DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
21st CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC) MEETING

Summary of Meeting
November 6, 2013

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

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
BETHESDA, MARYLAND
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The 21st meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was held on Wednesday, November 6, 2013, at 9:00 a.m. in Conference Room 10, C-Wing, 6th floor, Building 31, on the National Institutes of Health (NIH) main campus in Bethesda, MD. The CTAC Acting Chair, Dr. Peter C. Adamson, Chair, Children's Oncology Group; Chief, Division of Clinical Pharmacology & Therapeutics, The Children's Hospital of Philadelphia, presided. The meeting was adjourned at 3:12 p.m.

Acting Chair
Peter C. Adamson

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

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

Executive Secretary
Sheila A. Prindiville, NCI

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WEDNESDAY, NOVEMBER 6, 2013

I. CALL TO ORDER AND OPENING REMARKS—DR. PETER C. ADAMSON

Dr. Adamson called the 21st meeting of the CTAC to order and then reviewed the confidentiality and conflict-of-interest practices required of Committee members during their deliberations. Members of the public were invited to submit written comments related to items discussed during the meeting to Dr. Sheila A. Prindiville, Director, Coordinating Center for Clinical Trials (CCCT), within ten days of the meeting. Any written statements by members of the public will be given careful consideration and attention. Dr. Adamson reminded members that the meeting was being videocast by NIH Events Management.

Motion. A motion to accept the minutes of the 20th meeting of the CTAC held on July 10, 2013, was approved unanimously.

II. DEPUTY DIRECTOR'S REPORT—DR. JAMES H. DOROSHOW

Dr. James H. Doroshow, Deputy Director, Clinical and Translational Research, NCI, reviewed the meeting agenda and provided an update on news and activities related to clinical and translational research at the Institute. He thanked his colleagues across NCI who, during the 16 days of the government shutdown, maintained critical functions. Dr. Doroshow noted that 18 of about 800 staff of the Division of Cancer Treatment and Diagnosis (DCTD) were exempted from the furlough. These staff worked in Frederick to maintain the mouse collections or in roles related to clinical trials and dealing with adverse events.

The review of the NCI National Clinical Trials Network (NCTN) occurred in July and the results were presented to and accepted by the senior leadership committee of NCI. Five groups will be supported—one pediatric group and four adult groups. There will be one Canadian group and an organizational infrastructure to support imaging and radiation therapy. The number of institutional and translational research grants that are supported by NCI will depend on fiscal year (FY) 2014 budget allocations.

Dr. Doroshow answered several questions prior to beginning his update.

Questions and Discussion

Ms. Nancy Roach, Consumer Advocate, C3: Colorectal Cancer Coalition, asked when the funding decisions will be announced. Dr. Doroshow responded that the funding allocations for Requests for Applications (RFAs) and grants will be announced after NCI receives a budget for FY2014.

Dr. Kevin J. Cullen, Director, University of Maryland Greenebaum Cancer Center, asked if another funding opportunity announcement (FOA) will be released for additional Network Lead Academic Participating Sites (U10) to participate in the NCTN. Dr. Jeffrey S. Abrams, Associate Director, Cancer Therapy Evaluation Program (CTEP), stated that the decision to support additional U10 sites will depend on future funding levels.

Dr. Nancy E. Davidson, Director, University of Pittsburgh Cancer Institute, questioned whether funding will be available to support the NCTN if the government must operate on a Continuing Resolution (CR) into FY2014. Dr. Doroshow said that the NCTN will continue to be supported based on the amount of funding available.

Dr. Doroshow reviewed the agenda and noted the need for input on these topics from CTAC members. He then updated members regarding the Program Planning Working Group, chaired by Dr. Scott Lippman, Director of the U.C. San Diego Moores Cancer Center. The Working Group will be focusing on how to integrate issues such as the prioritization data coming back from the NCTN Working Group, information on clinical trial portfolios and what CTAC can affect in terms of what that portfolio does, and how to expand the purview of CTAC to look more deeply into the activities of the early-phase therapeutics programs that are supported by NCI and have not really been addressed by CTAC.

Dr. Doroshow then explained the purpose of a proposed short-term CTAC Specialized Programs of Research Excellence (SPORE) Working Group and requested CTAC approval for its establishment. The Working Group will be asked to evaluate the SPORE program announcement renewal and to provide advice on the value of the SPORE program to current NCI translational research efforts. The Working Group will be chaired by a CTAC member. A substantial amount of information already has been collected through a contract with the Science and Technology Policy Institute; however, an external group is needed to look at that information. The Working Group would be asked to evaluate the productivity of the program, suggest any programmatic changes that might be appropriate, and report back to CTAC. This report then would go back to Dr. Varmus as the Institute looks at renewing the program announcement in the spring.

Questions and Discussion

Ms. Roach asked if membership on the CTAC SPORE Working Group will be limited to CTAC members. Dr. Doroshow responded that it is not required for membership to be limited to CTAC members. Ms. Roach also asked if the CTAC SPORE Working Group will include an advocate representative. Dr. Doroshow affirmed that an advocate will be included on the Working Group.

Dr. Toby T. Hecht, Associate Director, Translational Research Program, Division of Cancer Treatment and Diagnosis (DCTD), NCI, clarified that approval of the SPORE program renewal will be needed by next spring; the new program announcement will request applications for submission in January 2015.

Motion. A motion to form a short-term CTAC Specialized Programs of Research Excellence Working Group was approved unanimously.

CTAC members interested in serving on the Working Group should contact Dr. Prindiville.

Dr. Doroshow concluded by presenting retiring CTAC members (Drs. Peter Adamson, Daniel Sargent, Mitchell Schnall, Susan Braun, and Olivera Finn) with plaques commemorating their service. He thanked these members for the valuable input that they have provided to the Committee.

III. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations, NCI, reported on the status of appropriations, congressional activities, and legislation of interest.

Appropriations Status. Congress reached the end of FY2013 without approving a budget for FY2014, thus causing the government to shut down. The shutdown lasted 16 days until Congress came to a bipartisan agreement on October 16th and passed a Continuing Resolution to fund the government until January 15, 2014. The government's authority to borrow money was extended until February 7, 2014. The CR provided funding at the FY2013 level of $1.4 billion; authorized back pay for furloughed federal employees; appointed a Budget Conference Committee to reconcile partisan differences and create a spending plan; and included the extension of reporting requirements associated with conferences costing over $100,000.

The Budget Conference Committee has been charged with creating a spending plan by December 13, 2013. If that were to occur, the Appropriations Subcommittees would use the new spending levels created by the plan to work on individual bills. The bills could be combined into an Omnibus bill and passed prior to January 15 when the CR expires. If this does not occur, Congress will need to pass another short-term CR, a full-year CR, or face another government shutdown.

Congressional Activities. Congress held five hearings (three in the House and two in the Senate) on the Affordable Care Act. For example, Secretary Sebelius testified in the House before the Energy and Commerce Committee and is scheduled to testify at a Senate hearing. The Director of the Center for Medicare and Medicaid Services (CMS) is scheduled to testify in the House before the Ways and Means Committee.

The Budget Conference Committee has held a press conference and is working to create its spending plan. The House is scheduled to be in session for 16 more days before the end of the year, finishing up on December 13. The Senate is expected to be in session through Thanksgiving as well as on the weekends.

There have been several congressional briefings at which NCI has been represented, including the Childhood Cancer Summit by Dr. Crystal Mackall of the NCI Center for Cancer Research, the Ovarian Cancer briefing by Dr. Elise Kohn of the Division of Cancer Treatment and Diagnosis, and the Cancer Health Disparities briefing by Dr. Worta McCaskill-Stevens of the Division of Cancer Prevention. The Senate Cancer Coalition also held a forum to discuss current trends in cancer treatment. Dr. Lou Staudt, Director of the NCI Center for Cancer Genomics, represented NCI. There have been congressional visits to the NIH campus by Senator Tammy Baldwin (D-Wisconsin), Representative Scott Peters (D-California), and the Senate Committee on Health, Education, Labor, & Pensions (HELP) staff.

Legislation of Interest. Senator Baldwin introduced the Next Generation Research Act on September 26th. This legislation would establish an NIH initiative to improve opportunities for trainees, enhance workforce diversity efforts, and improve success in awards/renewals; require an Institute of Medicine (IOM) study of barriers to success; and require the National Academy of Sciences (NAS) to report on the impact of sequestration on trainees in five years.

Questions and Discussion

Dr. Nikhil C. Munshi, Associate Director, Jerome Lipper Myeloma Center, Dana-Farber Cancer Institute, asked if the Next Generation Research Act will authorize additional appropriations. Ms. Erickson responded that the legislation will authorize training programs; however, appropriations for the authorization will not be included in the bill.

Dr. Mary S. McCabe, Director, Cancer Survivorship Program, Memorial Sloan Kettering Cancer Center, asked if Ms. Erickson has any knowledge about the impact of the Affordable Care Act on clinical trial accrual. There has been discussion that the Act could have a negative impact on accrual to trials. Ms. Erickson said that she is not aware of this but will watch for any relevant information.

IV. SMALL CELL LUNG CANCER (SCLC) WORKING GROUP UPDATE ON THE WORKSHOP ON SCLC: SEIZING ON OPPORTUNITIES TO TRANSLATE RECENT RESEARCH INTO THE CLINIC FOR NEW DIAGNOSTICS AND INTERVENTIONS—DR. CHARLES M. RUDIN

Dr. Charles M. Rudin presented an update on the efforts of the Small Cell Lung Cancer (SCLC) Working Group. SCLC is the sixth leading cause of cancer-related deaths in the United States. Two-thirds of SCLC patients present with extensive disease at diagnosis. With current therapies, these patients are considered incurable—facing a median survival time approximately nine months from the time of diagnosis. The current standard therapy for extensive-stage SCLC is essentially the same therapy used 30 years ago (a combination of cisplatin and etoposide). One-third of SCLC patients present with limited-stage disease and face a median survival time of approximately 18 months from the time of diagnosis. SCLC is a recalcitrant cancer in critical need of more effective therapies.

NCI initiated a working group to think about new ideas for approaching SCLC. The working group held a workshop in July 2013 that focused on opportunities to translate recent research into the clinic for new diagnostics and interventions. The workshop looked at emerging opportunities in "omics," molecular pathology, and early detection; preclinical models and targeting of cancer stem cells; and therapeutics and new drug targets. A session also was held on attracting new investigators to the field of SCLC. From the workshop discussions, five key opportunities for advancement were identified: 1) characterization of the SCLC genome, transcriptome, and epigenome; 2) analysis of acquired chemotherapy resistance in SCLC; 3) *TP53* and *RB* as gatekeeper mutations in SCLC; 4) MYC family members in SCLC; and 5) developmental and stem cell signaling pathways in SCLC.

Dr. Rudin highlighted recent scientific advances in each of the five SCLC opportunity areas. Based on these advances and discussions from the workshop, Dr. Rudin outlined recommendations to move the field forward. The first is to optimize the collection of SCLC biospecimens representing distinct phases of the disease. The need for additional biopsy material was a consistent theme throughout the workshop; there is a notable lack of paired samples of newly diagnosed and recurrent diagnosed disease. The second initiative is focused on mutational profiling. There is a need for much more extensive genomic and proteomic analysis to define targets and their frequencies (e.g., *FGFR1* amplification, PARP1 overexpression). Targeting driver oncogenes and tumor suppressors in SCLC is the third research initiative being considered by the SCLC Working Group.

Questions and Discussion

Dr. Mitchell D. Schnall, Eugene P. Pendergrass Professor of Radiology, and Chairman, Department of Radiology, University of Pennsylvania Medical Center, asked whether the SCLC Working Group has had any discussion on opportunities in early detection and screening for the disease. Dr. Rudin responded that early detection has been discussed in the context of the National Lung Screening Trial (NLST), which was a screening trial of over 50,000 patients at high risk for lung cancer. Trial data reviewed at the meeting suggested that SCLC was not detected early enough through screening to impact mortality.

Dr. Adamson asked if there are any opportunities for immunotherapy treatments in SCLC. Dr. Rudin responded in the affirmative; however, it is a research area within SCLC that has not been looked at extensively.

Dr. Davidson asked whether the SCLC Working Group has identified specific approaches to increase SCLC tissue acquisition. Dr. Rudin said that major medical centers now are beginning to obtain core biopsies of most lung cancer patients. The SCLC Working Group could push for this practice to be universally adopted across all medical centers. Dr. Davidson asked if Dr. Rudin sees any special benefit in being able to obtain recurrent disease biopsies. Dr. Rudin responded that obtaining recurrent disease tissue would require a clinical trial because it is not standard of care, but that there would be interest in that type of trial. There might be therapeutic targets that would come up in the types of profiling that can be done now.

Dr. J. Phillip Kuebler, Principal Investigator, Columbus Community Clinical Oncology Program, Columbus Oncology Associates, Inc., asked if anyone is looking at circulating tumor cells in resistant disease as a source of genetic analysis. Dr. Rudin said that SCLC is a resistant tumor type with high levels of circulating tumors cells, which could serve as a source of material for genetic analysis. This suggestion may be incorporated in the SCLC Working Group's final report.

Dr. Munshi suggested that the SCLC Working Group discuss how these trials are done and the setting. Dr. Rudin agreed that some more global thinking on how these trials are done and the choice of relevant targets could be helpful, as negative trial results could deter research in a particular molecular pathway of the disease. A committee like CTAC could provide advice on where to do trials and the context in which to do them.

Dr. George J. Weiner, C.E. Block Chair of Cancer Research and Director, Holden Comprehensive Cancer Center, asked if NCI has put any focus on the patient drug xenografts (PDX) program, looking at drug resistance in SCLC. Dr. Rudin responded that there is an ongoing effort to do so. His own research group has established about 12 patient drug xenografts in SCLC. A comprehensive national effort to collect patient drug xenografts would be helpful. Dr. Doroshow added that over the summer, NCI was able to fund tissue acquisition for developing its PDX repository. Some institutions are providing NCI with SCLC samples. A priority would be to obtain pre- and post-treatment biopsy samples, which then would be characterized and made available to the research community.

Dr. Gillian M. Thomas, Professor, Departments of Radiation Oncology and Obstetrics and Gynecology, University of Toronto Odette Cancer Center, questioned whether there are any outliers in the advanced SCLC disease group with longer survival rates from which tissue could be obtained. Dr. Rudin responded that this is a great idea; such patients would be exceedingly rare but potentially valuable.

Dr. Lisa A. Newman, Professor of Surgery and Director, Breast Care Center and Multidisciplinary Breast Fellowship Program, University of Michigan Comprehensive Cancer Center, asked if there is an actual pipeline problem in attracting scientists into the SCLC field, and whether SCLC patients are willing to participate in phase III clinical trials. Dr. Rudin responded that patient enrollment in clinical trials is probably not a major barrier. However, patients often are treated with a standard cycle of chemotherapy by the community oncologist prior to referral to an academic site, and trials need to be designed to take this into account. He also noted that there is a problem in attracting young investigators to the field; there is a need for more investigators who are interested in this tumor type.

Ms. Roach asked if workshop participants discussed the logistical and programmatic barriers to pursuing the most promising research opportunities and how to address those barriers. Dr. Rudin said the meeting largely focused on the science of SCLC, but there was some discussion of barriers such as the barriers to getting tissue and encouraging core biopsies.

Ms. Roach also asked what the next steps are moving forward. Dr. Rudin responded that the SCLC Working Group's final workshop summary document, ultimately, will be converted into a white paper to be presented to Congress as a companion to the pancreas cancer report. It is hoped that this will raise the profile of recalcitrant diseases on the national stage, although, it will be surprising if there is any dedicated funding for these diseases.

Dr. Scott M. Lippman, Director, Moores Cancer Center, University of California, San Diego, asked if SCLC was one of the diseases included in The Cancer Genome Atlas (TCGA) effort. Dr. Rudin answered that SCLC was not included in TCGA.

Dr. Adamson commented that optimizing collection of tissues representing distinct phases of disease could be a topic of discussion for CTAC. Strategic initiatives will need to be implemented in order to obtain consistently paired samples of newly diagnosed and recurrent disease. This is an issue that is a concern in diseases other than SCLC.

Dr. Davidson asked if NCI will be examining additional recalcitrant cancers as a result of the Recalcitrant Cancer Act. Dr. Doroshow explained that the legislation requires reports on two recalcitrant cancers. However, it is within the purview of CTAC to consider the other recalcitrant cancers. He noted that the CTAC Program Planning Working Group could identify other recalcitrant diseases on which CTAC could focus with or without congressional language in order to have similar workshops that provide a focus on these diseases.

Dr. Davidson asked for the definition of recalcitrant cancer in the context of the legislation. Ms. Erickson explained that the definition in the Act is any cancer with a five-year survival rate less than 50 percent. The requirements for action by NCI has a narrower definition—any cancer with a five-year survival less than 20 percent.

Dr. Weiner suggested that another way for CTAC to address recalcitrant cancers would be to identify barriers to progress that are common to multiple recalcitrant diseases (e.g., tissue acquisition, design of clinical trials, and exceptional responders).

V. NCI NATIONAL CLINICAL TRIALS NETWORK (NCTN) WORKING GROUP UPDATE: 2013 PORTFOLIO ASSESSMENT REPORT—DR. ROBERT B. DIASIO

Dr. Robert B. Diasio, Director, Mayo Clinic Cancer Center, presented the 2013 Portfolio Assessment Report from the NCI National Clinical Trials Network (NCTN) Working Group. The initial focus of the NCTN Working Group was to assess the strength and balance of the active NCTN clinical trials portfolio within and across all diseases and to recommend new strategic priorities and directions for the NCTN based on the current trial portfolio, evolving clinical needs, and emerging scientific opportunities.

To date, the NCTN Working Group has held four meetings to assess the NCTN clinical trials portfolio of the following cancer areas: gastrointestinal (GI), breast, genitourinary (GU), leukemia, lymphoma, myeloma, thoracic, brain, pediatric (solid tumor and heme), gynecologic, clinical imaging, symptom management and health related quality of life (SxQOL), and head and neck. Criteria used to evaluate trials have focused on feasibility, clinical importance, scientific contribution, and unique suitability for the NCTN program. The interim report includes ten cross-portfolio recommendations aimed at improving the disease portfolios that are directed jointly by the NCTN groups, Scientific Steering Committees (SSCs), and the NCI. The recommendations fall into five major categories:

1. Emphasize innovative science-driven trials.
    - NCTN Groups and Steering Committees should work together to achieve the appropriate balance of innovative, biology-driven randomized phase II trials and larger, more resource-driven, intensive phase III trials in each disease portfolio.
    - NCTN Groups and Steering Committees should emphasize biology-driven (e.g., molecularly driven, pathway-driven) trials that advance the science by incorporating genomics, biomarker tests, and correlative science into study designs.
2. Consider reallocation of NCTN resources.
    - NCI should conduct an analysis of resource allocation across diseases, taking into account current survival rates and likely cost/benefit from additional advances.
    - To empower innovative, biology-driven trials, additional NCI funding should be provided for correlative science studies, biomarker validation, and the development of molecular classification algorithms.
3. Enhance coordinated strategic planning.
    - Steering Committees should increase their involvement in strategic planning and guidance for future trials in collaboration with the NCTN groups.
    - Greater emphasis should be placed on sharing strategic and tactical best practices across diseases in terms of trial design, accrual, preliminary data requirements, etc.
4. Strengthen evaluation criteria.
    - Accrual challenges should be taken more seriously in proposing and approving trial concepts, balancing the importance of the clinical question with the perceived difficulty of accrual.

- More consideration should be given to competing European and industry trials in proposing and approving trial concepts, as well as to the potential for collaboration with European and industry partners.
- Steering Committees should develop standardized guidelines for the level and types of preliminary data required for trial concepts.

5. Optimize Steering Committee processes.
   - Steering Committees should optimize their use of task forces, working groups, and Clinical Trial Planning Meetings (CTPMs).

Dr. Diasio reviewed the summary conclusions and key recommendations for the thoracic, brain, gynecologic, symptom management/quality-of-life, and head and neck portfolios.

The NCTN Working Group has been conducting a series of portfolio-specific conference calls with appropriate stakeholders (i.e., NCTN Working Group Chairs, Steering Committee Chairs, NCTN Disease Committee Chairs, NCI staff, and Community Clinical Oncology Program (CCOP) Research Base Principal Investigators, etc.) to communicate their findings and recommendations. A final report will be presented to CTAC.

Dr. Diasio asked for discussion from CTAC members on two topics: the strengths and weaknesses of the NCTN Working Group process and the initial cross-disease recommendations.

Questions and Discussion

Dr. Lippman asked whether the NCTN Working Group has discussed the idea of conducting trials across different organ sites for diseases with similar molecular pathways and mutations. Dr. Diasio responded that the Working Group has discussed this idea and would like to see such trials considered and implemented in the future. Additionally, it is believed that perhaps the Groups could benefit because many of these pathways are shared in various diseases and there is an advantage of having cross-communication across the various disease modalities.

Ms. Roach suggested that there is a need to conduct research on what makes a particular trial accruable.

Dr. Monica M. Bertagnolli, Professor of Surgery, Harvard Medical School, Dana-Farber Cancer Institute, commented that at their December meeting, the NCTN Working Group will start to deal with the challenging issue of cross-disease recommendations. Institutions are very disease oriented and there are two levels of what will need to be done. On the operational level, there will be decisions on numbers of studies needed in one disease vs. another disease, and then whether there are really cross-disease initiatives that need to be done and how that will be operationalized in a disease-oriented model—for example, how to organize management of tissue. Dr. Diasio agreed that it will require additional resources.

Dr. Munshi commented that there are different entities (i.e., NCTN groups, Steering Committees, NCI, and the Working Group) deciding on the prioritization of recommendations. Dr. Diasio stated that the prioritization process will require communication between all entities.

Dr. Susan G. Arbuck, President of Susan G. Arbuck, M.D., LLC, noted that some pharmaceutical companies have successful models for conducting feasibility studies in advance to predict whether trials will accrue and that it might be worth looking at some of these models.

Dr. Cullen asked if the Working Group has focused on what diseases or classes of diseases may be fertile areas for testing new immunotherapy agents. Dr. Diasio responded that the Working Group has not yet addressed this issue.

Dr. Kuebler stated that the recommendation to standardize the amount and type of preliminary data necessary to move a drug or procedure forward in a trial might be useful for many different diseases.

Dr. Davidson requested that Dr. Diasio update CTAC on the Working Group's discussions on the analysis of resource allocation across diseases and how the Working Group envisions that analysis taking place. Dr. Diasio responded that the Working Group has been occupied with going through each of the disease trial portfolios and has not yet addressed the issue of resource allocation.

Dr. Richard Pazdur, Director, Division of Oncology Drug Products, U.S. Food and Drug Administration (FDA), asked what is being done to encourage the internationalization of clinical trials while protecting leadership in trial design. Dr. Diasio stated that the NCTN Working Group is recommending an increased awareness of and interaction with potential collaborators external to the United States, although the NCTN currently does not, except in rare situations, fund studies in other countries. Dr. Pazdur added that he sees a model that is basically collaboration with industry to elicit their expertise in other geographical areas, such as Eastern Europe and Asia, where the heaviest concentration of trial accrual exists.

Dr. Edith P. Mitchell, Clinical Professor of Medicine and Medical Oncology, Kimmel Cancer Center, Thomas Jefferson University, asked whether the NCTN Working Group has addressed the issue of reaching the right patient populations with specific trials (e.g., the high incidence of multiple myeloma in African Africans). Dr. Diasio responded that this is an issue that needs to be addressed moving forward.

