. Dr. Mankoff emphasized the potential benefits to both networks of learning from one another.

In response to a question from Dr. Mankoff, Dr. Ivy said that the ETCTN is using a reference laboratory instead of several laboratories to assess biomarkers, an approach that offers better quality assurance and quality control. Similarly, for investigational imaging, the network identifies centers that can do the required analyses. The goal is to be prepared to move into later-phase trials.

Dr. Arbuck asked about challenges working with industry, obtaining adequately characterized biomarkers, and obtaining funding for the biomarker studies. Dr. Ivy said that the ETCTN works closely with industry to make sure that NCI and industry development plans do not overlap and that drug development in NCI trials can be translated to industry. This approach has worked well in several cases. The ETCTN grants fund biomarker development and biopsy collection in phase I trials. Funds may also come from Specialized Programs of Research Excellence grants or industry.

## VIII. New Business and Announcements

*James L. Abbruzzese, MD*

Dr. Abbruzzese asked CTAC members to send him and Dr. Prindiville any unanswered questions or issues that should be presented or discussed at future CTAC meetings.

Dr. Abbruzzese announced that CTAC will form a working group to further discuss opportunities for intramural/extramural research collaborations with NCI.

## IX. Adjournment

*James L. Abbruzzese, MD*

There being no further business, the 25th meeting of CTAC was adjourned at 3:05 p.m. on Wednesday, November 12, 2014.

## Appendix

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

### CHAIR

**James L. Abbruzzese, MD, FACP 2015**
Chief, Division of Medical Oncology
Associate Director for Clinical Research
Department of Medicine
Duke Cancer Institute
Duke University Medical Center
Durham, NC

### MEMBERS

**Susan G. Arbuck, MD, MSc, FACP** **2014**
President
Susan G. Arbuck MD, LLC
Potomac, MD

**Curt I. Civin, MD (BSA)** **2014**
Associate Dean for Research
Professor of Pediatrics
Director
Center for Stem Cell Biology and Regenerative Medicine
University of Maryland School of Medicine
Baltimore, MD

**Kevin J. Cullen, MD (NCAB)** **2015**
Director
University of Maryland Greenebaum Cancer Center
Baltimore, MD

**Nancy E. Davidson, MD** **2015**
Director
University of Pittsburgh Cancer Institute
University of Pittsburgh
Pittsburgh, PA

**J. Philip Kuebler, MD, PhD** **2015**
Principal Investigator
Columbus Community Clinical Oncology Program
Columbus Oncology and Hematology Associates, Inc.
Columbus, OH

**Scott M. Lippman, MD** **2015**
Director, Moores Cancer Center
Senior Associate Dean, Associate Vice Chancellor for Cancer Research and Care, and Chugai Pharmaceutical Chair in Cancer Research
University of California, San Diego
La Jolla, CA

**Mary S. McCabe, RN** **2014**
Director
Cancer Survivorship Initiative
Memorial Sloan Kettering Cancer Center
New York, NY

**Edith P. Mitchell, MD** 2016
Clinical Professor of Medicine and Medical Oncology
Program Leader, Gastrointestinal Oncology
Sidney Kimmel Cancer Center
Thomas Jefferson University
Philadelphia, PA

**Nikhil C. Munshi, MD** 2016
Associate Director
Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, MA

**Lisa A. Newman, MD, MPH, FACS** 2014
Professor of Surgery and Director of Breast Care Center and Multidisciplinary Breast Fellowship Program
University of Michigan Comprehensive Cancer Center
Ann Arbor, MI

**Nancy Roach** 2015
Consumer Advocate
Fight Colorectal Cancer
Alexandria, VA

**Peter G. Shields, MD** 2014
Deputy Director
Comprehensive Cancer Center
Professor
College of Medicine
The Ohio State University Medical Center
Columbus, OH

**George W. Sledge, Jr., MD** 2015
Chief
Division of Oncology
Stanford University Medical Center
Stanford, CA

**Chris H. Takimoto, MD, PhD** 2016
Vice President and Head, Translational Medicine Early and Development, Oncology Therapeutic Area
Janssen Research & Development, LLC
Radnor, PA

**Gillian M. Thomas, MD, FRCPC, FRCR**
Professor 2014
Department of Radiation Oncology
Department of Obstetrics and Gynecology
University of Toronto
Odette Cancer Centre
Sunnybrook Health Sciences Centre
Toronto, Ontario
Canada

**Miguel A. Villalona-Calero, MD** 2014
Director
Division of Medical Oncology
The Ohio State University
Columbus, OH

**George J. Weiner, MD** 2015
C.E. Block Chair of Cancer Research
Professor, Department of Internal Medicine
Director
Holden Comprehensive Cancer Center
University of Iowa
Iowa City, IA

## Ad hoc Members*

**David F. Arons, JD**
Director of Public Policy
National Brain Tumor Society
Watertown, MA

**Susan M. Blaney, MD**
Vice President for Clinical and Translational Research
Vice Chair for Research
Department of Pediatrics
Baylor College of Medicine
Texas Children's Hospital
Houston, TX

**Walter J. Curran, MD, PhD**
Professor and Chairman
Department of Radiation Oncology
Emory University School of Medicine
Atlanta, GA

**Michael L. LeBlanc, PhD**
Research Professor
Department of Biostatistics
Fred Hutchinson Cancer Research Center
University of Washington
Seattle, WA

**David A. Mankoff, MD, PhD**
Gerd Muehllehner Professor of Radiology
Division Chief of Nuclear Medicine and Clinical Molecular Imaging
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA

**Louis M. Weiner, MD**
Director
Lombardi Comprehensive Cancer Center
Francis L. and Charlotte G. Gragnani Chair
Department of Oncology
Georgetown University Medical Center
Washington, DC

*Pending Appointment

## Ex Officio Members

**James H. Doroshow, MD**
Deputy Director for Clinical and Translational Research
National Cancer Institute
National Institutes of Health
Bethesda, MD

**Paulette S. Gray, PhD**
Director
Division of Extramural Activities
National Cancer Institute
National Institutes of Health
Bethesda, MD

**Rosemarie Hakim, PhD, MS**
Epidemiologist
Centers for Medicare and Medicaid Services
Baltimore, MD

**Lee J. Helman, MD**
Senior Investigator
Pediatric Oncology Branch
Scientific Director for Clinical Research
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, MD

**Michael J. Kelley, MD, FACP**
National Program Director for Oncology
Veterans Health Administration
Department of Veterans Affairs
Washington, DC

**Richard Pazdur, MD, FACP**
Director
Office of Hematology and Oncology Products
U.S. Food and Drug Administration
Rockville, MD

**Alan S. Rabson, MD**
Deputy Director
National Cancer Institute
National Institutes of Health
Bethesda, MD

**TBD**
John P. Murtha Cancer Center
Walter Reed Army Medical Center
Washington, DC

**Executive Secretary**

**Sheila A. Prindiville, MD, MPH**
Director
Coordinating Center for Clinical Trials
Office of the Director
National Cancer Institute
National Institutes of Health
Bethesda, MD