Dr. Adamson commented that CTAC will need to take an in-depth look at the NCTN Working Group's final report to provide input on how to implement recommendations. The Committee should discuss the silos in which research currently is conducted and the overall system in which ideas are designed to fail late.

Dr. Arbuck noted that there have been improvements in the time to initiate a study, but there needs to be a rethinking of the objectives, what the endpoints are, and then how to get there; there needs to be a new, shorter path to drug testing.

Dr. Newman stated that there will be a need to look again at how conflict-of-interest issues are handled as we partner more with industry and as we look at international populations. She noted that in U.S. university systems there are rigorous policies and restrictions on how investigators can partner with industry and what funds they can receive. These restrictions need to be lessened to promote productive collaboration with industry on an international level.

VI. PRECISION CANCER MEDICINE: EXCEPTIONAL RESPONDERS AND NCI-MATCH INITIATIVES—DR. BARBARA A. CONLEY

Dr. Barbara A. Conley, Associate Director, Cancer Diagnosis Program, Division of Cancer Treatment and Diagnosis, NCI, presented two NCI precision cancer medicine initiatives: Exceptional Responders and NCI-Molecular Analysis for Therapy Choice (MATCH). The Exceptional Responders Initiative is a collaborative effort between DCTD and the Center for Cancer Genomics. One to 10 percent of patients respond well to drugs that do not go on to receive FDA approval for that indication. Molecular mutations or changes in gene expression may explain these "exceptional responses," which could lead to the development of predictive assays for "inactive" drugs that sometimes are active in a subset of patients. This may improve the biologic understanding of disease and drug resistance for better therapeutics and diagnostics development.

An "exceptional response" is defined as either a complete response or partial response lasting at least six months to a drug that did not go on to FDA approval in that indication due to insufficient activity. The NCI Exceptional Responders initiative aims to obtain tumor tissue from exceptional responders, preferably just before drug treatment or at any time prior to treatment. Normal tissue (blood or other) also will be collected if available. Tissue samples and clinical data will be solicited from CTEP investigators, pharma, Cooperative Groups, U01s, N01s, and Cancer Centers. Participating sites will be reimbursed for their efforts. This screening method for potential exceptional responder cases will be done via a study in the Clinical Trials Support Unit Oncology Patient Enrollment Network (CTSU OPEN). There will be an eligibility phase and an enrollment phase. Data submitted through CTSU OPEN will be reviewed internally at NCI. If a case is exceptional, tissue samples and clinical data will be requested from the physician; if the case is not exceptional, a response letter will be sent to the submitting investigator. Patient DNA samples will be transferred to a TCGA Sequencing Center and remaining tissue will be stored in a biorepository for use in future studies.

The approximate timeline for this initiative anticipates solicitation of exceptional cases and tissues from October 2013 to September 2015. Sequencing and analysis will take place December 2013 to September 2015. The resulting data will be posted on a controlled-access website between January 2014 and December 2015. The timeline has been somewhat delayed due to the government shutdown; however, the protocol should be ready for review by the Central Institutional Review Board (CIRB) by the beginning of 2014.

The NCI-MATCH initiative is an umbrella protocol for multiple, single-arm phase II trials for molecular subgroups matched to a targeted agent. The submission of an Investigational New Drug (IND) application for the protocol template is planned. The umbrella protocol can be amended to add new study arms or remove completed arms as the trial progresses. NCI-MATCH initially is focused on single agents (commercial or experimental). Combinations will be considered that have phase II data and information that it is effective for some target. The study will be reviewed by the NCI CIRB.

NCI-MATCH seeks to identify mutations/amplifications/translocations in patient tumor samples for eligibility determination. Approximately 3,000 patients are proposed to be screened to enroll 500 to 1,000 on the study. If the patient has an "actionable mutation," she or he will be assigned to the relevant agent/regimen, and tumor biopsies and sequencing at progression will be conducted to illuminate drug resistance mechanisms. The current eligibility criteria are: (1) patients with solid tumors or lymphomas that have progressed after at least one standard treatment (histologies from a given arm will be excluded if

the targeted treatment is already FDA approved for that indication or if lack of efficacy for the particular histology has been previously documented); (2) tumors accessible for biopsy and patients willing to undergo biopsy; (3) patients at least 18 years of age (there is discussion to expand to pediatric patients); (4) and good performance status and adequate organ function.

The intent is that 25 percent of the total enrollment will be patients with "rare" tumors. "Common" tumors are being defined as breast, non-small cell lung, colon, and prostate cancers. Enrollment to an arm will be terminated if it is not accruing after five years. The drugs that will be included in NCI-MATCH have been categorized into four levels of evidence: (1) the drug is FDA approved for some indication with either a companion diagnostic or an available selection assay; (2) a clinical endpoint has been met, such as a target or progression-free survival for some disease with evidence of target inhibition and plausible evidence that there may be an associated predictive assay; (3) the agent has demonstrated some evidence of clinical activity but not met a clinical endpoint with evidence of target inhibition; and/or 4) there is preclinical, logical evidence that this target might be amenable to inhibition by a particular agent and there is a hypothesis for a selection assay. There are also levels of evidence for the genes selected in the study and for how they will be assigned. A next-generation sequencing assay will be used to analyze tumor tissue. The platform will be the Ion Torrent Personal Genome Machine with custom Ampliseq panel of 200-300 actionable genes. A network of approximately four Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories across the country will run the same assay using standardized procedures and controls. NCI and the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) are going to lead the study with the full cooperation of the NCTN. There will be individual Principal Investigators for each study arm. NCI-MATCH will be posted on the CTSU.

Questions and Discussion

Dr. Cullen asked how information on exceptional responders will be used; for example, in a situation where 40 out of 40 patients with seven different diseases have a common mutation and respond to the same drug. Because it is so rare, there will never be sufficient patients who have that mutation within each of the seven diseases for a trial. Dr. Pazdur commented that a drug could be approved by FDA for the treatment of a specific mutation, although this has not yet happened. There is nothing in the FDA regulations that states that a drug must be approved for an established histological subtype. He also noted that, for very rare mutations, FDA is considering full approval of drugs on the basis of single-arm trials if the response rates are robust (e.g., a response rate of 60–80% for even a small group of patients could be considered a clinical benefit). Archival material showing that these patients did not get that type of response with conventional chemotherapy can get around the need for a randomized trial. Dr. Abrams noted that some centers already are doing these kinds of studies with rare mutations. He predicted that this will become more common as sequencing is done more frequently and there are leads for specific mutations.

Dr. Adamson asked if the Exceptional Responders study is open to pediatric patients. Dr. Conley responded in the affirmative.

Dr. Munshi asked what will happen to the clinical data collected from patients not subsequently enrolled in NCI-MATCH. Dr. Conley said that CLIA-certified laboratories will be conducting the sequencing assays. If a patient's sample is sequenced and does not have a mutation for which the trial has

an agent, the laboratory will retain the sequencing information, which could be used for another study outside of NCI-MATCH. The patient can have that information. If a patient has multiple mutations within different pathways, the mutations will be prioritized based on allele frequency to determine in which NCI-MATCH trial arm the patient should be placed. If the patient progresses on the first drug, she or he potentially will receive the drug for the other mutation.

Dr. Arbuck commended NCI for making available a program that has a lot of interest but is not accessible to a lot of people. It also could be used to publicize the clinical trials program. She asked how drugs will be selected and how the drugs will come into the NCI-MATCH program. Dr. Conley responded that the pharmaceutical industry has pledged close to 40 agents for the trial. Companies are reaching out to NCI to determine whether they are interested in pledging drugs to NCI-MATCH. Dr. Conley said that NCI has a committee working on appropriate drug selection; the first priority will be drugs that have been approved and have specificity with a certain abnormality or pathway. Additionally, Dr. Conley noted that it is not necessary for a company to have a Cooperative Research and Development Agreement (CRADA) with NCI for this study; a clinical trials agreement will be sufficient, and companies will not be asked to financially support the sequencing.

Dr. Arbuck asked what the timeline is for NCI-MATCH study arms to open. Dr. Conley responded that this committee work should be completed, for the most part, by December 2013. The earliest that a study will open is the summer of 2014, with the possibility of adding additional drug arms at a later date.

Dr. Sargent noted that the goal of 35 percent progression-free survival is fairly modest, and it is not clear what that will mean in a subtype where it is not known if that is a prognostic group or whether these are indolent tumors. He asked how that is viewed. Dr. Conley said they are looking only at molecular features and it is not known whether the same mutation across tumor types means the same thing. Therefore, if a signal comes out of a trial, there will need to be another prospective trial to evaluate its significance, including whether it is a prognostic factor.

Dr. Bertagnolli asked what input NCI is looking for from the investigator community and when NCI will notify investigators of the mutations, pathways, and agents that will be available in NCI-MATCH. Dr. Conley stated that the co-Principal Investigators on the study are having discussions with the NCTN subcommittees to determine whether there are investigators who are particularly interested in specific drugs and pathways to join the effort. Additionally, there have been discussions with patient advocate groups within ECOG and the NCTN about how to educate clinicians and patients about this study, which is a different type of study than ever has been done in the Cooperative Groups. All information about the trial will be released to the investigator community prior to the study opening.

Ms. Roach asked whether all levels of evidence for drugs will be included in NCI-MATCH. Dr. Conley responded that Levels 1 and 2 will be prioritized but some Level 3 and 4 drugs likely will be included. Ms. Roach expressed concern about the trial not being set up to fail early. Dr. Conley noted that the trial is already quite complex with 30 different arms and that the concern is to find a signal from somewhere. If no signal emerges from 30 patients entered per arm, then no further follow-up will be undertaken of that molecular group with that particular treatment.

Dr. Kuebler asked what the time delay will be for patients with progressive disease who have been sequenced to wait to be assigned to a drug and given treatment. Dr. Conley said NCI anticipates the delay will be about three weeks.

Dr. Cullen asked what will happen if a patient who is sequenced elsewhere has a mutation that matches one of the trial arm's pathways. Would the patient have to be resequenced? Dr. Conley stated that NCI has decided to sequence the patient again with the central assay platform.

VII. NCI-AACR CANCER PATIENT TOBACCO USE ASSESSMENT TASK FORCE—DR. STEPHANIE R. LAND

Dr. Stephanie R. Land, Program Director and Statistician, Tobacco Control Research Branch, Division of Cancer Control and Population Sciences (DCCPS), NCI, discussed tobacco use by cancer patients in clinical trials to inform CTAC about an initiative that has just begun and to solicit early input. The problem from the clinical perspective is that cancer patients and survivors who smoke cigarettes have worse health outcomes, including higher all-cause and cancer-specific mortality, and risk of tobacco-related second primary cancer, than do cancer patients who do not smoke. They also may have higher risk of recurrence, poorer response to treatment, and increased toxicity. Many scientific questions related to tobacco use in the cancer patient population remain to be answered and cannot be addressed with data as they currently are collected.

Currently, tobacco use is not widely assessed in trials or practice. Tobacco use assessment methods are inconsistent, and there is little follow-up during/after treatment. A survey of NCI-designated Cancer Centers found that fewer than 50 percent include tobacco use as a vital sign in the medical record. Only 22 percent of NCI-funded phase III Cooperative Group trials record cigarette smoking status at enrollment, and 4 percent record it during follow-up. Attention to this issue has been increasing in recent years. In 2009, NCI held a conference on tobacco use dependence treatment in NCI-designated Cancer Centers. Discussions on this issue continued among conference attendees via email. From 2009 to the present time, there has been increasing attention from a number of organizations, including the American Association for Cancer Research (AACR), the American Society for Clinical Oncology, IOM, and the *Journal of Clinical Oncology (JCO)*, among others. The NCI-AACR Cancer Patient Tobacco Use Assessment Task Force was formed in 2013. The purpose of the Task Force is to develop recommendations for tobacco use measures, timing of assessment, and a research agenda.

Dr. Land presented results of the North Central Cancer Treatment Group (NCCTG) phase III trial N0147. Over 2,600 resected stage III colon cancer patients were randomized to receive FOLFOX only or FOLFOX in combination with cetuximab. The study also included a baseline smoking assessment in nearly 2,000 patients. The researchers were able to analyze the trial endpoints with respect to smoking status among patients in the study; the results were published in *JCO* in June. Three-year disease-free survival was 70 percent for ever smokers versus 74 percent for never smokers.

Cigarette smokers seem to have greater morbidity and poorer clinical outcome, but evidence needs to be strengthened. Some of the questions identified by the NCI-AACR Task Force that need to be answered include: Is the association actually due to exposure history, use during cancer therapy, or continued accrual of risk after therapy? What is the improvement in prognosis with cessation for a given history of exposure? Does quitting smoking actually impact the outcome of cancer, or is the damage already done? Does tobacco use diminish treatment efficacy? Why does smoking affect virtually all disease sites for most treatment modalities? Task Force members discussed a number of additional questions and noted that understanding the mechanisms may provide a model of general therapeutic

resistance that would have implications beyond tobacco use. Issues of cost also were brought up with respect to adding items to studies; however, those costs ultimately might be offset with the understanding of how behavior and tobacco use are impacting a therapy that is, in itself, quite expensive.

Near-term deliverables on which the NCI-AACR Task Force currently is working include recommended measures to be made available online; a protocol for tobacco use measurement (also available online); and a published research agenda. At present, the Task Force is engaged in expert and stakeholder dialog. The recommended measures and protocol will be disseminated and implemented in selected NCTN trials. The Task Force also will develop an NCI guidance.

Dr. Land closed her presentation by asking for feedback from CTAC on the barriers to incorporating tobacco use items either in selected trials or, in the future, in all NCTN phase III clinical trials.

Questions and Discussion

Ms. Roach asked what the end goal is for this initiative. Dr. Land responded that helping patients quit smoking is one of the ultimate goals. At present, the real focus of the initiative is on assessment with the goal of pursuing the scientific agenda.

Dr. Peter G. Shields, Deputy Director, Comprehensive Cancer Center, The Ohio State University Medical Center, commented that follow-up data on tobacco use need to be collected, in addition to the data collected upon first patient visit, in order to answer the important scientific questions.

Dr. Cullen stated that answering questions such as whether the dose of chemotherapy should be adjusted in smokers would be a costly endeavor. It may not be a worthwhile way to invest limited resources moving forward. Dr. Cullen also stated that collecting the information makes sense if it can be done given the resources. Dr. Shields commented that, typically, even a basic set of data, such as four Tier 1 items, is not available. Dr. Cullen agreed that collecting the Tier 1 level of data is reasonable.

Dr. Thomas commented that it may make more sense to conduct behavioral trials to get people to stop smoking, period, as opposed to focusing on the cancer population. Behavioral trials are where large gains could be made in terms of life years saved. Dr. Land countered that if adding smoking assessment measures to ongoing trials is low cost, both types of studies could be conducted without the need for additional resources.

Dr. Kuebler expressed concern about the accuracy of patient recall. He asked whether cotinine levels will be measured in patients to obtain more accurate data on current smoking status. Dr. Land said the Task Force has discussed this issue; biochemical validation (such as cotinine measurement) may be worthwhile when feasible with respect to cost and logistical barriers.

Dr. Daniel J. Sargent, Director, Cancer Center Statistics, Mayo Clinic Foundation, stated that the cost of adding tobacco use assessment measures is modest for a trial that already is using a survey questionnaire instrument. However, adding those measures for a trial that is not collecting survey data could add substantial complexity to the study. He recommended ensuring that a trial is appropriate before adding tobacco use assessment to it. Dr. Land commented that the potential for treatment moderation

among cancer patients is so ubiquitous that there may be scientific rationale for conducting tobacco use assessment more broadly.

Dr. Lippman commented that it would be difficult to find a situation in which having tobacco use information is not helpful, as it can affect treatment compliance and drug interactions. Even without a specific hypothesis at the time of trial development, it could be a confounder or stratification factor. This information is important in analyzing trials and different effects.

Dr. Pazdur commented that collecting data for the sake of collecting data is not productive unless there are specific scientific questions that can be answered; the proposed tobacco-related questions are difficult to answer.

Dr. Shields stated that in order to answer the difficult scientific questions, hypothesis-generating data first need to be collected. Dr. Lippman agreed that collecting data to look for signals is important. Dr. Lippman also commented that smoking seems to be affecting a number of outcomes, including issues of compliance.

VIII. PATIENT-REPORTED OUTCOMES-COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (PRO-CTCAE)—DRS. LORI M. MINASIAN AND SANDRA MITCHELL

Dr. Lori M. Minasian, Deputy Director, Division of Cancer Prevention, NCI, gave an overview of patient-reported outcomes (PROs) in NCI-sponsored clinical trials. Multiple NCI and NIH initiatives and activities currently are ongoing, each of which has a specific purpose, is in a specific stage of development, and requires specific expertise. There is a need for clarity in the incorporation of PROs in health-related quality of life (HRQOL) into NCI-sponsored clinical trials.

Dr. Minasian highlighted key NCI initiatives and activities. NCI is incorporating PRO endpoints into its clinical trials—secondary endpoints in treatment trials and primary endpoints in symptom management trials. There is an effort, in the initial stages, to curate HRQOL tools for caDSR (NCI's repository of common data elements, metadata, and data standards). This is a key step to integration into Medidata Rave (NCI's Remote Data Capture System). About 30 percent of PRO content has been curated based upon best practices. Users need to review and retire redundant PRO content. A project plan has been developed and there soon will be a call for membership for the HRQOL Curation Working Group. This Working Group will facilitate integration with Medidata Rave.

NCI also has identified PRO core domains—a collection of common PRO domains across clinical trials as well as disease-specific domains. This initiative was presented to CTAC in March 2013 and recommendations will be published in a forthcoming paper in the *Journal of the National Cancer Institute*. PROs are available for symptoms, toxicities, functional assessments, and HRQOL, yet a framework is needed for the inclusion of these available tools in NCI-supported clinical trials. This would be an overall concept for inclusion that does not dictate but, rather, provides guidance to investigators and reviewers on the use of PROs.

Existing and planned coordination activities include the following efforts. The Symptom Management and Health-Related Quality of Life Steering Committee has been involved in the discussion

of PROs. The Steering Committee has reviewed symptom management trials and appointed liaisons to Disease Steering Committees for PRO and HRQOL review on treatment trials. An NIH/FDA Outcomes Assessment Working Group has focused on the development and validation of tools for assessing outcomes in clinical trials. There is internal support to move forward with an NCI Patient-Reported Outcomes Working Group for NCTN/NCORP (NCI Community Oncology Research Program) Clinical Trials. This Working Group would coordinate and finalize the internal NCI ad hoc discussion and build on the success of coordination of PRO-CTCAE. This would be a short-term working group (i.e., duration of 12-18 months) comprising external PRO investigators and NCI staff. The group would develop a framework for inclusion of different PRO assessments across NCTN/NCORP clinical trials.

Dr. Sandra Mitchell, Program Director and Research Scientist, Outcomes Research Branch, Applied Research Program, DCCPS, NCI, discussed the PRO version of the Common Terminology Criteria for Adverse Events—an initiative that stemmed from the jointly sponsored NCI and American Cancer Society PROACT conference in 2006.

Treatment-related toxicity (safety and tolerability) is a fundamental outcome when drawing conclusions about therapeutic effectiveness, including comparative effectiveness. Currently, toxicity is evaluated by clinicians using CTCAE. One of eight of the adverse events listed in CTCAE is a symptom outcome. Evidence suggests that the validity of symptom outcomes reports is eroded when those reports are filtered through research staff and clinicians. Additionally, staff-based adverse event reporting occurs at clinic visits; thus, adverse events that occur between visits may be missed. The PRO-CTCAE effort emerges from the hypothesis that real-time ascertainment of symptomatic adverse events using PROs could improve the precision and reproducibility of adverse event reporting. A survey of trialists in the Cooperative Groups conducted by Bruner et al. (2011) reached a conclusion that the inclusion of patient-centered reporting of adverse treatment effects is valued by trialists.

PRO-CTCAE is a patient-reported outcome measure that ascertains, in real time, the presence, severity, and interference of symptomatic toxicities experienced by patients participating in cancer clinical trials. Under the leadership of DCCPS, this initiative is cofunded and has strategic oversight from the Division of Cancer Prevention (DCP), DCTD, and the Center for Biomedical Informatics and Information Technology (CBIIT). The work is being accomplished through contracts awarded to Memorial Sloan-Kettering Cancer Center. The PRO-CTCAE measurement system consists of two elements. The Symptom Library contains 78 symptomatic adverse events drawn directly from CTCAE and PRO-CTCAE questions crafted to evaluate symptom occurrence, frequency, severity, and interference. The System for Survey Administration is a web-based system built to customize surveys and manage survey administration. A patient responds to surveys using the web, a tablet, or an interactive voice response (IVRS) telephone system. The electronic system allows for conditional patterns (skip patterns) to reduce survey respondent/patient burden. It also allows for write-ins (unsolicited adverse events) to be reported with automated mapping to standardized terminology. The web-based system has undergone a rigorous and iterative cycle of usability testing with both clinicians and patients. The item library also has been tested using qualitative and quantitative techniques. The system has been designed to accommodate patients with limited English proficiency and digital literacy. The ultimate goal of PRO-CTCAE is to supply meaningful data to improve understanding of symptomatic adverse events.

PRO-CTCAE currently is being implemented in two Cooperative Group trials (RTOG 1012 and NCCTG 1048). There are also 35 early adopters in academic settings and in industry across more than 8 countries testing PRO-CTCAE in trials and observational studies. Collaboration agreements have been established with these investigators to stimulate efficient and coordinated testing of PRO-CTCAE in

clinical trials and generate evidence about best approaches for particular study contexts and patient populations. These agreements also allow for data sharing and collaborative analysis. Key issues to be addressed moving forward include: identifying trial contexts and investigational therapies where PRO-CTCAE will be particularly useful; interpreting PRO-CTCAE scores to assign a grade; delineating principles for design and interpretation of trials that incorporate patient self-reporting of adverse effects and yield interpretable and meaningful information; and determining the utility of PRO-CTCAE at different clinical trial phases.

As the PRO-CTCAE initiative scales toward implementation, it will be incorporated into a future version of the CTCAE. NCI is engaged in demonstrating clinical validity, interpretability, and utility across trial designs and populations so that integration into CTCAE is empirically driven. Efforts are ongoing to embed PRO-CTCAE into existing clinical trials and observational studies, make PRO-CTCAE amenable for use with pediatric oncology patients, and integrate PRO-CTCAE into Medidata Rave.

Questions and Discussion

Dr. Davidson asked whether any European colleagues would be included on the proposed NCI Patient Reported Outcomes Working Group. Dr. Minasian said that NCI would like to invite European researchers to participate in the effort.

Dr. Arbuck asked whether there has been a review of PROs used in the past to determine which are the most beneficial. Dr. Minasian responded that in 2006, NCI and the American Cancer Society cosponsored the PROACT conference to review the incorporation of PROs and HRQOL into clinical trials. Efforts focused on PROs and HRQOL have been ongoing since the conference.

Dr. Pazdur commented that the validity of PRO-CTCAE endpoints would best be determined if they are implemented in blinded, randomized trials to eliminate the introduction of any perceived bias. However, this will be difficult as there are few truly blinded trials. PRO-CTCAE measures would work best in trial situations where there are subjective toxicities for which a high degree of interpretation is expected (e.g., evaluation of mucositis or diarrhea). Dr. Pazdur suggested conducting a separate trial where the primary endpoint is a PRO—to focus on patients who have symptoms [of the disease] and what those symptoms are going to be.

Dr. Munshi asked if PROs have been evaluated in comparison with physician-reported outcomes. Dr. Mitchell replied that there has been a lot of work in this area. It has been found that symptoms are not as accurately reported when reported by the physician. Dr. Minasian added that several studies have looked at discrepancy in reporting. The more subjective a symptom is, the more discrepant the reporting by clinicians.

Dr. Adamson asked if there is evidence showing that increasing PROs and HRQOL measures improves patient safety by giving a better understanding of drug action and effects. Dr. Pazdur replied that the evidence likely does not exist.

Dr. Adamson asked if there are areas of medicine other than cancer where PROs are used. Dr. Pazdur stated that PROs are the basis for approval of all psychiatric drugs. Dr. Adamson asked if NCI is learning from those other areas of medicine. Dr. Pazdur replied that PROs in other fields are used in

blinded trials; however, the drugs used in cancer trials are much more toxic than in other therapeutic areas, which can unmask the blinding of trials.

Dr. Thomas commented that PROs could be a useful additional endpoint in trials where there are only small improvements in progression-free survival.

Dr. Arbuck stated that moving forward with the PRO-CTCAE initiative, NCI should compare PRO endpoints with other trial results in similar studies to ensure that patient bias is not occurring. Dr. Arbuck also expressed concern over physicians reacting to PROs without understanding them.

IX. CLINICAL TRIALS REPORTING PROGRAM (CTRP): 2013 UPDATE—DR. SHEILA A. PRINDIVILLE

Dr. Prindiville provided an update on NCI's Clinical Trials Reporting Program (CTRP) on behalf of the CCCT and colleagues in CBIIT. During her opening remarks, she noted that CTRP is a comprehensive database containing regularly updated information on all NCI-supported clinical trials, including accrual. It is a central repository of trials with information collected using standardized data elements and was designed to support NCI's clinical trials portfolio management.

Currently, CTRP collects information not available in ClinicalTrials.gov that enhances NCI's clinical trials portfolio management, including accrual data; biomarker data (assay type, purpose, tissue specimen type, and collection method); protocol documents for abstraction (except for industry trials); data needed to create Cancer Center Support Grant (CCSG) Data Table 4 (e.g., funding category, funding sponsor, anatomic site); and results of a search of trial data enhanced by consistent application of indexing terminology.

CTRP also enhances compliance with ClinicalTrials.gov reporting requirements. CTRP facilitates submission of required data to ClinicalTrials.gov, minimizing the need for duplicate data entry by NCI awardees. CTRP supports management of NCI's ClinicalTrials.gov account and compliance with the FDA Amendment Act of 2007 for NCI-sponsored trials.

The Association of American Cancer Institutes (AACI)-NCI CTRP Strategic Subcommittee defined CTRP reporting requirements and timelines in a report presented to CTAC in July 2011. At that time, initial registration of interventional trials open to accrual on or after January 1, 2009, was to be completed by September 2011. Ongoing registration of new trials began in September 2011. The initial registration was completed by NCI-designated Cancer Centers, CTEP, DCP, and the Center for Cancer Research (CCR). The registration of new trials is ongoing, and registration of non-interventional trials is accepted. Registration of trials by other NCI awardees has not begun consistently. As of this month, 10,257 trials have been registered and abstracted. Forty percent of those trials are institutional; only 14 percent are national trials.

NCI-designated Cancer Centers are reporting amendments, updates, and status changes to trials. The timing of these submissions complies with ClinicalTrials.gov reporting requirements. CTRP will implement an automated process for a reminder to facilitate update reporting. The import of accrual data from NCI managed trials (CTEP, DCP, CCR) is under way. Cancer Centers reporting of patient-level accrual on institutional trials for which they are the lead organizations is in progress. Cancer Centers

reporting of summary accrual counts for industrial trials on which they are participating also is in progress. Initial CTRP automated CCSG Data Table 4 reports have been developed by CBIIT. Beginning in January 2014, initial reports will be reviewed with each Cancer Center to ensure that the list of registered trials is accurate and complete and that accrual is complete and correctly reported in CTRP for the Center and its affiliates.

The development of CTRP has been a collaborative effort among many groups within NCI, as well as with the NIH/National Library of Medicine (NLM). CCCT has held regular meetings with NLM to facilitate NCI and extramural community compliance with Food and Drug Administration Amendments Act (FDAAA) reporting requirements for ClinicalTrials.gov. An "Upload from CTRP" function has been developed and implemented, which allows sponsors to retrieve CTRP data for trial registration for upload to ClinicalTrials.gov. CTRP also imports industrial trial data from ClinicalTrials.gov for trials for which Cancer Centers have indicated participation.

A future consideration for CTRP is whether to expand the scope of trials required for reporting to include non-interventional trials. The AACI/NCI 2011 report recommended deferral of outcome reporting to CTRP for three to five years. NCI needs to determine whether outcome reporting is feasible and of value to NCI and the oncology community. The initial reporting focus of CTRP has been on Data Table 4, but it has the capacity to produce additional reports. Stakeholder input is needed to determine future reporting requirements. A working group to address these issues is being established.

Questions and Discussion

Dr. Sargent requested that outcome reporting data not be included in the CTRP. The new NCTN guidelines require reporting of data to the public within six months of publication, which should fulfill the need for outcome reporting.

Dr. Cullen asked whether the CTRP services for commercial vendors are in place. Dr. Prindiville responded in the affirmative. Dr. Jose Galvez, Director, NCI Enterprise Informatics, CBIIT, said that services for commercial vendors are available for registration and trial updates. A service is also available for vendors to start submitting accrual data.

Dr. Cullen also asked how the data in CTRP are being used. Dr. Prindiville stated that the primary focus at present is to develop automated Data Table 4.

Dr. Munshi asked who will have access to the CTRP data. Dr. Prindiville stated that user policies need to be developed and consistent with NIH policies regarding data sharing.

Dr. Weiner commented that it could be a challenge to collect and report data for observational trials. Dr. Prindiville responded that stakeholder input is needed to decide whether observational trial data should be collected and how to do so.

X. ADJOURNMENT—DR. PETER C. ADAMSON

There being no further business, the 21st meeting of the CTAC was adjourned at 3:12 p.m. on Wednesday, November 6, 2013.

National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

NCI Legislative Update

Clinical Trials and Translational Research Advisory Committee

November 6, 2013

Susan Erickson

Director, Office of Government and Congressional Relations

Discussion Topics

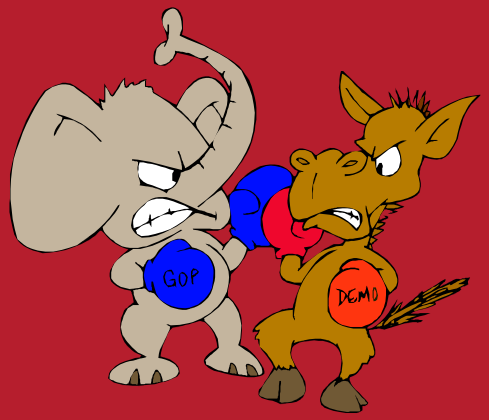
Appropriations Status

Congressional Activities

Legislation of Interest

Appropriations Status – FY 2014

What Happened?



Where are we now?

- Continuing Resolution PL 113-46 on Oct. 16
- Funding at FY 2013 level (NCI= $1.4 B)
- Expires January 15, 2014

Appropriations Status – FY 2014

What's in the CR?

- Government re-opened immediately
- Debt Limit extended through Feb. 7
- Budget Conference Committee to be appointed
- Pay for furloughed federal employees
- Reporting requirements – conferences > $100K

Appropriations Status – FY 2014

What's Next?

- Budget conferees create spending plan by 12/13
- Appropriation Subcommittees use new spending level to work on individual bills
- Bills combined into Omnibus bill and passed

If Not --

Full year CR? - Short term CR? - Another shutdown?

Congressional Activities

Hearings on Affordable Care Act

- House (3)
- Senate (2)

Budget Conference Committee Meetings

Projected Schedule

- House (16 days – finish up Dec. 13)
- Senate (through Thanksgiving – weekends)

Congressional Activities - NCI

Briefings

- Childhood Cancer Summit
- Ovarian Cancer
- Cancer Health Disparities

Senate Cancer Coalition Forum

Visits to NIH

- Sen. Baldwin (WI)
- Rep. Peters (CA)
- Committee Staff (HELP)

Visit – and - Legislation

Sen. Baldwin met with trainees at NIH July 15

Sen. Baldwin introduced legislation Sept 26

Legislation of Interest

Next Generation Research Act – S. 1552

- NIH Initiative to improve opportunities
  - Strengthen mentoring
  - Enhance workforce diversity efforts
  - Improve success in awards/renewals
- IOM study of barriers to success
- NAS report on impact of sequestration in 5 yrs

NATIONAL® CANCER INSTITUTE

November 6, 2013

Legislative Update
for the
Clinical Trials and Translational Research Advisory Committee
Activities of the 113th Congress-
First Session

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I. Appropriations

The federal government is currently operating under a continuing resolution (PL 113-46) that funds most agencies, including NIH and NCI, at the FY2013 level, at a rate of operations that reflects the sequestration cuts and all rescissions in the last continuing resolution (PL 113-6), excluding Hurricane Sandy supplemental funding. It provides for funding at this level through 1/15/14 or until enactment of new applicable appropriations, whichever occurs first. NCI's appropriation through 1/15/14 is approximately $1.4 billion.

The continuing appropriations act passed in the Senate by a vote of 81-18 and in the House by a vote of 285-144 on 10/16/13. It was signed into law by the President on 10/17/13, ending the October 2013 government shutdown.

The law also extends the debt limit through 2/7/14, and provides for pay and benefits for furloughed federal employees. It allows for funding flexibility for a number of agencies to ensure that certain activities are carried out, including funding for biological and chemical preparedness. It also extends through FY2014 certain federal agency reporting requirements for conferences costing more than $100,000.

Additionally, per the agreement negotiated by Senate Democratic and Republican leaders, House and Senate budget conferees have been appointed to continue negotiations aimed at reaching an agreement on a budget for the remainder of FY2014, with a deadline to deliver the spending plan to Congress by 12/13/13. Led by House Budget Chair Paul Ryan (R-WI), and Senate Budget Chair Patty Murray (D-WA), the 29 members of the conference committee have significant differences to resolve, with the House entering negotiations set on maintaining sequestration cuts and proposing an overall spending limit of $967 billion, and the Senate basing its proposal of $1.058 trillion on the assumption that Congress will repeal sequestration. The House budget proposal also protects funding for the Defense, Military Construction-VA, and Homeland Security, and as a result, imposes sharp cuts on non-defense discretionary spending, which includes NIH. For example, the Defense bill would increase 5.4%, while the Labor-HHS bill (which funds HHS/NIH/NCI) would be cut by 18.6% below the current, post-sequestration level (a $35 billion cut).

Despite this impasse, which was evident well ahead of the October shutdown, the appropriations committees continued to move FY2014 spending bills. Priro to the August recess, the House Appropriations Committee advanced all but two spending bills out of committee (Labor-HHS and Interior-Environment), and four bills – Military Construction-VA, Homeland Security (DHS), Defense, and Energy-Water – were passed by the House. The Senate Appropriations Committee advanced all but the Interior-Environment bill out of committee. The Senate Appropriations Committee passed a Labor-HHS Appropriations bill in July (providing $30.955 billion for NIH, an increase of $307 million from FY2013) – as noted, the House Appropriations Subcommittee has not released a Labor-HHS appropriations bill for comparison.

Also of note, during the government shutdown, the House passed a resolution that would have provided continuing appropriations specifically for the NIH. Referred to as the "Research for Lifesaving Cures Act," the bill proposed continuing appropriations for the NIH through December 15, 2014 or until applicable appropriations are made for FY2014, whichever occurs first. Like the agreement that was ultimately reached to restore funding for the entire government, the act proposed funding at FY2013 levels, including reductions imposed by sequestration. The proposal also would have authorized compensation and benefits to avoid furloughs of NIH employees. The act was introduced by Rep. Jack Kingston (R-GA), Chairman of the House Labor-HHS Appropriations Subcommittee on 10/2/13 and passed in the House by a vote of 254-171 on the same day. The act was one of many House proposals to provide funding to re-open individual agencies or programs during the October 2013 government shutdown. The Senate never considered these proposals, as majority leadership indicated only a proposal to fund and re-open the entire government would receive consideration in the Senate.

Most recently, Rep. Allyson Schwartz (D-PA), introduced a bill to provide $3 billion in supplemental appropriations to the NIH for the remainder of FY2014. In an effort to be deficit neutral, the "Inspiring Scientific Research and Innovation Supplemental Appropriations Act, 2014" would offset this additional funding to NIH by eliminating a provision in the Internal Revenue Code that provides a tax break for corporate jet owners. Rep. Schwartz cited the support of various health systems and research organizations in her press release announcing the introduction of the bill, including the University of Pennsylvania Health System, the Children's Hospital of Philadelphia, and the Sandy Rollman Ovarian Cancer Foundation.

II. Special Topics

FDA Regulation of Tobacco: E-Cigarettes, Pending Legislation, and Trade Negotiations

Members of Congress, public health advocates, and the National Association of Attorneys General are now calling on President Obama and the FDA to assert regulatory authority over electronic cigarettes, or e-cigarettes, a cigarette-shaped product designed to deliver vaporized nicotine (derived from tobacco plants), along with little cigars, cigars, and other tobacco products yet to be regulated by the agency. At the same time, members of Congress are also calling on e-cigarette manufacturers to disclose more information on their marketing practices, including specific tactics shown to appeal to minors.

Four democrats on the House Energy and Commerce Committee, including Ranking Member Rep. Henry Waxman (D-CA), and Subcommittee on Health Ranking Member Rep. Frank Pallone (D-NJ), wrote to FDA Commissioner Margaret Hamburg on 9/16/13, urging the FDA to regulate e-cigarettes. The advocates' letter, sent to the President on 9/19/13, makes a similar request, and points out that while fruit and candy flavors are prohibited in cigarettes, smokeless and roll-your-own (RYO) tobacco, these flavors are still permitted – and widely available – via cigars, little cigars and e-cigarettes (in flavors such as cotton candy, gummy bear, bubble gum, grape, and strawberry). The letter is signed by 14 organizations, including the American Academy of Pediatrics, the American Lung Association, the American Cancer Society Cancer Action Network, the American Heart Association, the American Public Health Association, and the Campaign for Tobacco-Free Kids.

On 9/24/13, Attorneys General from 41 states echoed the advocates' call in a letter to Commissioner Hamburg, asking the FDA to issue proposed regulations by 10/31/13 to address e-cigarettes, and pointing to the growing e-cigarette market and the product's appeal to youth. They emphasized the need for regulation by highlighting the lack of safety information available, noting, "Consumers are led to believe that e-cigarettes are a safe alternative to cigarettes, despite the fact that they are addictive, and there is no regulatory oversight ensuring the safety of the ingredients in e-cigarettes."

The Family Smoking Prevention and Tobacco Control Act was signed into law on 6/22/09, giving the FDA the authority to regulate tobacco products – specifically cigarettes, smokeless and RYO tobacco – and the ability to expand its regulatory scope to include other tobacco-related products through its rule-making process. For example, in accordance with the Act, on 9/22/09, the FDA issued the rule banning cigarettes, smokeless and RYO tobacco with fruit, candy, and clove flavors. On 6/22/10 the FDA issued a rule restricting the sale and distribution of cigarettes and smokeless tobacco, in an effort to make these products less accessible and less attractive to children and adolescents.

The FDA had indicated its intention to issue a proposed rule regarding e-cigarettes, cigars, and other tobacco products by 10/31/13, however delays occurred due to the government shutdown, which postponed Office of Management and Budget review. In the meantime, legislation is still pending that would exempt cigars from FDA regulation. The Traditional Cigar Manufacturing and Small Business Jobs Preservation Act of 2013 was introduced in the House on 2/15/13, and in the Senate on 4/18/13. Similar legislation has been introduced in past sessions of Congress and has never moved out of committee. While e-cigarettes have not been the focus of federal legislation,

a number of states have passed and are considering legislation to restrict access to and use of e-cigarettes, with 23 states already prohibiting the sale of e-cigarettes to minors. Massachusetts prohibits the use of e-cigarettes in the workplace, and pending proposals include a bill that has already passed the California Senate that would ban e-cigarette use wherever smoking is banned. Connecticut has similar legislation pending, as does the District of Columbia.

Additionally, the Centers for Disease Control (CDC) reported survey results on 9/6/13 indicating e-cigarette use has doubled among middle and high school students in just one year, from 4.7% to 10.0% among high school students during 2011-2012. The CDC estimates that 1.78 million middle and high school students used e-cigarettes in 2012. Mitch Zeller, director of FDA's Center for Tobacco Products, commented on the study, alluding to the expected FDA rule, "These findings reinforce why the FDA intends to expand its authority over all tobacco products and establish a comprehensive and appropriate regulatory framework to reduce disease and death from tobacco use."

Twelve members of Congress, Democrats in both the House and Senate, expressed their concerns about these rising numbers in letters to the nine manufacturers of e-cigarettes, sent on 9/26/13. The letters focused specifically on the marketing and sale of e-cigarettes to minors, and noted the product's lack of federal regulation, "Currently, e-cigarettes are not subject to federal laws and regulations that apply to traditional cigarettes. For example, federal laws and regulations prohibit traditional cigarettes from being sold to persons younger than 18, distributed as free samples, advertised on television and radio, and having characterizing fruit flavors that appeal to kids. . . . For more than four decades a federal ban on cigarette ads for radio and television has helped to deglamorize smoking for young people. We are concerned that e-cigarette makers are using a broad range of marketing techniques previously employed by traditional cigarette companies to entice youth to use their products." The letter presented twenty questions to the companies, and requested written responses by 10/25/13. Signatories include Assistant Majority Leader Sen. Richard Durbin (D-IL) and Health, Education, Labor, and Pensions Chairman Sen. Tom Harkin (D-IA), as well as Reps. Waxman and Pallone.

Additionally, on 9/12/13, Sen. Sherrod Brown (D-OH), who also signed the September 26 letter, spoke on the Senate floor about ongoing negotiations of the Trans-Pacific Partnership (TPP) trade agreement, and also sent a letter to the U.S. Trade Representative (USTR) regarding this issue. In his floor remarks, Sen. Brown commented that the USTR had originally proposed a "safe harbor" clause for tobacco, which would limit the tobacco industry's ability to challenge the tobacco control policies of the countries party to the agreement.

Sen. Brown voiced his concern that if the TPP proceeds without a tobacco safe harbor clause, the U.S. Family Smoking Prevention and Tobacco Control Act could be open to an "investor-state" trade dispute, where a company would be able to challenge the public health law in trade court. He cited examples of the tobacco industry bringing such suits in other countries, challenging Australia's Tobacco Plain Packaging Act of 2011, and Uruguay's graphic warning labels for tobacco products.

The TPP currently contains a general exception for matters necessary to protect human life or health, and the USTR has proposed a provision to clarify the parties' understanding that this exception applies to tobacco health measures. The USTR has also proposed adding a provision to the TPP requiring that the health authorities of concerned parties to the agreement must meet to discuss any potential challenge to another party's tobacco regulatory measure before formally initiating a challenge through the TPP dispute settlement process. HHS has stated that these proposals will make a difference for tobacco control and public health efforts, describing the inclusion of these provisions in the TPP as an "important step forward for public health in the international trade community."

Most recently, on 10/30/13, more than 50 members of Congress wrote to President Obama expressing their concerns about the USTR's position regarding tobacco and the TPP. They encouraged the President to urge USTR to reconsider its position and include a safe harbor provision.

STEM Education Legislation

Science, technology, engineering, and mathematics (STEM) education continues to be a topic of Congressional interest. Federal agencies, as well as the private and public sectors, rely on knowledgeable, properly trained, and skilled STEM workers to ensure a highly qualified workforce to fulfill organizational goals and advance science and innovation. Improvements to STEM education programs, from preschool to post-doctoral programs, are aimed at stimulating interest in STEM disciplines and providing the foundation to fulfill the growing demand for STEM workers within the United States.

Recognizing this need, many members of Congress are focused on improving STEM education and have introduced several bills in the 113th Congress. Sen. Tammy Baldwin (D-WI) introduced a STEM education bill on 9/26/13 of particular interest to NIH: the Next Generation Research Act (S. 1552). The main goal of this bill is to increase opportunities to develop future researchers through the establishment of the Next Generation of Research Initiative within the NIH. The proposed initiative would promote efforts aimed at improving opportunities for new researchers, including efforts to strengthen mentorship programs pairing new and veteran researchers, to enhance workforce diversity efforts, and to help improve new researchers' success in obtaining renewal funding. The legislation would also call upon the NIH to study factors that affect the next generation of biomedical researchers and make recommendations for how to incentivize students to pursue research careers.

While none of the STEM education bills introduced during this Congress have been signed into law, some have gained several cosponsors – this suggests continuing interest in this area and the trend has been particularly apparent among Democrats. Rep. Mike Honda (D-CA) introduced two STEM education bills on 3/12/13. H.R. 1089, the Stepping up STEM Act of 2013, which currently has 42 cosponsors, includes provisions that would coordinate the nation's STEM education initiatives and create an office of STEM Education in the Department of Education and an Advanced Research Projects Agency for Education (ARPA-ED). H.R. 1090, the Elementary Educator STEM Content Coach Act of 2013, has 10 cosponsors to date and would create a cohort of educators with deep content knowledge in STEM disciplines.

In addition, Sen. Jeff Merkley (D-OR) introduced S. 854, the STEM Education for the Global Economy Act of 2013, on 4/25/13, to improve student academic achievement in STEM subjects through a capacity-building competitive grant program. On 4/26/13, Rep. Marc Veasey (D-TX) introduced H.R. 1816, the Veterans' STEM Education program, to provide additional assistance under the Post-9/11 GI Bill for veterans pursuing STEM degrees. H.R. 1816 was introduced as a companion bill to S. 514, introduced by Sen. Sherrod Brown (D-OH) on 3/11/13.

III. Congressional Briefings and Visits

NCI Staff Spoke at Childhood Cancer Summit (9/19/13) – At the request of Representatives Michael McCaul (R-TX) and Chris Van Hollen (D-MD), co-chairs of the House Childhood Cancer Caucus, Dr. Crystal Mackall, Chief, Pediatric Oncology Branch, Center for Cancer Research, NCI, spoke about pediatric cancer research. Representatives Michael McCaul, Chris Van Hollen, and Dana Rohrabacher (R-CA) provided brief remarks. Representative John Carney (D-DE) also attended but did not make remarks.

NCI Staff Spoke at Press Event (9/19/13) – At the request of Hyundai Hope on Wheels, Dr. Crystal Mackall, Chief, Pediatric Oncology Branch, Center for Cancer Research, NCI, gave a brief presentation about the importance of public/private partnerships in advancing biomedical research. Representatives Chris Van Hollen (D-MD), Mike Kelly (R-PA), Chaka Fattah (D-PA), Janice Hahn (D-CA), and G.K. Butterfield (D-NC) gave remarks. This event was linked to, but separate from, the Childhood Cancer Summit.

NCI Staff Spoke at Senate Cancer Coalition Forum (9/18/13) – At the request of Senators Dianne Feinstein (D-CA) and Johnny Isakson (R-GA), chair and co-chair, respectively, of the Senate Cancer Caucus, Lou Staudt, Director,

Center for Cancer Genomics, NCI, participated in a panel discussion entitled, "Innovative Treatment Options and Breakthroughs in Cancer Care. Senator Feinstein moderated the event and Senator Richard Blumenthal (D-CT) made brief remarks.

NCI Staff Spoke at Congressional Lunch Briefing on Ovarian Cancer (9/17/13) – At the request of the Society for Women's Health Research, Dr. Elise Kohn, Head, Gynecologic Cancer Therapies, Division of Cancer Treatment and Diagnosis, NCI, spoke about ovarian cancer research. Representative Rosa DeLauro (D-CT) sponsored the event.

HELP Committee Staff Visited NCI (8/20/13) – At the request of Barbara Damron, Health Policy Fellow, staff members from the Senate Committee on Health, Education, Labor and Pensions (HELP) visited the NIH campus to meet with NCI investigators. The group met with Dr. Lee Helman, Scientific Director for Clinical Research, Center for Cancer Research (CCR), and visited a clinic setting with Dr. Ola Landgren, Senior Investigator, Metabolism Branch, CCR, and toured the lab of Dr. Carole Parent, Deputy Laboratory Chief, Laboratory of Cellular and Molecular Biology, CCR.

NCI Staff Spoke at Congressional Briefing on Cancer Health Disparities (7/24/13) – At the request of the American Association of Cancer Research, Dr. Worta McCaskill-Stevens, Director, Community Oncology Research Program, NCI, spoke at a briefing entitled, "Reducing Cancer Health Disparities Through Research." Representatives Elijah Cummings (D-MD), Barbara Lee (D-CA), Raul Grijalva (D-AZ), and Rodney Davis (R-IL), sponsored the event with Representative Davis providing remarks. Howard Koh, Assistant Secretary for Health, HHS, also was a featured speaker.

Representative Peters Visited NIH (7/19/13) –Rep. Scott Peters (D-CA) and staff visited NIH. They met with Drs. Francis Collins, Director, NIH, and Eric Green, Director, NHGRI, and toured two labs in the Clinical Center: the NHGRI Undiagnosed Disease Program and the NCI Molecular Imaging Clinic.

Senator Tammy Baldwin Visited NIH (7/15/13) –Sen. Tammy Baldwin (D-WI) visited the NIH campus and met with Drs. Francis Collins, Director, NIH, Sally Rockey, Deputy Director for Extramural Research, James Anderson, Deputy Director for Program Coordination, Planning, and Strategic Initiatives, and Michael Gottesman, Deputy Director for Intramural Research. They discussed new investigator and early career awards, met with young investigators in the intramural program, and toured NCI facilities.

III. Legislation of Interest

The following resolutions and bills were selected for inclusion in this update due to anticipated interest among the BSA membership. More detailed information about these bills and others are available on our website under Legislative Topics: http://legislative.cancer.gov/topics

Selected Bills With Recent Activity or Interest (113th Congress)

CHIMP Act Amendments of 2013 (S. 1561)

- This bill would amend provisions in the Public Health Service Act relating to the federal sanctuary system for surplus chimpanzees. Specifically, the bill provides the authority for the NIH to continue to fund the sanctuary system beyond the current $30 million cap if the Secretary of HHS determines that it would enable the NIH to operate more efficiently and economically by decreasing the overall federal cost of supporting and maintaining chimpanzees from FY 2014 through FY 2023.
- In addition, the bill amends a provision so that the Secretary, in consultation with the federal sanctuary Board of Directors, determines if another facility meets the standards of care in the NIH regulations instead of the Board of Directors solely making that determination.
- The Act was introduced by Senator Tom Harkin (D-IA) on 9/30/13, and was referred to the HELP

Committee. The bill was passed in the Senate by unanimous consent on 10/30/13.

Grant Reform and New Transparency (GRANT) Act of 2013 (H.R. 3316)

- The bill would amend title 31, United States Code, to provide transparency and require certain standards in the award of federal grants. The provisions include requirements for posting grant award information for each competitive grant awarded by a federal agency on a public web site. Specifically, the bill would require the posting of:
    - The executed grant agreement;
    - A copy of the grant proposal, application or plan;
    - The award decision documentation and rankings;
    - A justification for deviating from rankings; and
    - The disclosure of information on individuals who served as peer reviewers on the grant.
- The bill does include an exception to the requirement for posting grant applications if posting the full proposal would adversely affect an applicant or agency.
- In addition, the bill would require the posting of grant performance information within 60 days after the end of the period for completion of the grant.
- The Act was introduced by Rep. James Lankford (R-OK) on 10/23/2013 and was referred to the House Committee on Oversight and Government Reform. A committee consideration and mark-up session was held on 10/29/13 and the bill was voted out of committee.

Additional Information: To date, no companion bill has been introduced in the Senate.

Drug Quality and Security Act (H.R. 3204)

- The bill aims to clarify laws related to human drug compounding, and to strengthen the drug supply chain.
- Regarding drug compounding, the bill:
    - Distinguishes compounders engaged in traditional pharmacy practice from those making large volumes of compounded drugs without individual prescriptions.
    - Allows compounders who prefer to practice outside the scope of traditional pharmacy practice to register as outsourcing facilities. Compounders who choose to remain traditional pharmacies will continue to be primarily regulated by State Boards of Pharmacy as they are in current law.
    - Defines the FDA's role in oversight of outsourcing facilities, with these facilities subject to FDA oversight in much the same way as traditional manufacturers.
    - Gives providers and patients the option of purchasing products from outsourcing facilities that comply with FDA quality standards.
    - Requires the FDA to list FDA-regulated outsourcing facilities on its website, requires detailed labeling on compounded drugs, and prohibits false and misleading advertising.
    - Clarifies current federal law regarding pharmacy compounding by resolving the patchwork of current federal regulation and applying a uniform standard nationwide.
- Regarding a "track and trace" system for prescription drugs, the bill:
    - Replaces the current state product tracing laws with a uniform standard, in an effort to implement electronic, interoperable unit-level product tracing throughout the country over a ten year implementation period.
    - Requires, over seven years, that the major sectors of the pharmaceutical supply chain share and track key information about each drug's distribution history. Within ten years, supply chain stakeholders will be required to participate in electronic, interoperable product tracing.
    - Strengthens licensure requirements for wholesale distributors and third-party logistics providers. In addition, the bill would require the FDA to keep a database of wholesalers that will be available to the public through the FDA's website.
    - Establishes nationwide drug serial numbers, to be implemented by four years after the date of enactment.
- The Act was introduced by Rep. Fred Upton (R-MI), Chairman of the House Energy and Commerce Committee, on 9/28/13 and passed in the House by a voice vote on 9/28/13.

Next Generation Research Act (S. 1552)

- The main goal of this bill is to increase opportunities for the development of our next generation of researchers through the establishment of the Next Generation of Research Initiative within the National Institutes of Health (NIH).
- The proposed initiative would promote efforts aimed at improving opportunities for new researchers including efforts to strengthen mentorship programs pairing new and veteran researchers, to enhance workforce diversity efforts, and to help improve new researchers' success in obtaining renewal funding.
- The bill would require the National Academy of Sciences (NAS) to conduct a comprehensive study of legislative, administrative, educational, and cultural barriers to providing for a successful next generation of biomedical researchers.
- In addition, a report to Congress would be required within five years of the date of enactment concerning the results of the NAS study including an evaluation of the impact of sequestration on the next generation of researchers and recommendations for the implementation of policies to incentivize, improve entry to, and sustain careers in research.
- The bill was introduced by Sen. Tammy Baldwin (D-WI) on 9/26/13 and was referred to the HELP Committee.

Additional Information: During her July visit to NIH, Sen. Baldwin discussed her concerns about the limited opportunities for young scientists – at the time of her visit she was considering introducing legislation to incentivize careers in science.

PEPFAR Stewardship and Oversight Act of 2013 (S.1545/H.R.3177)

- The bill would extend authorities related to global HIV/AIDS and promote oversight of the United States Programs. The reported version of the bill would add to the requirement for an annual report a description, globally and by country, of specific efforts to address co-infections and comorbidities of HIV/AIDS, including the number and percent of people in HIV care or treated who started tuberculosis treatment; and the number and percentage of eligible HIV positive patients starting isoniazid preventative therapy.
- The Senate Committee Report indicates that the description of efforts to limit co-morbidities should include a discussion on AIDS-related cancers, including trends with respect to cervical cancer, and efforts to address such cancers.
- The Act was introduced by Sen. Robert Menendez (D-NJ) on 9/24/13 and was reported favorably out of the Senate Committee on Foreign Relations on October 2, 2013. The Act was introduced in the House by Rep. Eliot Engel on September 25, 2013, and was referred to the House Committee on Foreign Affairs.

MODERN Cures Act of 2013 (H.R. 3116)

- The bill's full title is the Modernizing Our Drug & Diagnostics Evaluation and Regulatory Network Cures Act of 2013, and it aims to address potential regulatory and reimbursement challenges that may be precluding new treatments from reaching patients, particularly those with rare and/or chronic conditions, and to remove the disincentives for the development of therapies for these unmet needs.
- If passed, the Act would establish an Advanced Diagnostics Education Council within the Department of Health and Human Services, to promote an improved understanding of key concepts related to innovative diagnostics by recommending standard terms and definitions. Members of the council would include an NIH representative.
- The bill encourages the development of drugs abandoned in the development process by creating a new category of drugs known as dormant therapies for compounds with insufficient patent protection that offer the promise to treat conditions with unmet medical needs, and also proposes steps toward creating incentives for companion diagnostics.
- The bill calls on the Secretary HHS to consider various factors in determining payment for diagnostics under the Centers of Medicare and Medicaid Services fee schedule – this includes input from patients, clinicians, and technical experts through the establishment of an independent advisory panel. The Secretary would also be required to issue public justifications of payment determinations for new diagnostic tests.

- The Act was introduced by Rep. Leonard Lance (R-NJ) on 9/17/13 and was referred to the House Committees on Energy and Commerce, Ways and Means, and Judiciary. On 9/20/13 the bill was referred to the Energy and Commerce Subcommittee on Health.

FOIA Oversight and Implementation Act of 2013 (H.R. 1211)

- The bill proposes to amend the Freedom of Information Act to provide for greater public access to information, specifically in an electronic, publicly accessible format.
- The bill would require OMB to establish a single FOIA website, accessible to the public at no cost, which allows the public to submit requests for public records and to receive automated information about the status of a request.
- The bill would also require agencies to post online all records that have been released through FOIA three or more times.
- The bill was introduced by Rep. Darrell Issa (R-CA) on 3/15/13 and was amended and approved by the Committee on Oversight and Government Reform on 3/20/13. The bill was reported to the full House on 7/16/13.

Additional Information: If enacted, these amendments would change current procedures as all FOIA requests are currently received by mail, fax, or email and requested records are not generally made available online.

Selected New Bills (113th Congress)

Breast Density and Mammography Reporting Act of 2013 (H.R. 3404):

- The bill would amend the Mammography Quality Standards Act (MSQA) of 1992 to require mammography results to include the patient's relative breast density, and for that information to be reported to patients.
- The Act was introduced by Rep. Rosa DeLauro (D-CT), along with Rep. Steve Israel (D-NY), on 10/30/13 and was referred to the Committee on Energy and Commerce.

Additional Information: Reps. DeLauro and Israel introduced a similar bill in the 112th Congress and it did not move out of committee. Bill text is not yet available for H.R. 3404. Based on Rep. DeLauro's press release, the bill appears to be similar to her earlier proposal, which would have also required patients be informed of their relative risk of developing breast cancer associated with their level of breast density, as well as communication to patients that individuals with more dense breasts may benefit from supplemental screening. The release also notes that Sen. Dianne Feinstein (D-CA) plans to introduce a companion bill in the Senate. Additionally, independent of this legislative proposal, the FDA has already scheduled a notice of proposed rule making for a breast density reporting amendment to the MSQA for December 2013.

Eliminating Disparities in Breast Cancer Treatment Act of 2013 (H.R. 3295)

- The bill would amend title XVIII of the Social Security Act to require development of a uniform set of consensus-based breast cancer treatment performance measures for a 6-year quality reporting system and value-based purchasing system under the Medicare program (with an aim of eliminating disparities in treatment based on race, level of education, income, and health insurance status).
- The bill would establish that beginning in October 2017 Medicare base payments would be tied to the quality of care provided as assessed by the standards established through the quality reporting system. Additionally, if providers fail to submit data in accordance with the bill's requirements, the Secretary HHS shall reduce their payments.
- The proposal also calls for reporting every six months, beginning 10/1/15, that would include an evaluation of the number of health care providers submitting data, an analysis of whether the system is successful in reducing disparities in breast cancer treatment, and recommendations on whether and to what extent to extend the system.
- The Act was introduced by Rep. Kathy Castor (D-FL) 10/16/13 and was referred to the Committee on Ways and Means and the Committee on Energy and Commerce.

Biennial Budgeting and Appropriations Act of 2013 (HR 3059)

- The bill proposes a biennial budget process that will authorize and appropriate funds for both fiscal years within each biennium beginning on October 1 of every odd-numbered year.
- The bill was introduced on 8/2/13 by Rep. Ed Whitfield (R-KY) and was referred to the Committees on Budget, Oversight and Government Reform, and Rules.

The Conference Accountability Act of 2013 (S 1347)

- The bill seeks to provide transparency, accountability, and limitations on Government sponsored conferences.
- The bill would:
    - Not allow any agency to pay travel expenses for more than 50 employees to attend an international conference;
    - Limit annual travel expenses for FY 2014 through FY 2018 to not more than 80 percent of the aggregate amount of travel expenses in FY 2010;
    - Limit agencies to $500,000 to support a single conference and to funding only one conference by an outside organization during any fiscal year; and
    - Require a report to be posted on the agency's public website outlining all travel expenses paid during the preceding quarter.
- The bill was introduced on 7/23/13 by Sen. Tom Coburn (R-OK) along with Sens. McCain (R-AZ), Chiesa (R-NJ), Enzi (R-WY), and Ayotte (R-NH) and was referred to the Committee on Homeland Security and Governmental Affairs.

Critical Care Assessment and Improvement Act of 2013 (H.R. 2651)

- The bill would require the HHS Secretary to coordinate with the Institute of Medicine and submit a report to Congress on the current national state of critical care services and develop recommendations to strengthen critical care capabilities.
- The bill directs the NIH to establish a Critical Care Coordinating Council specifically requiring representation from NHLBI, NINR, NICHD, NIGMS, and NIA, but allowing the inclusion of additional ICs as appropriate. Directives for this council include coordinating and catalyzing funding opportunities, coordinating and analyzing current research on critical care issues, and providing an annual report with recommendations to the NIH director.
- Additional provisions include:
    - HRSA – update a 2006 study on of critical care workforce, and expand it to address supply and demand regarding the spectrum of health care professionals involved in critical care.
    - CMS – implement a project designed to improve the quality and efficiency of care provided to critically ill patients.
- The bill was introduced by Rep. Erik Paulsen (R-MN) on 7/10/2013 and referred to the House Committees on Energy and Commerce, and Ways and Means. The bill was then referred to the Energy and Commerce Subcommittee on Health on 7/12/13.

Caroline Pryce Walker Conquer Childhood Cancer Reauthorization Act (H.R. 2607/S. 1251)

- This bill is a reauthorization of the original Caroline Pryce Walker Conquer Childhood Cancer Act that was passed unanimously in the House and the Senate in 2008 (named in honor of former Representative Deborah Pryce's daughter, Caroline).
- The bill would authorize appropriations through 2018 (the Senate version offers such sums as necessary; the House version caps the authority at $10 million per year), and changes the authorized activities, substituting the following:
    - The bill would expand on existing childhood cancer biorepository resources to include specimens and clinical and demographic information from children, adolescents, and young adults (CAYA) diagnosed with cancer (not just those enrolled in NCI-sponsored studies) in comprehensive pediatric cancer biorespositories with the goal of including 90 percent of CAYA in the effort.

    - The bill would also authorize the CDC to award grants for state cancer registries to enhance and expand infrastructure for identifying and tracking incidences of CAYA cancers.
    - The bill would direct a GAO study to investigate the feasibility of expanding FDA requirements for pediatric studies of adult oncologic drugs and make recommendations for overcoming any research barriers.
- H.R. 2607 was introduced by Rep. Chris Van Hollen (D-MD) on 6/28/13 and was referred to the House Energy and Commerce Committee. On 7/5/13, the bill was referred to the Subcommittee on Health. S. 1251 was introduced by Sen. Jack Reed (D-RI) on 6/27/13 and referred to the Senate Committee on Health, Education, Labor, and Pensions.

Additional Information: This bipartisan reauthorization was introduced in the House by Rep. Chris Van Hollen (D-MD) and Rep. Michael McCaul (R-TX), co-chairs of the Childhood Cancer Caucus.

<u>Pediatric, Adolescent, and Young Adult Cancer Survivorship Research and Quality of Life Act (S. 1247) and Childhood Cancer Survivors' Quality of Life Act of 2013 (H.R. 2058)</u>

- Both bills would authorize $15 million each year for five years for the HHS Secretary to award grants for pilot programs to develop or evaluate model systems for monitoring and caring for childhood cancer survivors.
- Both bills would authorize an additional $5 million each year for five years for the HHS Secretary to establish a Workforce Development Collaborative on Medical and Psychosocial Care for Pediatric Cancer Survivors. The collaborative would include educators, consumer and family advocates, and providers of psychosocial and biomedical health services.
- The House bill would also authorize $10 million each year for five years for the NIH Director to award grants for research on the causes of health disparities in pediatric cancer survivors and conduct or support research on follow-up care for pediatric cancer survivors
- S. 1247 was Introduced by Sen. Jack Reed (D-RI) on 6/27/13 and referred to the Committee on Health, Education, Labor, and Pensions. H.R. 2058 was introduced by Rep. Jackie Speier (D-CA) on 5/20/13 and was referred to the Energy and Commerce Committee, Subcommittee on Health on 5/24/13.

Additional Information: Both bills are similar to the Pediatric, Adolescent, and Young Adult Cancer Survivorship Research and Quality of Life Act of 2011 which was introduced by Rep. Speier and Sen. Reed in the 112th Congress. The legislation was never considered in the House or the Senate in the 112th Congress.

<u>Planning Actively for Cancer Treatment (PACT) Act of 2013 (H.R. 2477)</u>

- The bill states that people diagnosed, treated, or having survived cancer should, with a medical professional, have the ability to construct, modify, and re-examine, a treatment/survivorship plan of action for a primary or re-occurring diagnosis of cancer.
- The bill was introduced by Lois Capps (D-CA) on 6/25/13 and was referred to the House Committee on Energy and Commerce, and the Committee on Ways and Means. On 6/28/13, the bill was referred to the Subcommittee on Health.

Additional Information: Sen. Mark Warner introduced a similar bill, the Care Planning Act of 2013 (S 1439), on 8/1/13. This bill encompasses a broad range of late-stage diseases (not limited to cancer) and would provide for advanced illness care coordination services, including the development of a care plan, for Medicare beneficiaries. This bill was referred to the Committee on Finance on 8/1/13.

<u>Women's Preventive Health Awareness Campaign (H.R. 2457)</u>

- This bill directs the HHS Secretary to carry out a national public outreach and education campaign to raise awareness of women's preventive health measures including cancer screenings (e.g. cervical and breast), immunizations, and prenatal visits.
- The bill would require a media and website component, information dissemination about screening and prevention services, and address health disparities in women's prevention.
- Funding would come from existing DHHS monies.
- The bill does not mention any component of the NIH.

- The bill was introduced by Rep. Ami Bera (D-CA) on 6/20/13 and was referred to the House Committee on Energy and Commerce. On 6/21/13 the bill was referred to the Subcommittee on Health. The bill has 47 co-sponsors.

Selected Recent Resolutions (113th Congress)

This section highlights resolutions introduced to raise awareness about specific diseases. It is important to note that resolutions are different than bills, in that they are used to express the sentiment of one chamber (House or Senate) on an issue. As such, resolutions do no not require concurrence of the other chamber or approval by the president, and they do not have the force of law.

Passed

Designating September 2013 as National Ovarian Cancer Awareness Month (S. Res. 205)

- This resolution designates September 2013 as National Ovarian Cancer Awareness Month.
- S. Res. 205 was introduced by Sen. Debbie Stabenow (D-MI) on 7/30/13 and was adopted by unanimous consent.

Additional Information: A similar resolution was introduced in the House on 7/16/13 by Rep. Steve Israel (D-NY). The resolution was referred to the Committee on Oversight and Government Reform, but it has not been adopted.

Designating September 2013 as National Prostate Cancer Awareness Month (S. Res. 206)

- This resolution designates September 2013 as National Prostate Cancer Awareness Month.
- S. Res. 206 was introduced by Sen. Jeff Sessions (R-AL) on 7/30/13 and was adopted by unanimous consent.

Introduced

Expressing Support for Designating September 26, 2014 as "National Pediatric Bone Cancer Awareness Day" (H. Res. 362; 113th Congress)

- This resolution expresses support for the designation of September 26, 2014 as "National Pediatric Bone Cancer Awareness Day."
- H. Res. 362 was introduced by Rep. Blake Farenthold (R-TX) on 9/27/13 and was referred to the Energy and Commerce Committee.

A resolution expressing the sense of the Senate that the USPSTF should reevaluate its recommendations against PSA-based screening for prostate cancer (S. Res. 251; 113th Congress)

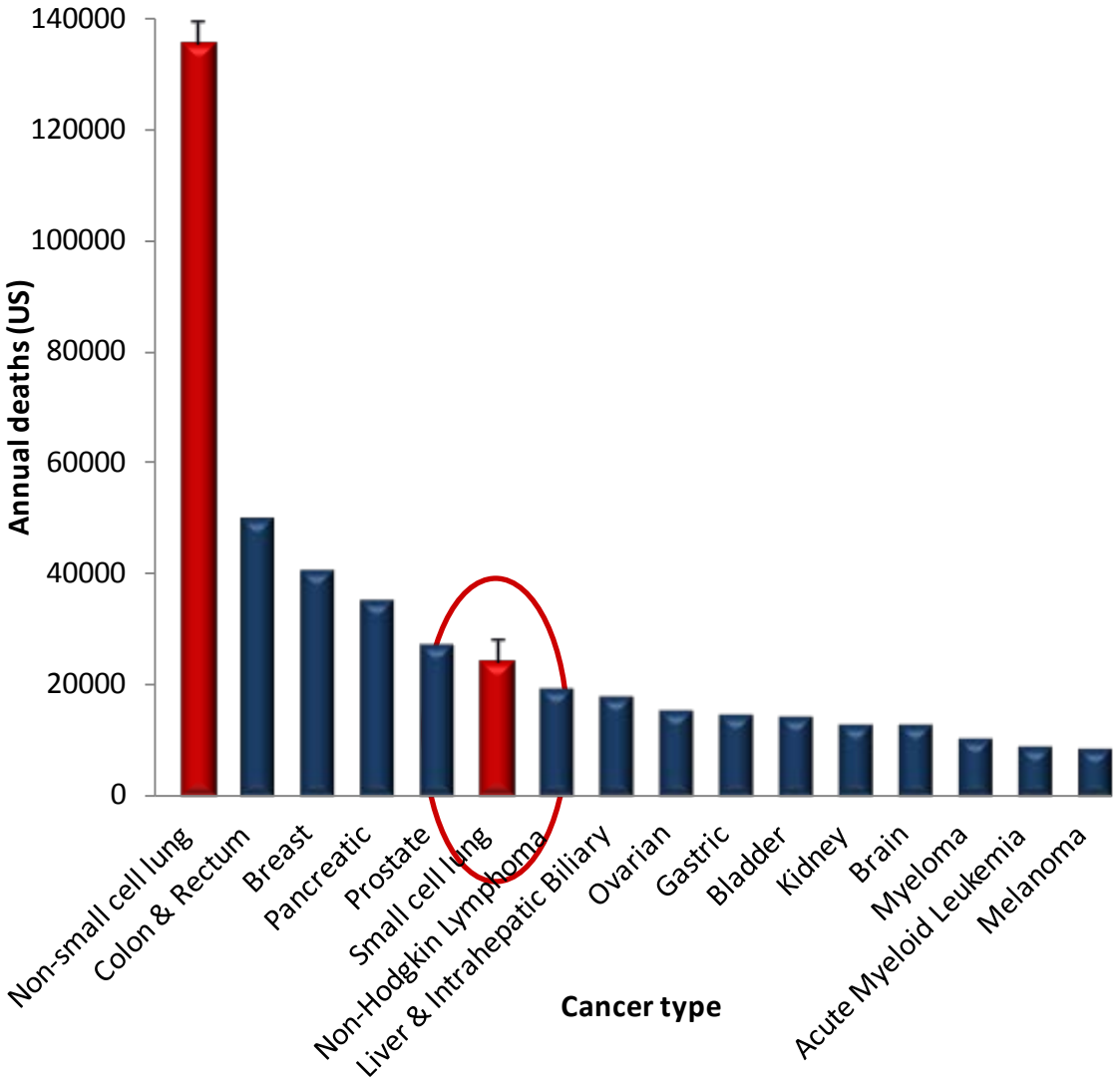
- A resolution expressing the sense of the Senate that the United States Preventive Services Task Force should reevaluate its recommendations against prostate-specific antigen-based screening for prostate cancer for men in all age groups in consultation with appropriate specialists.
- This resolution was introduced by Sen. Jeff Sessions (R-AL) on 9/23/13 and was referred to the Committee on Health, Education, Labor, and Pensions.

Interim Report to NCI CTAC: Small Cell Lung Cancer Working Group

Charles Rudin MD PhD

Memorial Sloan-Kettering Cancer Center

US cancer deaths



Small cell lung cancer: a recalcitrant cancer in need of novel approaches

- 2/3 patients present with extensive stage at diagnosis
  - Median survival approximately 9 months from diagnosis
  - Standard combination chemotherapy
    - 1980: Cisplatin + etoposide
    - 2011: Cisplatin + etoposide
- 1/3 present with limited stage disease
  - Median survival approximately 18 months from diagnosis
  - Same standard chemotherapy, plus concomitant radiation
- There is a *critical need* for more effective therapy for this disease

NCI Workshop on Small Cell Lung Cancer

July 8 – 9, 2013; Bethesda

Chairs: Rudin and Minna

- Emerging opportunities in omics, molecular pathology, and early detection
  - Chairs: Steve Baylin and Eric Haura
  - Speakers: Linnoila, Wistuba, Thomas, Byers, Poirier
- Emerging opportunities in preclinical models and targeting cancer stem cells
  - Chairs: Anton Berns and Tyler Jacks
  - Speakers: Peacock, McFadden, Jahchan, Berns, Ball, White
- Emerging opportunities in therapeutics and new drug targets
  - Chairs: Bruce Johnson and Joan Schiller
  - Speakers: Teicher, Krug, Pietanza, Hann, Dylla
- Attracting investigators to the field of small cell lung cancer
  - Chair: Paul Bunn
- Summary and recommendations
  - Chairs: John Minna and Charles Rudin

Recent scientific advances and emerging research questions

- Characterization of the SCLC genome, transcriptome, and epigenome
- Analysis of acquired chemotherapy resistance in SCLC
- *TP53* and *RB* as gatekeeper mutations in SCLC
- MYC family members in SCLC
- Developmental and stem cell signaling pathways in SCLC

Recent progress in defining drivers and targets in SCLC

Comprehensive genomic analysis identifies *SOX2* as a frequently amplified gene in small-cell lung cancer

Charles M Rudin[1,8], Steffen Durinck[2,3,8], Eric W Stawiski[2,3,8], John T Poirier[1,8], Zora Modrusan[2,8],

NATURE GENETICS VOLUME 44 | NUMBER 10 | OCTOBER 2012

Recurrent mutations in *PTEN*, *PIK3CA, EP300, MLL2*; amplification of *SOX2*, recurrent fusion of *RLF-MYCL1*

Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer

Martin Peifer[1,2,57], Lynnette Fernández-Cuesta[1,2,57], Martin L Sos[1–4], Julie George[1,2], Danila Seidel[1,2,5],

VOLUME 44 | NUMBER 10 | OCTOBER 2012 NATURE GENETICS

Recurrent mutations in *CREBBP*, *EP300*, *MLL*; mutations in *PTEN*, *SLIT2*, *EPHA7*; amplification of *FGFR1*

A framework for identification of actionable cancer genome dependencies in small cell lung cancer

Martin L. Sos[a,b,c,d,1,2], Felix Dietlein[a,b,1], Martin Peifer[a,b], Jakob Schöttle[a,b], Hyatt Balke-Want[a,b], Christian Müller[a,b],

17034–17039 | PNAS | October 16, 2012 | vol. 109 | no. 42

Cell line sensitivity screening suggests aurora kinase inhibitors active in *MYC*-amplified SCLC

Proteomic Profiling Identifies Dysregulated Pathways in Small Cell Lung Cancer and Novel Therapeutic Targets Including PARP1

Lauren Averett Byers, Jing Wang, Monique B. Nilsson, et al.

SEPTEMBER 2012 CANCER DISCOVERY | 799

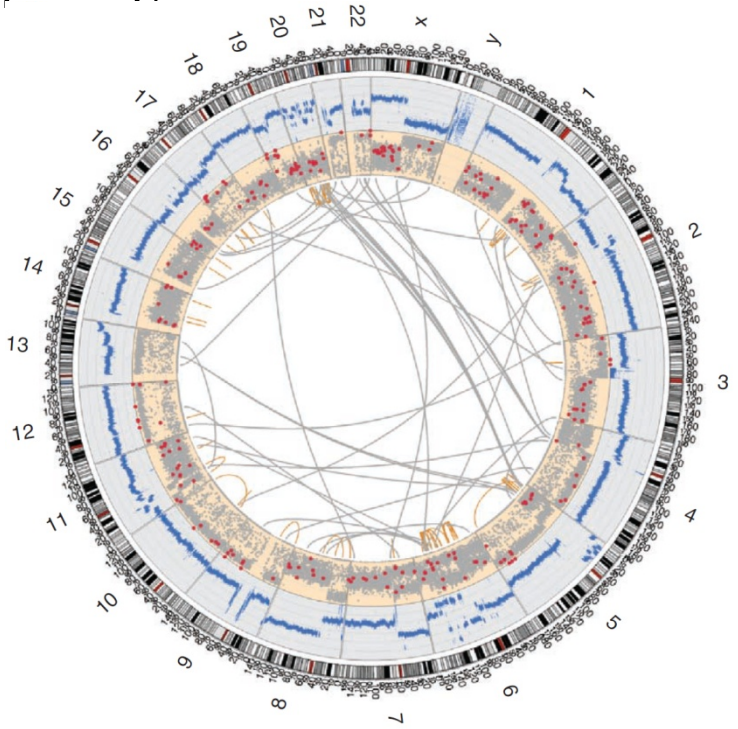
Proteomic profiling suggests EZH2 and PARP1 as therapeutic targets in SCLC

Characterization of the SCLC genome

- 2 comprehensive genomics papers last year defined important aspects of the genomic landscape of SCLC
  - *Rudin et al.* 35 primary tumors and 28 cell lines
  - *Peifer et al.* 29 primary tumors
  - These provide needed insight into the genomic landscape of SCLC
  - However, for tumors of this complexity, this N is not sufficient

Non-synonymous mutation rate
5.5/Mb

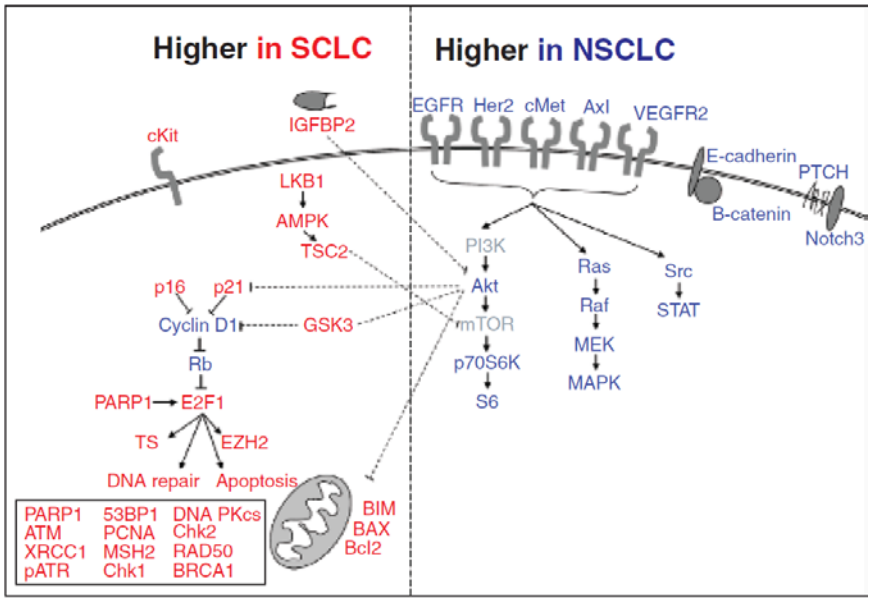
175
mutations per tumor

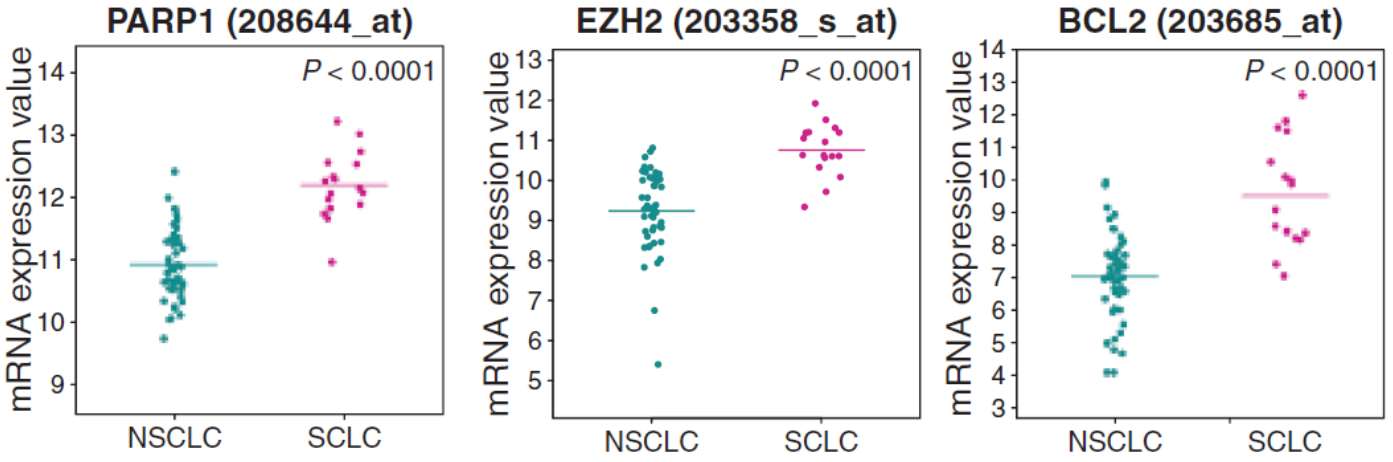


Approaches to identifying relevance

- Hot spot mutations
  - *TP53, RB1, PIK3CA, CDKN2A, PTEN*
  - RAS family regulators (*RAB37, RASGRF1, RASGRF2*)
  - Chromatin modifiers (*EP300, DMBX1, MLL2, MED12*, etc.)
- Hot spot mutations *PLUS* q-score
  - *RUNX1T1, CDYL, RIMS2*
- Gene families and pathways
  - PI3K pathway, Notch and Hedgehog, glutamate receptor family, DNA repair/checkpoint, SOX family
- Focal amplifications
  - *MYC, SOX2, SOX4, KIT*
- Recurrent translocations and fusion genes
  - Recurrent: *RLF–MYCL1*
  - Kinase fusions
- ...

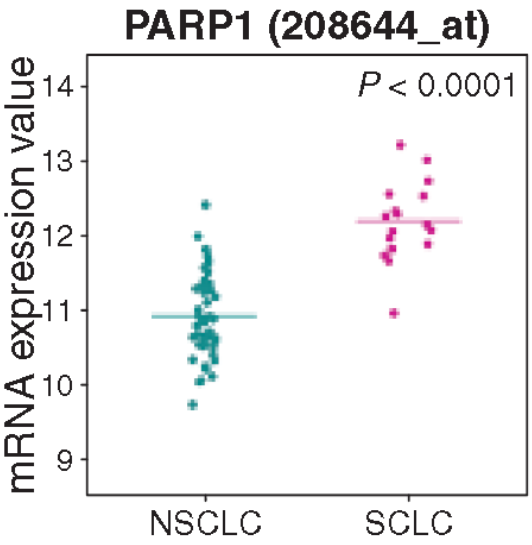
Proteomic profiling in SCLC using RPPA

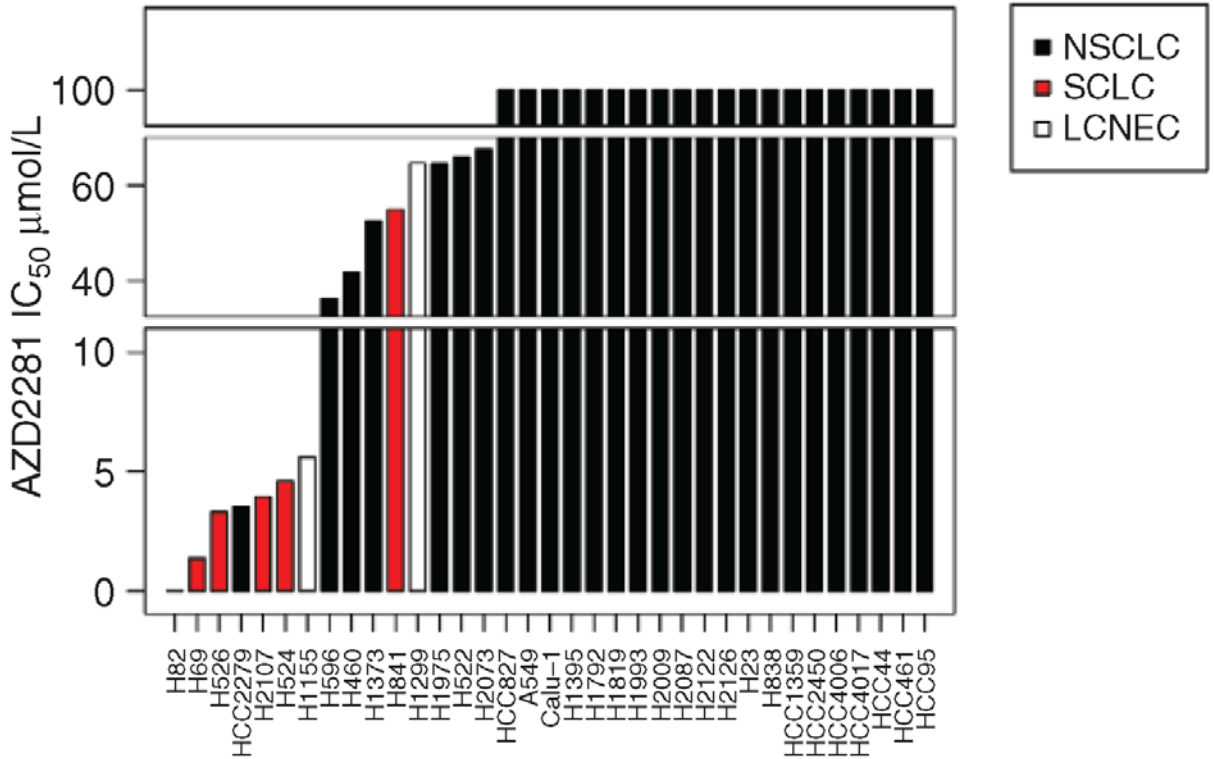




Byers et al., *Cancer Discovery* 2012

PARP1 expression and sensitivity to PARP inhibitor therapy

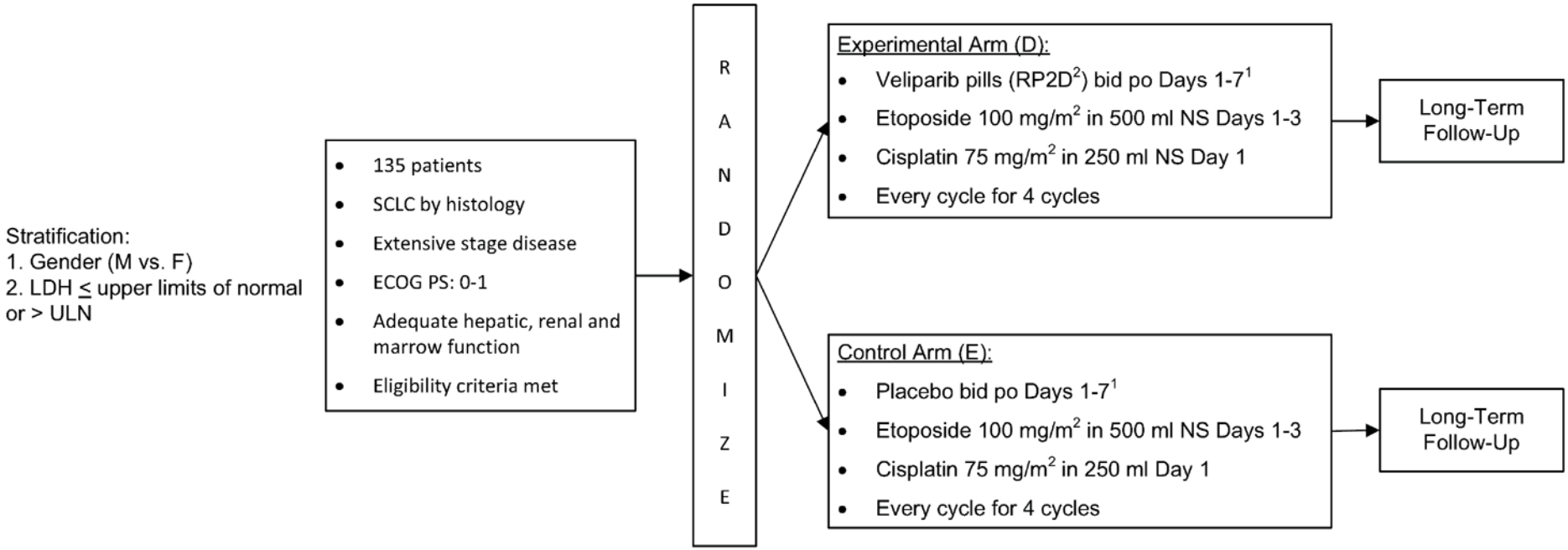




Byers et al., *Cancer Discovery,* 2012

ECOG 2511
Phase I/II cisplatin/etoposide +/- veliparib (ABT-888)

- Placebo-controlled first line randomized phase II study



Phase II Accrual Goal = 150
Cycle = 3 weeks (21 days)
IV doses are based on actual weight

Study Chair: Taofeek Owonikoko MD PhD

Analysis of acquired chemotherapy resistance in SCLC

- One of the exceptional features of SCLC is its initial responsiveness to therapy (70% RR for extensive stage disease; higher for limited with XRT)
- These responses are remarkably short-lived, with acquired resistance rapidly developing, resulting in chemorefractory recurrence and median survival of 9 mo (extensive stage) or 18 mo (limited stage) from diagnosis

- The basis for this shift from *de novo* chemosensitivity to subsequent chemoresistance is almost entirely unstudied.
  - Lack of repeat biopsies

TP53 and *RB* as gatekeeper mutations in SCLC

- Almost all SCLC are characterized by concomitant loss of these two key tumor suppressor genes
- A mouse model in which these 2 genes are deleted in lung epithelial cells results in a cancer closely resembling SCLC
  - Anton Berns
  - Further analyzed by Tyler Jacks and Julien Sage

- The biology of the interaction between these 2 signature events has not been extensively studied
  - Does this create unique tumor cell vulnerabilities?

MYC family members in SCLC

- *c-MYC* is amplified and/or overexpressed in many SCLC
- A recurrent fusion transcript *RFL-MYCL1* was found in genomic profiling of SCLC
  - In a primary SCLC and 2 cell lines
  - *MYCL1* siRNA suppresses proliferation

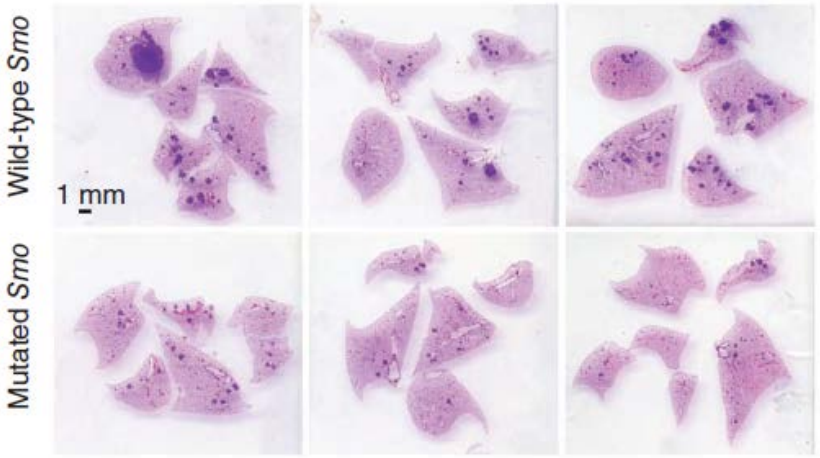
- Could a focused program to look at anti-MYC strategies yield progress in SCLC
  - Direct and indirect inhibitors (e.g. BRD4 inhibitors)

Developmental and stem cell signaling pathways in SCLC

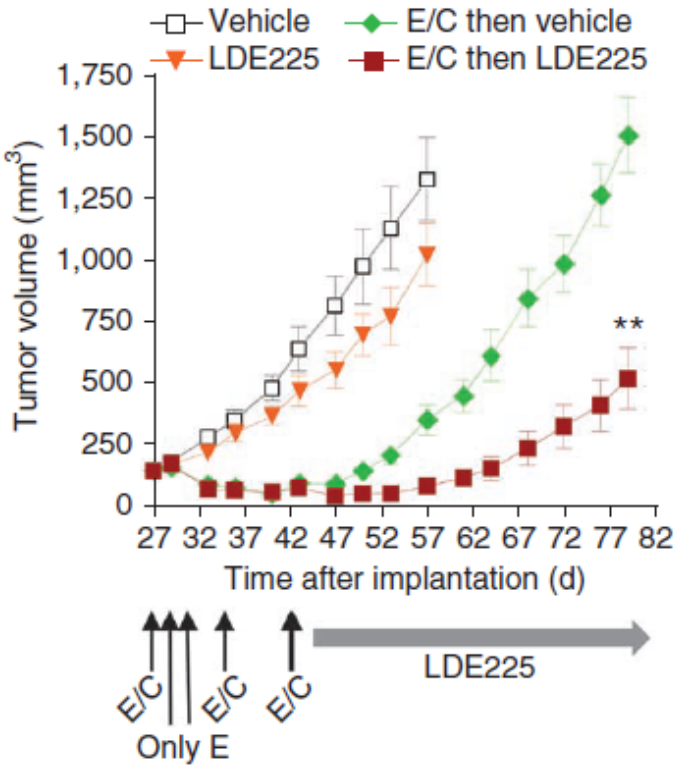
- SCLC is a highly clonogenic tumor characterized by early and widespread metastasis
- Multiple developmental regulatory pathways that may influence clonogenic capacity have been implicated in SCLC biology
  - ASCL1/Notch
  - Hedgehog
    - The first clinical trial of a HH inhibitor in extensive stage SCLC was negative
  - SOX2
- Might these represent unique targets of vulnerability in SCLC?

An apparent requirement for Hedgehog signaling

Oncogenesis in p53$^{-/-}$ RB$^{-/-}$ conditional mutant mouse

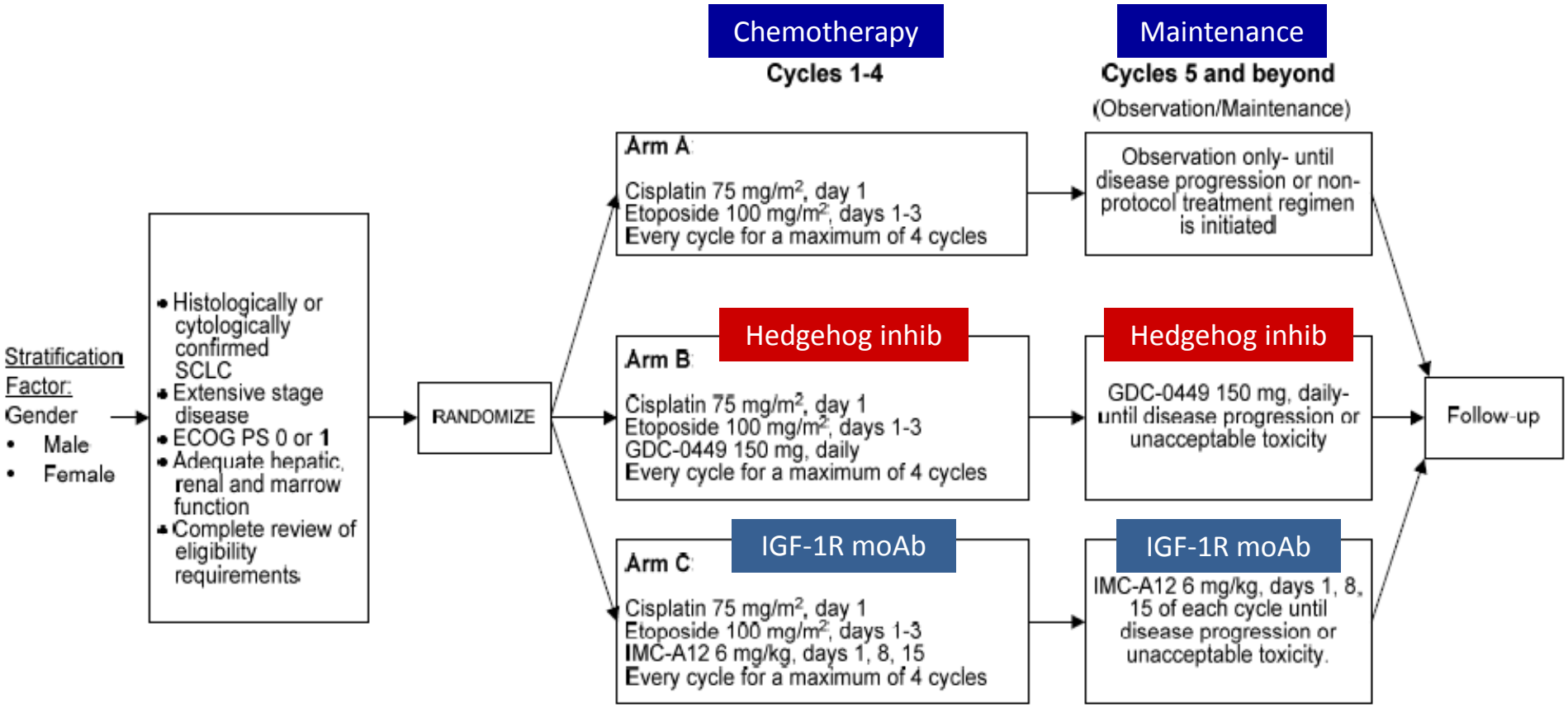


Inhibition of growth in a human PDX model



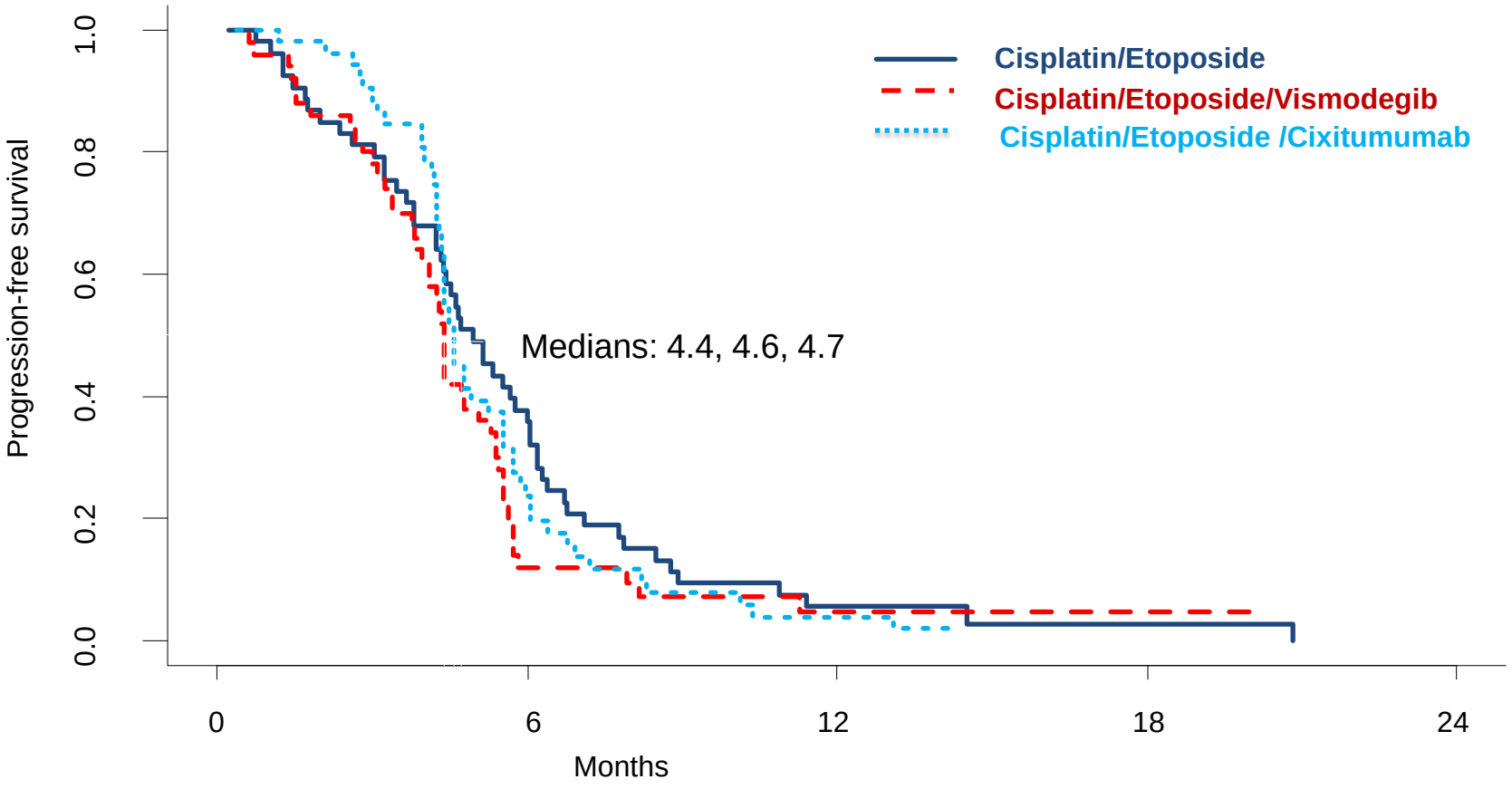
Park et al., *Nature Med* 2011

E1508: a randomized phase II study of chemotherapy +/- inhibitors of Hedgehog signaling or IGF-1R



Belani & Rudin

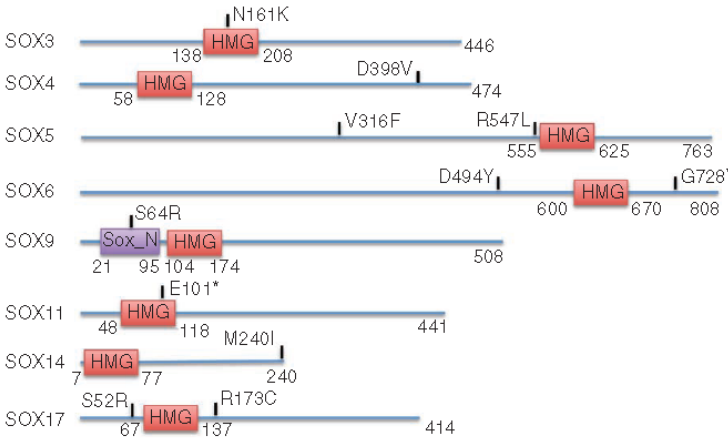
Neither targeted inhibitor improved outcome in patients with SCLC

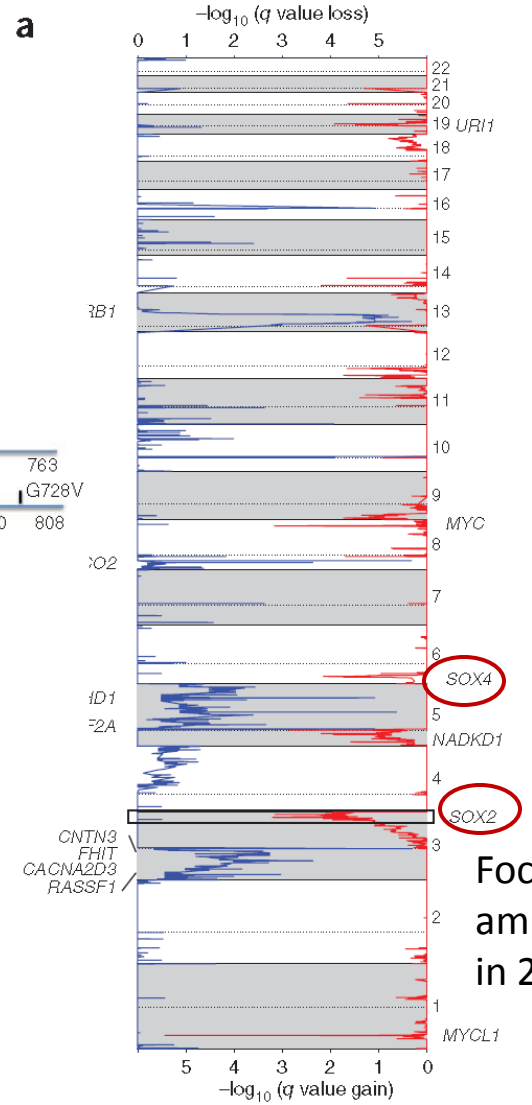


Belani & Rudin

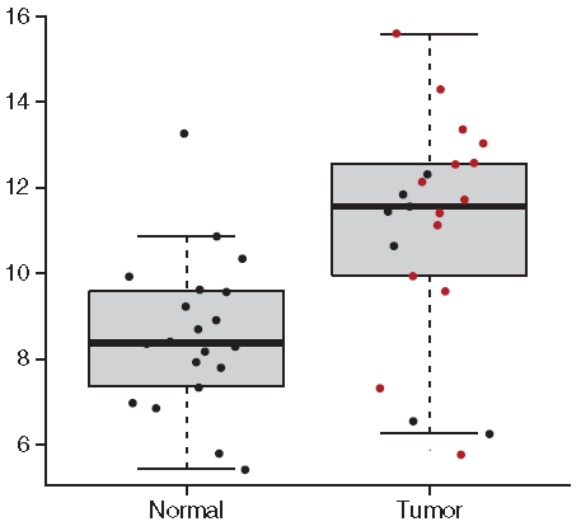
SOX family dysregulation in SCLC

SOX family mutations



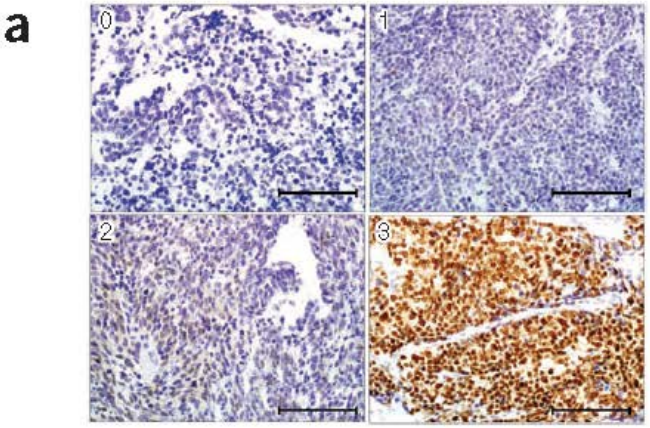


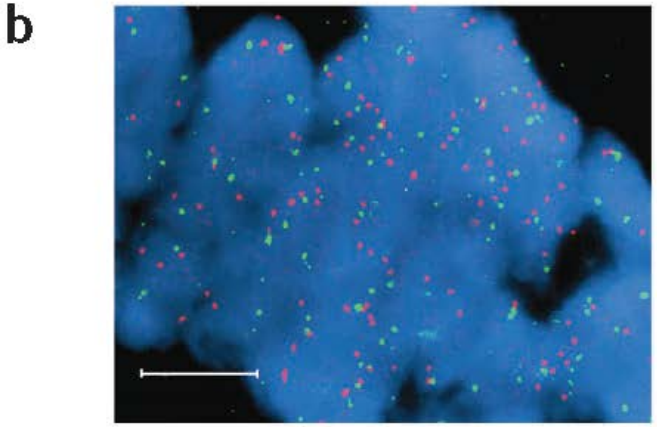
SOX2 expression

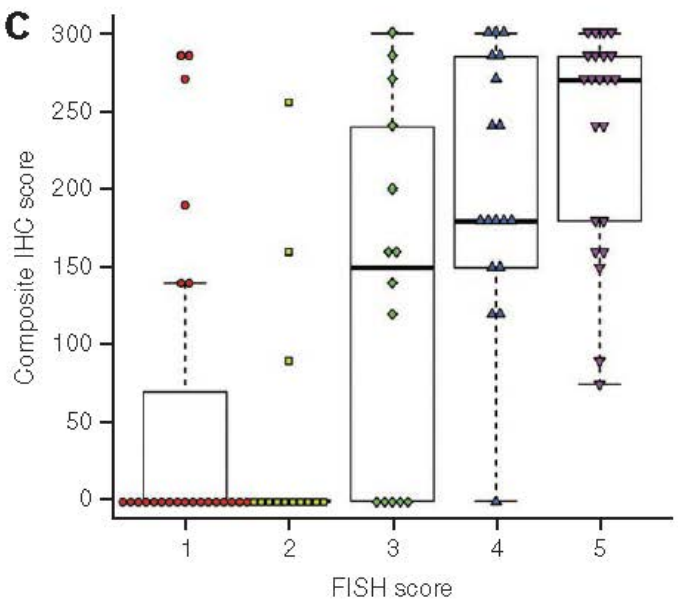


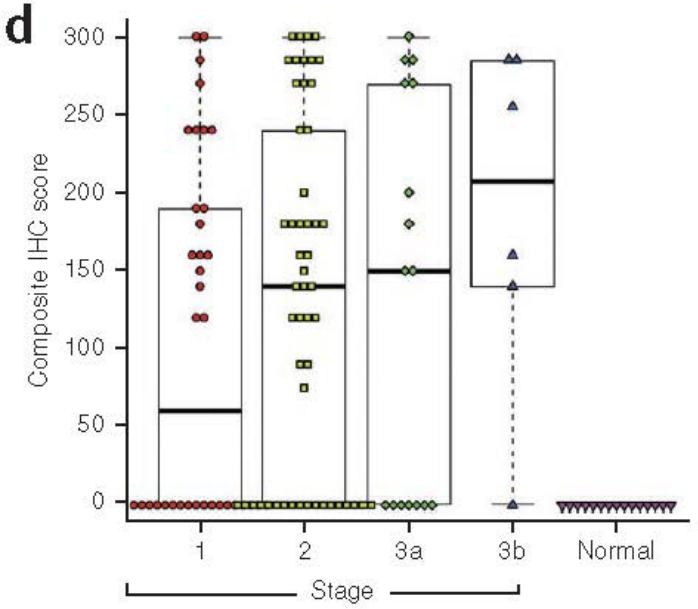
Focal amplification in 27%

SOX2 copy number correlates with expression and stage

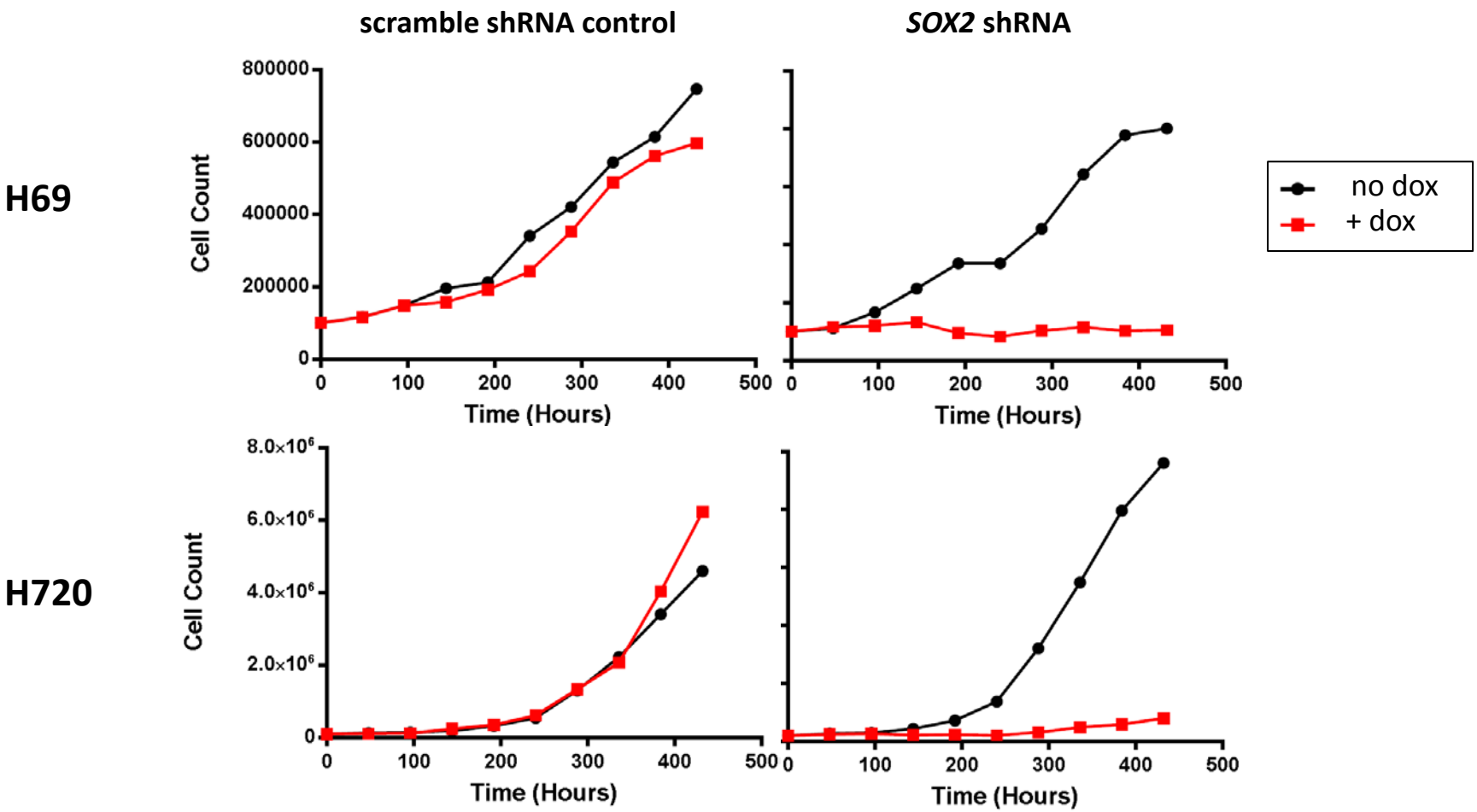








Targeted *SOX2* inhibition blocks SCLC proliferation



Recommended initiatives

- Optimizing collection of SCLC representing distinct phases of the disease
  - Need for additional biopsy material was a consistent theme
  - Notable lack of paired samples of newly diagnosed and recurrent dx

- Focused mutational profiling
  - Need for much more extensive genomic and proteomic analysis to define targets and their frequencies (e.g. *FGFR1* amplification; PARP1 overexpression)

- Targeting driver oncogenes and tumor suppressors in SCLC
  - *TP53/RB*
  - *MYC* family members
  - Developmental regulatory pathways

NCTN Working Group Interim Report

Robert Diasio, MD
George Sledge, MD
Co-Chairs, NCTN Working Group

November 6, 2013

NCI Clinical Trials and Translational Research Advisory Committee

NCTN WG Charge

Initial Focus

1) Assess the strength and balance of the active NCTN clinical trials portfolio

- Within each *disease*
- *Across all diseases*

2) Recommend new strategic priorities and directions for the NCTN based on:

- Current trial portfolio and gaps
- Evolving clinical needs
- Emerging scientific opportunities

3) Review and assess the CTWG Evaluation process and results

- Quality of completed trial outcomes
- Operational performance of Scientific Steering Committees
- Efficiency of clinical trial conduct

4) Provide strategic advice to enhance NCTN clinical trial operations

- E.g. Collaboration and timeliness

Portfolio Assessment Overview

- **4 meetings held to assess the NCTN trial portfolio**
  - Assessed strength and balance of the NCTN portfolio
  - Recommended strategic priorities and directions

- **Portfolios from 14 Steering Committees assessed**

Meeting Date	Portfolios Assessed
July 2012 (pilot)	Colorectal cancer from GI portfolio
Dec. 2012	Breast, GI (minus colorectal), GU, leukemia, lymphoma
Mar. 2013	Myeloma, thoracic, brain (adult and pediatric), pediatric (solid tumor and leukemia and lymphoma)
July 2013	Gynecologic, clinical imaging, symptom management/quality of life, head and neck

Criteria for Evaluating Trials

Feasibility	• Accrual difficulty • Time and cost to implement at sites
Clinical Importance	• Importance of study question relative to state of the science in the disease • Benefit per patient and for population (e.g. life years saved) • Benefit in light of disease context
Scientific Contribution	• Tests important scientific or clinical proof of principle question • Importance of integral or integrated correlative study questions
Unique Suitability for NCTN Program	• Understudied/rare diseases or understudied populations • Radiotherapy/surgery/imaging techniques • Combination trials • Therapy optimization trials (e.g., alternative regimens) • Unlikely to be performed by industry • Provides important tissue or data resources for public use

Cross-Portfolio Recommendations

- **Aimed at improving the portfolios and are directed jointly to the NCTN Groups, Scientific Steering Committees and the NCI**

- **Fall into 5 major categories**
  - **Emphasize Innovative Science Driven Trials**
  - **Consider Reallocation of NCTN Resources**
  - **Enhance Coordinated Strategic Planning**
  - **Strengthen Evaluation Criteria**
  - **Optimize Steering Committee Processes**

Emphasize Innovative Science Driven Trials

- NCTN Groups and Steering Committees should work together to achieve the appropriate balance of innovative, biology-driven randomized phase 2 trials and larger, more resource intensive phase 3 trials in each disease portfolio.

- NCTN Groups and Steering Committees should emphasize biology-driven (e.g., molecularly-driven, pathway-driven) trials that advance the science by incorporating genomics, biomarker tests and correlative science into study designs.

Consider Reallocation of NCTN Resources

- NCI should conduct an analysis of resource allocation across diseases, taking into account current survival rates and likely cost/benefit from additional advances.

- To empower innovative, biology-driven trials, additional NCI funding should be provided for correlative science studies, biomarker validation and the development of molecular classification algorithms.

Enhance Coordinated Strategic Planning

- Steering Committees should increase their involvement in strategic planning and guidance for future trials in collaboration with the NCTN Groups.

- Greater emphasis should be placed on sharing strategic and tactical best practices across diseases in terms of trial design, accrual, preliminary data requirements, etc.

Strengthen Evaluation Criteria

- Accrual challenges should be taken more seriously in proposing and approving trial concepts, balancing the importance of the clinical question with the perceived difficulty of accrual.

- More consideration should be given to competing European and industry trials in proposing and approving trial concepts as well as to the potential for collaboration with European and industry partners.

- Steering Committees should develop standardized guidelines for the level and types of preliminary data required for trial concepts.

Optimize Steering Committee Processes

- Steering Committees should optimize their use of Task Forces, Working Groups and Clinical Trial Planning Meetings.

CTAC Reporting on Portfolio Assessment

Meeting Date	Portfolios Assessed	Presented to CTAC?
July 2012 (pilot)	Colorectal cancer from GI portfolio	Previously presented
Dec. 2012	Breast, GI (minus colorectal), GU, leukemia, lymphoma	
Mar. 2013	Myeloma, **thoracic**, **brain** (adult and pediatric), pediatric (solid tumor and leukemia and lymphoma)	**Bold** presented today, remainder presented at a future meeting
July 2013	**Gynecologic**, clinical imaging, **symptom management/quality of life, head and neck**	

Thoracic Portfolio

- **Summary conclusions**
  - Strength of concepts submitted to the Steering Committee has improved over time
  - Excellent job carving out NCTN niche and not directly competing with industry
  - Recent trials incorporate local treatment modality approaches and biomarkers, in addition to testing new agents
  - Master screening protocols linked with testing of multiple therapies viewed as an important advance, including the collaboration with TCGA to sequence specimens from the ALCHEMIST screening protocol

- **Key recommendations**
  - Find ways to accrue a larger proportion of screened patients to NCTN trials
  - Form closer collaborations with industry so that screened patients ineligible for NCTN studies can be referred to industry protocols
  - Ensure that screened patients are representative of national population

The Steering Committee has done a good job working together and should consider ways to examine and mitigate barriers to accrual.

Brain Portfolio

- **Summary conclusion**
  - Pediatric brain cancer generally viewed as a strong portfolio of trials

- **Key recommendations**
  - Focus on developing more biology-based, genomics-based, and pathway-directed trials involving biomarkers
  - Integrate genomics and correlative science into future protocols whenever possible perhaps through collaboration with the adult brain SPOREs
  - More consideration should be given as to whether studies should be designed as phase 2 or phase 3
  - Explore combination therapies as single agents are often not optimally effective
  - Broaden scope of adult brain portfolio beyond bevacizumab and try to develop some late phase trials

The Steering Committee should strive for better collaboration with the NCTN Groups and should consider reviewing all phase 2 protocols for adult brain cancer, as they do for pediatric brain cancer.

Gynecologic Portfolio

- **Summary conclusions**
  - Recent increase in randomized phase 2 and phase 3 trials over single arm phase 2 trials
  - Strong international collaborations and generally strong accrual record

- **Key recommendations**
  - Work to achieve better balance between innovative, science-driven trials and incremental/ confirmatory trials
  - Focus on translational science with clear endpoints and goals including greater collaboration with SPOREs and other translational investigators
  - Pursue more systematic design of trials based on past positive or negative results
  - For ovarian trials, include endpoints other that PFS and expand beyond the current focus on bevacizumab
  - The cervical portfolio should focus more on detection, prevention and radiation therapy trials

The Steering Committee and GOG along with NCI should work together more closely in developing future strategic directions.

Symptom Management/Quality of Life Portfolio

- **Summary conclusions**
  - Addresses wide variety of symptoms across many disease sites
  - Good accrual record and uniquely suited to the NCTN program

- **Key recommendations**
  - Emphasize trials of new interventions over trials that disprove or confirm current interventions
  - Strengthen the basic science and preclinical foundation for trials, collaborate with symptom management scientists working in other fields to leverage synergies
  - Conduct fewer, but more in depth, trials based on strong biological evidence, exploring innovative agents , comparing interventions against one another rather than placebo, and employing multi-agent therapies
  - Pursue more systematic design of trials based on past positive or negative results

The Steering Committee , the CCOP Research Bases, and NCI should collaborate in developing strategic directions and standard data definitions, endpoints, etc. so trials can more easily be compared.

Head & Neck Portfolio

- **Summary conclusions**
  - Strong portfolio , potentially practice-changing trials, endpoints aggressive and seek major increases in benefit instead of incremental progress
  - Uniquely suited to the NCTN program
  - Successfully employs biomarker stratification for understanding subpopulations
  - Good collection of tissue samples given access issues
  - Effective pursuit of international collaborations

- **Key recommendations**
  - Improve incorporation of biological and translational advances such as next-generation sequencing and understanding of disease mechanisms into trial designs
  - Place more emphasis on designing strong translational science studies to make optimal use of collected tissues
  - Pursue more interaction with SPOREs to address the lack of translational science
  - Pursue more interaction with investigators performing single arm phase 2 trials outside the NCTN Program to identify emerging opportunities

The Steering Committee has achieved appropriate balance of review and collaborative development of concepts.

Communication of NCTN WG Findings & Recommendations

- Series of portfolio specific conference calls with appropriate stakeholders, i.e., NCTN WG Chairs, Steering Committee Chairs, NCTN Disease Committee Chairs, NCI staff, CCOP Research Base PIs, etc. (10 of 13 complete)

- Final report to be presented to CTAC after the NCTN WG meeting on December 19, 2013

December 19, 2013 NCTN WG Meeting

- Review stakeholder feedback and finalize Portfolio Assessment Report
- Discuss implementation of NCTN WG recommendations
- Discuss cross-portfolio prioritization process
- Review Gynecologic and Gastrointestinal Steering Committee pilot evaluation findings

Discussion Topics

- **Strengths and Weaknesses of the NCTN WG Process**
- **Feedback on Cross-Disease Recommendations**

Extra Slides

Scoring Rubric for the Five Criteria and Overall

Scoring Category	December 2012 Meeting	March and July 2013 Meetings
Individual criteria (*Stayed the same*)	• High • Medium • Low	• High • Medium • Low
Overall (*Changed*)	• High • Medium • Low	• 1 – Exceptional • 2 – Excellent • 3 – Good • 4 – Fair • 5 – Poor

NCTN Working Group Interim Report

George Sledge, MD
Co-Chair, NCTN Working Group
March 13, 2013

NCI Clinical Trials and Translational Research Advisory Committee

NCTN Working Group Update Topics

- **Recap of NCTN WG charge and initial focus**
- **December 2012 meeting summary**
- **Interim report and recommendations**
- **Proposed plan for implementation of disease-specific recommendations**
  - Communication with Steering Committee leadership
  - Communication with NCTN Group Disease Committee Chairs
- **Future plans**

NCTN WG Charge

Initial Focus

1) **Assess the strength and balance of the active NCTN clinical trials portfolio (Cross-Disease Portfolio Management)**
   - Within each *disease*
   - *Across all diseases*

2) **Recommend new strategic priorities and directions for the NCTN based on:**
   - Current trial portfolio and gaps
   - Evolving clinical needs
   - Emerging scientific opportunities

3) **Review and assess the CTWG Evaluation process and results**
   - Quality of completed trial outcomes
   - Operational performance of Scientific Steering Committees
   - Efficiency of clinical trial conduct

4) **Provide strategic advice to enhance NCTN clinical trial operations**
   - E.g. Collaboration and timeliness

Criteria for Evaluating Trials

- **Feasibility**
  - Accrual difficulty
  - Time and cost to implement at sites
- **Clinical Importance**
  - Importance of study question relative to state of the science in the disease
  - Benefit per patient and for population (e.g. life years saved)
  - Benefit in light of disease context
- **Scientific Contribution**
  - Tests important scientific or clinical proof of principle question
  - Importance of integral or integrated correlative study questions
- **Relative cost/resources**
  - Total number of patients required
  - Length of study (accrual and follow-up)
- **Appropriateness for NCTN Program**

Summary of December 2012 NCTN WG Meeting

- **Evaluated the Breast, Leukemia, Lymphoma, Gastrointestinal and Genitourinary portfolios**

- **Cross-disease comments and recommendations highlight that some disease portfolios have more scientific opportunities than others resulting in more highly rated trials.**

- **Some common concerns emerged:**
  - A tension between selection of more nimble, biology driven, randomized phase 2 trials versus larger, more resource-intensive phase 3 trials;
  - Lack of drug availability due to pharma/biotech unwillingness to collaborate in certain areas; and
  - Difficulties of predicting accrual feasibility in advance.

- **Recommendations focused on how to best advance cutting-edge science in the genomic era in a time of fiscal constraint**

Interim Cross-Disease Recommendations

(slide 1)

1. NCI should conduct an analysis of resource allocation across diseases, taking into account current survival rates and likely cost/benefit from additional advances.
2. NCTN Groups and DS SSCs should work together to achieve the appropriate balance of innovative, biology-driven randomized phase 2 trials and larger, more resource intensive phase 3 trials in each disease portfolio.
3. NCTN Groups and DS SSCs should emphasize biology-driven (e.g., molecularly-driven, pathway-driven) trials that advance the science by incorporating genomics, biomarker tests and correlative science into study designs.
4. To empower innovative, biology-driven trials, additional NCI funding should be provided for correlative science studies, biomarker validation and the development of molecular classification algorithms.

Interim Cross-Disease Recommendations

(slide 2)

5. Accrual challenges should be taken more seriously in proposing and approving trial concepts, balancing the importance of the clinical question with the perceived difficulty of accrual.
6. More consideration should be given to competing European and industry trials in proposing and approving trial concepts as well as to the potential for collaboration with European and industry partners.
7. DS SSCs should increase their involvement in strategic planning and guidance for future trials in collaboration with the NCTN Groups.
8. DS SSCs should develop standardized guidelines for the level and types of preliminary data required for trial concepts.
9. DS SSCs should optimize their use of Task Forces (TFs), Working Groups (WGs) and Clinical Trial Planning Meetings (CTPMs).
10. Greater emphasis should be placed on sharing strategic and tactical best practices across diseases in terms of trial design, accrual, preliminary data requirements, etc.

Breast Cancer Portfolio

- **Summary conclusions**
  - addresses several key clinically important questions
  - studies are multidisciplinary
  - good balance of systemic and local-regional trials

- **Key recommendations**
  - incorporate smaller, nimble randomized phase II trials of newer approaches to balance large adjuvant studies
  - priority should be given to molecularly-driven trials, marker validation, correlative science
  - incorporate studies on limiting toxicity, improving QoL, and assessing survivorship

The BCSC can facilitate change by providing strategic guidance for concept selection, developing standards for trial design, and optimizing the use of TFs, WGs, and CTPMs.

Leukemia Portfolio

- **Summary conclusions**
  - includes many innovative, biologically-based, and scientifically important trials
  - addresses several key clinically important questions
  - strong CLL trial in older adults

- **Key recommendations**
  - priority should be given to molecularly-driven trials, marker validation, correlative science, and imaging technologies
  - prioritize biospecimen collection
  - develop molecular classification algorithms for patient stratification

The LKSC should build on its strengths in strategic planning, collaboration, and refining trial ideas by working collaboratively with the NCTN Groups to make these improvements and work to enhance accrual.

Gastrointestinal Cancer Portfolio

- **Summary conclusions**
  - addresses several key clinically important questions
  - addresses questions industry would not
  - includes rare cancers

- **Key recommendations**
  - greater focus on scientific innovation, biology, and genomics
  - promote studies that incorporate pathways, biomarker screening, and targeted therapies
  - promote use of molecular classification for treatment selection

The GISC should leverage its strengths in organization, efficiency, use of TFs and intergroup and global collaboration to work collaboratively with the NCTN Groups to make these improvements and improve the process for assessing accrual feasibility.

Lymphoma Portfolio

- **Summary conclusions**
  - concern that competition from industry and Europe has resulted in the best new agents in lymphoma not being developed through the NCTN
- **Key recommendations**
  - focus on innovative, correlative and translational science
  - incorporate integral biomarkers and molecular characterization into trial concepts
  - develop a niche in applying molecular science to trial concepts
  - work on data standardization and address accrual issues

The LYSC should continue its strategic planning and guidance of early concept development and work with the NCTN Groups to promote development of phase II trials that inform or lead to phase III trials.

Genitourinary Cancer Portfolio

- **Summary conclusions**
  - recent and ongoing trials are likely to have only moderate scientific and clinical impact
  - addresses questions industry would not
- **Key recommendations**
  - in addition to the focus on prostate cancer, include trials in diseases with poorer outcomes such as renal and bladder
  - focus on scientifically important, molecularly-driven, multidisciplinary trials with greater clinical impact
  - leverage new drugs, and move toward smaller phase II studies
  - incorporate more molecular correlates and biomarkers, technology assessment, QOL and patient reported outcomes into concept designs

The GUSC and the NCTN Groups should develop a strategic plan to guide concept development and decision-making processes, and balance prostate and large phase III trials with other diseases and trial types.

Summary of the December 2012 NCTN WG Meeting

- **Completed comprehensive and critical review of the five disease-specific portfolios**
- **Allowed for critical assessment of the strengths and weaknesses of the portfolios presented**
- **Developed interim recommendations to improve clinical cancer research portfolios supported by the NCI**
- **Recommendations will be further refined based on the review of the trial portfolios for the remaining diseases**

NCTN Current Status & Future Plans

- **Anticipate a total of 3 meetings needed to complete the assessment of the strength and balance of the active phase 3 and large phase 2 clinical trials currently conducted by the NCTN Program:**
  - **December 2012:**
    - Analyzed the breast, GI, GU, leukemia, and lymphoma portfolios
  - **March 2013**
    - Analyze the myeloma, brain, thoracic, and pediatric portfolios
  - **Summer 2013**
    - Review remainder of the portfolio including symptom management trials
- **Cross-disease portfolio assessment activities to follow the individual disease portfolio assessments.**

Proposed Implementation of Disease-specific Recommendations

- **Communication with Steering Committee Leadership**
- **Communication with NCTN Group Disease Committee Chairs**
- **Achieving recommended goals will require collaboration between NCI, NCTN Groups, and SSC**
- **Series of disease specific conference calls with NCTN WG Chairs, SSC Chairs, and NCTN Disease Committee Chairs**

Discussion Topics

- **Strength and Weakness of Process**
  - **Comments from NCTN WG members**
  - **Comments from Strategic Planning Subcommittee**

- **NCI Pipeline**
  - **How to integrate information on NCI's early clinical trials programs, i.e., SPORE, IDB, CTSU Flex, etc into portfolio development**

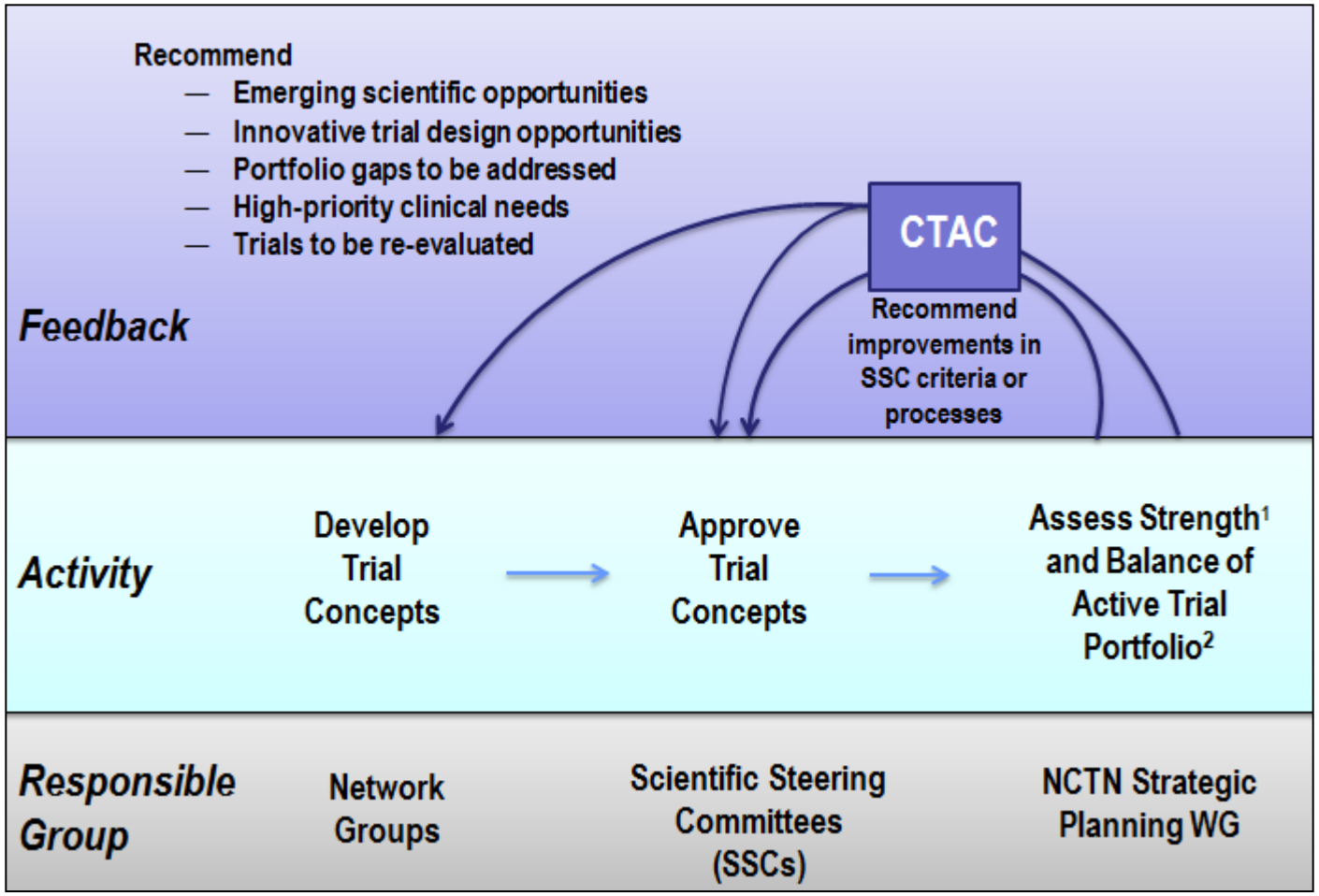
- **Implementation of disease-specific versus cross-disease recommendations**

Extra Slides

NCTN Clinical Trials Portfolio Prioritization Process

- **3 groups assist NCI in managing & prioritizing the portfolio:**
  - **Network Groups (Cooperative Groups**) develop trial concepts and conduct trials.
  - **Scientific Steering Committees (SSCs)** evaluate trial concepts and approve those judged scientifically and clinically meritorious and worthy of the expenditure of NCI resources.
  - **NCTN WG of CTAC** assesses the strength and balance of the active trial portfolio and recommends improvements through the Clinical Trials Strategic Planning Subcommittee of CTAC.
- **Continuous collaboration and feedback through CTAC and its Clinical Trials Strategic Planning Subcommittee**
  - Identify emerging scientific opportunities
  - Assess portfolio strengths and gaps
  - Respond to high priority clinical needs

Collaborative NCTN Clinical Trials Prioritization Model



[1]Trial "strength" is the potential for generating high quality trial outcomes.

[2]Includes active phase 3 and large randomized phase 2 trials and concepts approved by an SSC but not yet activated.

Summary of First NCTN WG Meeting *July 2012*

- **Piloted the process to assess the strength and balance of the NCTN trials utilizing the colorectal cancer clinical trials portfolio as the test case.**
- **Concluded review of individual trials within a disease is appropriate and feasible.**
- **Refined criteria for evaluating trials.**
- **Recommended assigning each trial an overall score based on individual trial evaluation criteria.**
- **Concluded presentations of clinical trial portfolio and strategy in disease area by CTEP Medical Officer and Steering Committee Chair is valuable for putting trials in context and understanding the basis for Steering Committee decisions.**
- **Recommended summary information on other major ongoing trials outside of NCTN (e.g., industry, international) in disease area be provided.**
- **Recommended that WG members be assigned to disease based subgroups to take the lead in the review of each disease area.**

National Cancer Institute

Precision Cancer Medicine Exceptional Responders NCI-MATCH

Barbara A. Conley, MD
Associate Director, Cancer Diagnosis Program, DCTD

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Exceptional Responders Initiative

Phenotype to Genotype

National Cancer Institute

Exceptional Responders Initiative: Pilot Study

- 1-10% of patients respond well to drugs that do not go on to receive FDA approval for that indication
- Molecular mutations or changes in gene expression may explain these “exceptional responses”
- “Inactive” drugs are sometimes active in a subset of patients
- Could lead to development of predictive assays
- Improve biologic understanding for better therapeutics/diagnostic development

Exceptional Responders

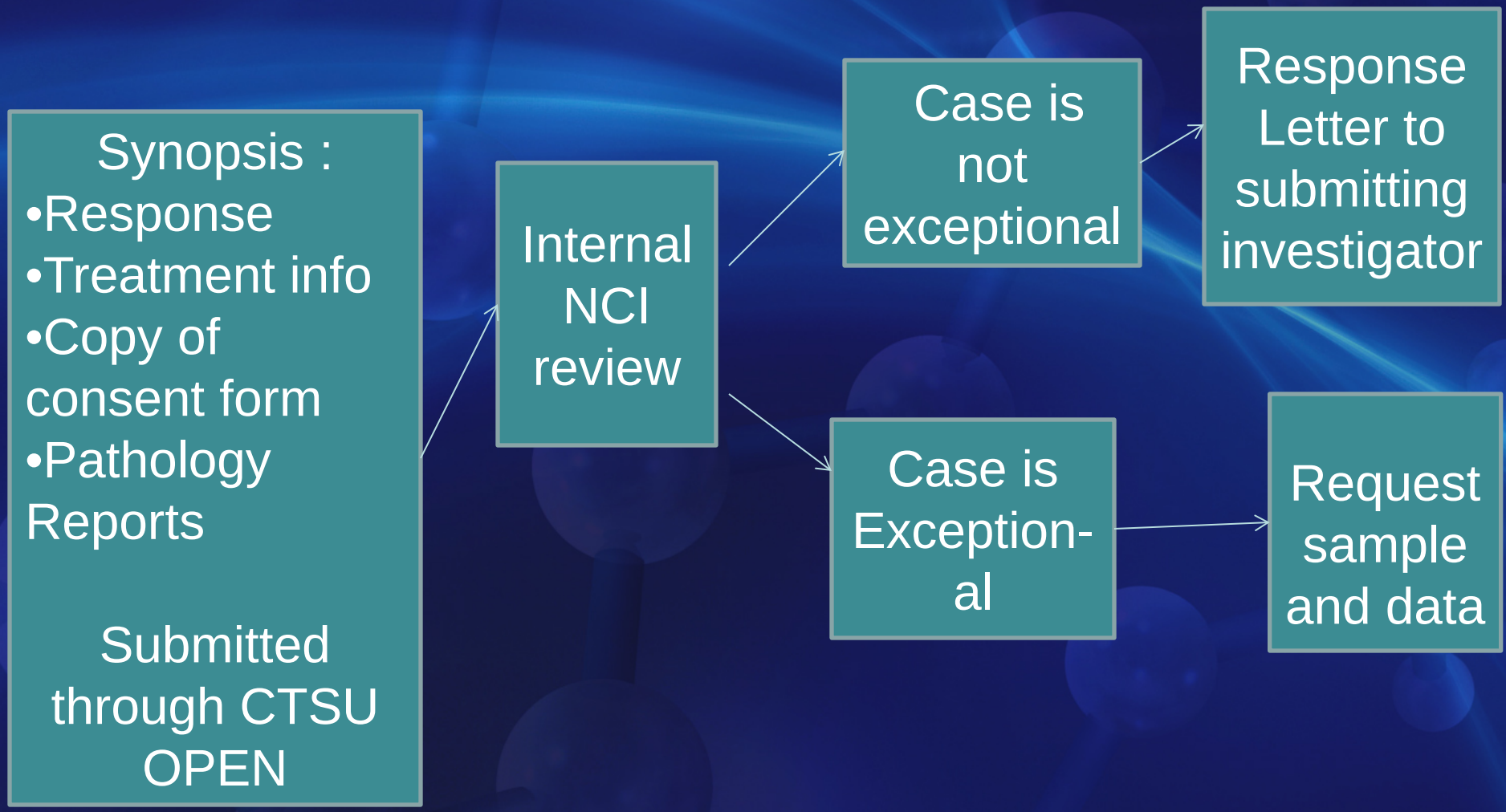
- Definitions
  - CR, or PR lasting at least 6 months
  - Drug did not go on to FDA approval in that indication due to insufficient activity
- Tissue
  - Prefer just before drug treatment; otherwise any prior
  - 50% tumor
  - FFPE, Frozen, core acceptable
  - Normal: blood or other

Solicitation of Exceptional Responders Cases

- Solicit Tissue Samples and Clinical Data
  - Letters to CTEP investigators for identified ER cases
  - Pharma
  - Cooperative Groups, U01s, and N01s
  - Cancer Centers
- Sites will be reimbursed for effort

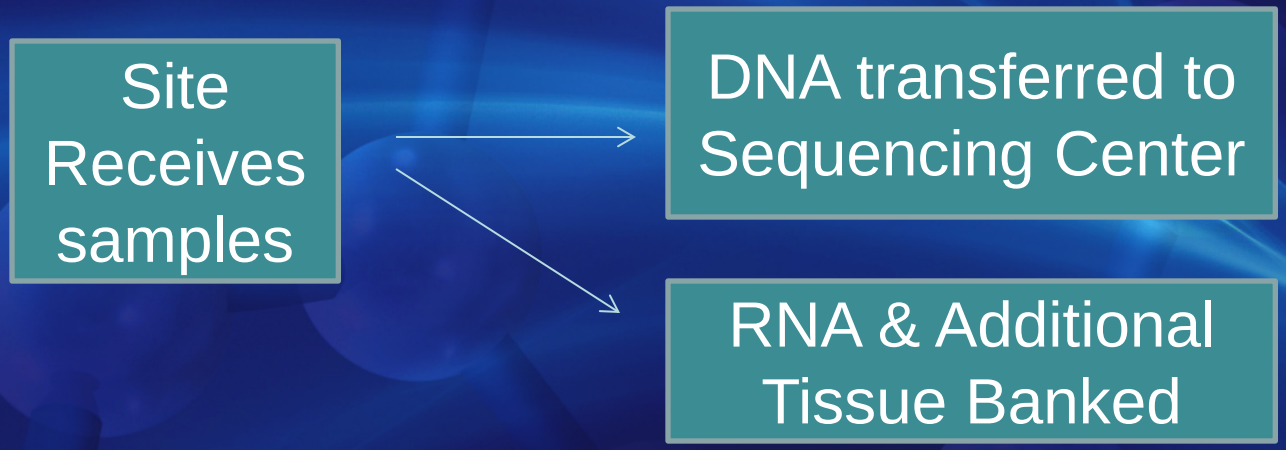
Screening of Potential ER Cases

Sites Submit Data through the CTSU's OPEN – Eligibility Stage



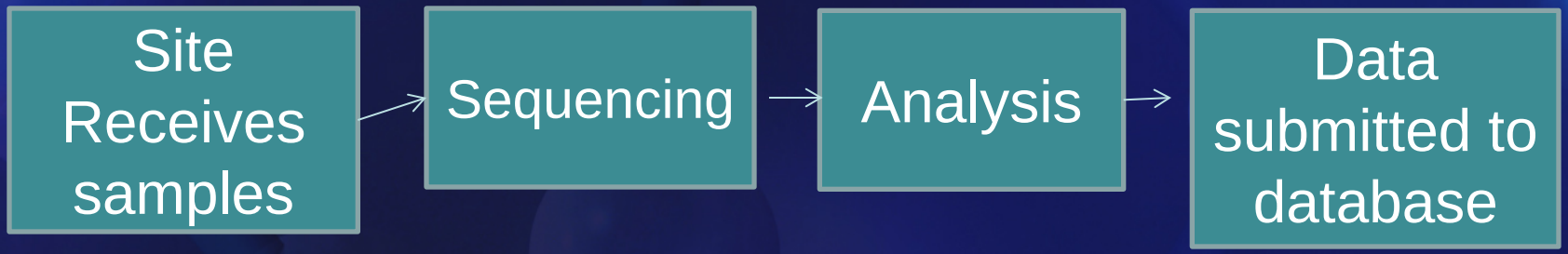
Sample Submission and Preparation

Central Biorepository: Nationwide Children's Hospital



Sequencing and Analysis of Samples

Contract Existing TCGA Sequencing Center



Timeline

Oct. 2013- Sept. 2015

Solicit exceptional cases and tissues

Dec. 2013- Sept. 2015

Sequencing and analysis

Jan. 2014 –Dec. 2015

Posting on controlled access website

Molecular Analysis for Therapy Choice (NCI-MATCH)

Genotype to Phenotype

National Cancer Institute

NCI-MATCH

- Umbrella protocol for multiple, single-arm phase II trials
  - Each molecular subgroup matched to a targeted agent
- IND for protocol template
  - Arms could be added or deleted without affecting other arms
- Initially focused on single-agents (commercial or experimental)
  - Combinations will be considered for targets that have validated combination targeted therapy
  - Need minimum dose/safety established in phase 1 trials
- Study will be reviewed by the CIRB

NCI MATCH

- Identify mutations/amplifications/translocations in patient tumor sample - eligibility determination
- Assign patient to relevant agent/regimen
- Tumor biopsies & sequencing at progression to illuminate resistance mechanisms
  - De-identified samples submitted to central labs
  - Whole-exome sequencing (research purposes) to detect nonambiguous germline variants

Eligibility

- Solid tumors and Lymphomas that have progressed following at least one line of standard therapy
  - Exclude histologies from a given arm if already FDA approved for that indication or lack of efficacy documented
- Tumor accessible for biopsy and patient willing to undergo biopsy
- At least 18 years of age
- Performance status ECOG 0-2
- Adequate organ function

Patient population considerations

- Target: at least 25% of total enrollment to be patients who have “rare” tumors
- “Common” defined as breast, NSCLC, colon, prostate
- Terminate enrollment to an arm if accrual on pace to require > 5 years to accrue

Levels of Evidence: Drugs

- Level 1: FDA approved; evidence of target inhibition, or proof of mechanism; demonstration that patient selection with CDx are more likely to respond
- Level 2: Agent met a clinical endpoint (objective response, PFS, or OS); with evidence of target inhibition; plausible evidence of a predictive or selection assay/analyte
- Level 3: Agent demonstrated evidence of clinical activity with evidence of target inhibition; some evidence of a predictive or selection assay/analyte
- Level 4: Preclinical evidence of anti-tumor activity and evidence of target inhibition; hypothesis for a predictive or selective assay/analyte

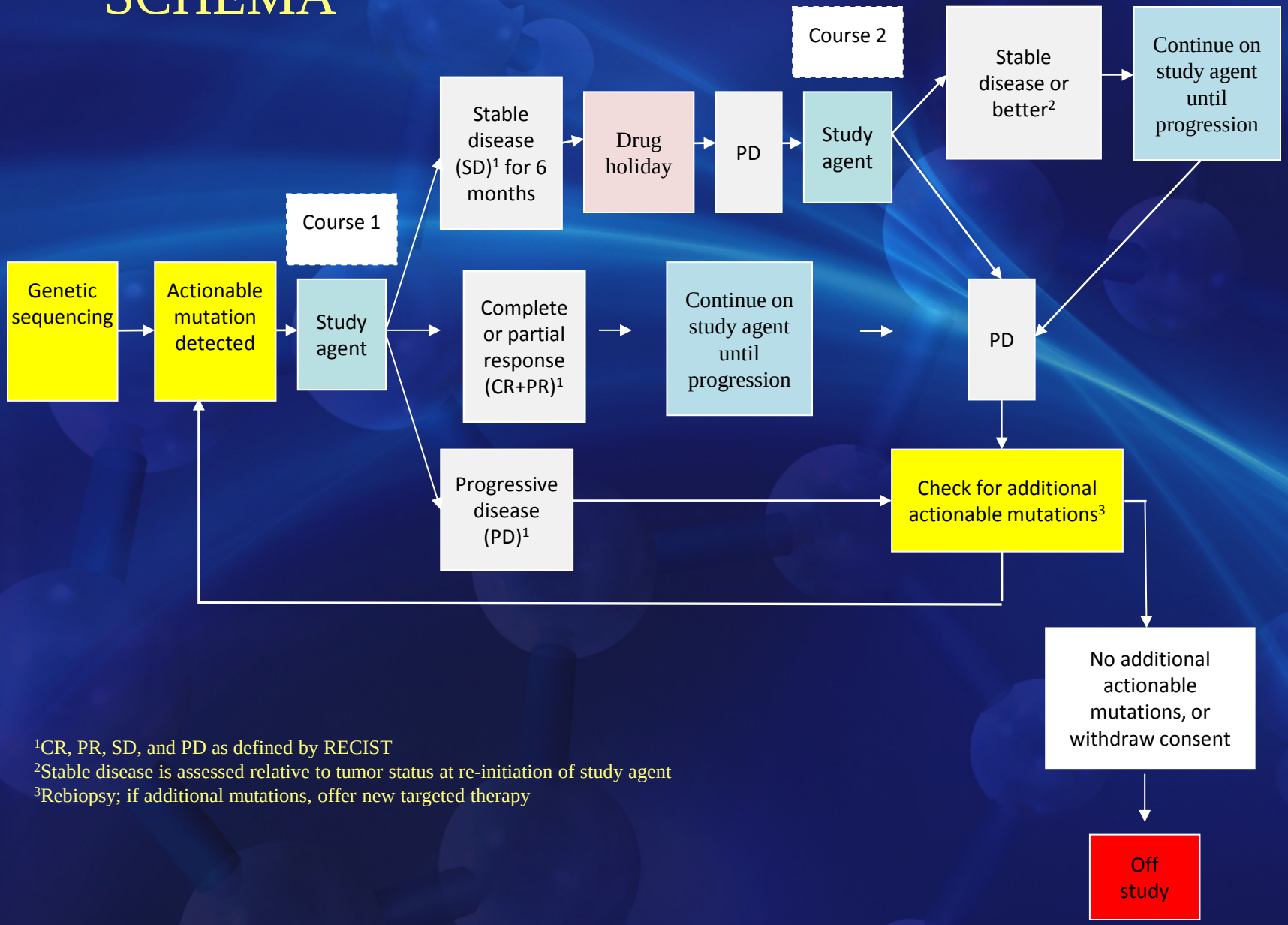
Levels of Evidence: genes

- Gene variants = target of an approved drug; and robust clinical data are lacking re: efficacy in certain cancer subtypes harboring that variant.
- Activating mutations in genes upstream of the molecular target of the agent in the associated signaling pathway(s)
- Inactivating mutations in genes that result in unique susceptibility to a specific molecular point of intervention (e.g., BRCA1 mutation and PARP inhibitors).
- Other genes of interest that have appropriate justification for inclusion based on scientific evidence regarding unique susceptibility to a specific molecular targeted therapy (potential future drug targets, potential biological/clinical interest).

Assays

- NGS: Ion Torrent PGM with custom Ampliseq panel of 200-300 actionable genes
- Validation in network of CLIA certified labs: RFP thru Leidos
- IHC, FISH?
- Rule driven treatment assignment

SCHEMA



[1]CR, PR, SD, and PD as defined by RECIST
[2]Stable disease is assessed relative to tumor status at re-initiation of study agent
[3]Rebiopsy; if additional mutations, offer new targeted therapy

Statistical Design

(within each mutation-drug match)

- Dual Primary Endpoints: ORR 5% vs. 25% or PFS 6 months 15% vs 35%
- Simon 2-stage design 30 patients total
- Drug holiday for patients with stable disease
- Compare PFST1 to PFST2

ORR = proportion of patients with objective response (PR+CR) on initial course of study agent
PFS6 = proportion of patients alive and progression free at 6 months from initiation of study agent
PFST1 = Time until death or progression from start of drug holiday for a patient with stable disease at 6 months
PFST2 = Time until death or progression from therapy re-initiation for a patient who goes on drug holiday and progresses, but survives to have study agent re-initiated

Study Participation

- ECOG-ACRIN to lead with full cooperation of NCTN
  - individual PIs for each arm to rotate leadership positions
- Posted on CTSU
- CCOPs

Questions

- Exceptional responders:
  - Is whole exome sequencing or targeted sequencing likely to lead to more usable information?
  - Are there other types of patients or data that should be considered?

MATCH

- What hurdles are to be expected for this study with respect to accrual or willingness for clinicians to participate?

Other Questions /Comments

National Cancer Institute

Tobacco Use by Cancer Patients in Clinical Trials

Stephanie Land, PhD

Tobacco Control Research Branch
Behavioral Research Program
Division of Cancer Control and Population Sciences

Formerly: Statistician, National Surgical Adjuvant Breast and Bowel Project (NSABP) and University of Pittsburgh Cancer Institute (1999-2011)

Purpose of today's presentation

- To inform CTAC of initiative
- To solicit early input

- Problem
- Scene
- Science
- Action
- Feedback

problem scene science action feedback

Problem (Clinical)

Cancer patients and survivors who smoke cigarettes have worse health outcomes (including higher all-cause and cancer-specific mortality, and risk of tobacco-related second primary cancer).

Smokers may have higher risk of recurrence, poorer response to treatment, and increased toxicity.

Clinical significance of smoking by cancer patients

- Relative risk of all-cause mortality*
  - Current smokers 1.5 (relative to never smokers)
  - Former smokers 1.3
- Relative risk of cancer-specific mortality**
  - Current smokers 1.6 (relative to never smokers)
  - Former smokers 1.05

* Phipps, 2011 (colorectal cancer)
** Kenfield, 2011 (prostate cancer)

Problem (Scientific)

There are many scientific questions related to tobacco use in the cancer patient population.

Current approaches to data collection:

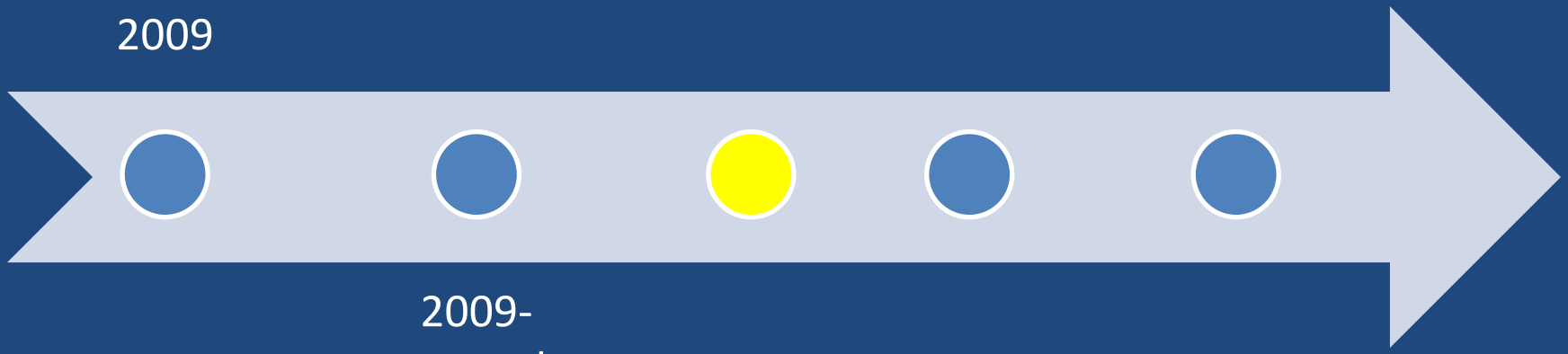
- Not widely assessed in trials or practice
- Inconsistent tobacco use assessment methods
- Little follow-up during/after treatment

Current practice

- NCI-Designated Cancer Centers
  - < 50% include tobacco use as a vital sign in the medical record
- NCI-funded phase III Cooperative Group trials
  - 22% record cigarette smoking status at enrollment, and
  - 4% during follow-up.

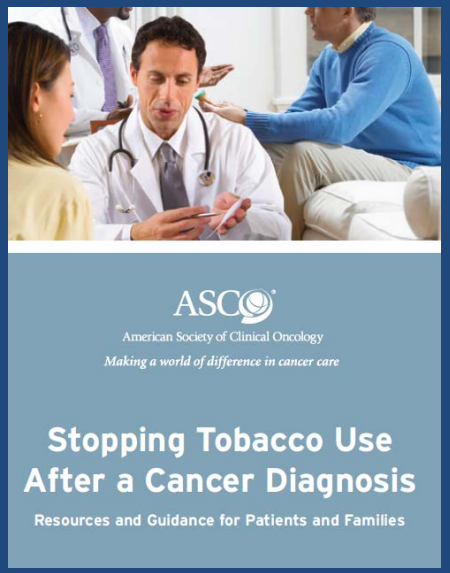
Goldstein, NTR, 2012; Warren, IJC, 2012

Action Timeline



problem **scene** science action feedback

Recent action and dissemination



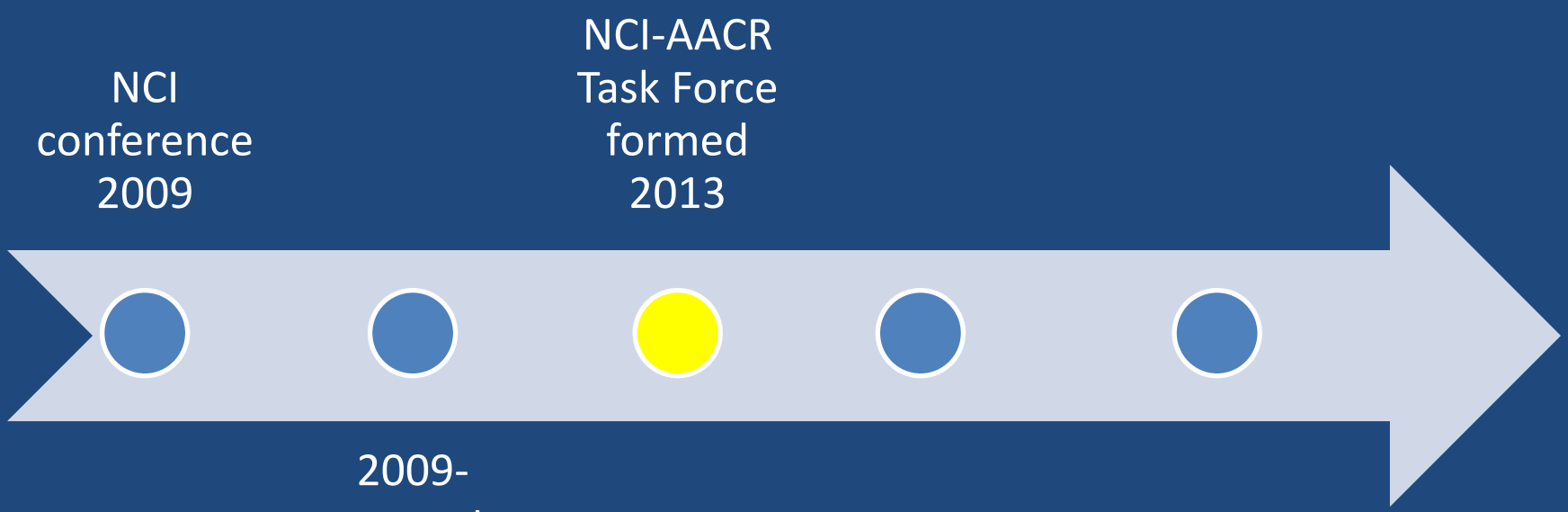
Land, JCO, 2012
Peters, JCO, 2012
Ganz, JCO, 2012
IOM, 2012
Warren, JOP, 2013
Warren, JTO, 2013
Toll,CCR, 2013
Hanna, JCO, 2013

“In the oncology setting, tobacco use should be addressed at presentation and throughout treatment.”

“If tobacco use data are systematically collected and analyzed, the information would provide clinicians and regulatory agencies with the data needed to understand the impact of existing and new tobacco products.”

Hanna, et al, Tobacco Cessation and Control a Decade Later: American Society of Clinical Oncology Policy Statement Update, *JCO*, 2013

Action Timeline



Scope and Purpose of NCI-AACR Cancer Patient Tobacco Use Assessment Task Force

From the scientific and medical perspective, develop recommendations for

- tobacco measures,
- timing of assessment,
- research agenda

Task Force Roster

Jeffrey S. Abrams, MD
Thomas H. Brandon, PhD
Jan C. Buckner, MD
Paul M. Cinciripini, PhD
K. Michael Cummings, PhD, MPH
Carolyn Dresler, MD, MPA,
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Peter Shields, MD
Benjamin Toll, PhD
K. (Vish) Viswanath, PhD
Graham Warren, MD, PhD

See handout for titles and affiliations.

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Graham Warren, MD, PhD

Cooperative Group leadership and committee membership

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ASCO leadership and committee membership

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Cancer centers

NCCTG Phase III Trial N0147 (Alliance)

- 2686 resected stage III colon cancer randomized
- FOLFOX ± cetuximab
- Statistical power 90% to detect DFS HR=0.75 cetuximab
- No DFS benefit with cetuximab (Alberts, JAMA, 2012)
- Baseline smoking assessment (n=1968):
  - Smoked ≥100 cigarettes in lifetime
  - Currently smoker
  - Age initiation
  - Age quit
  - Average number of cigarettes smoked per day

Associations between Cigarette Smoking Status and Colon Cancer Prognosis among Participants in NCCTG Phase III Trial N0147 (Alliance)

- Phipps, Shi, Newcomb, Nelson, Sargent, Alberts, Limburg for the Alliance for Clinical Trials in Oncology *JCO Jun 1, 2013*
- Land, SR: New Evidence of the Clinical Significance of Cigarette Smoking by Colon Cancer Patients [podcast] , *JCO*
- 3-year DFS 70% for ever-smokers vs 74% never-smokers
- Current vs never-smokers (DFS HR=1.47; 95% CI 1.04 to 2.09)
- Former vs never-smokers (DFS HR=1.20; 95% CI 0.99 to 1.46)
- Interaction with BRAF mutation (P=.03):
  ever-smoking was associated with
  - shorter DFS in pts with BRAF wild-type (HR=1.36; 95% CI, 1.11 to 1.66)
  - not in BRAF mutated (HR=0.80; 95% CI, 0.50 to 1.29) colon cancer.

Scientific questions

- Cigarette smokers seem to have greater morbidity and poorer clinical outcomes, but:
  - Evidence needs to be strengthened
  - Is the association actually due to exposure history, use during cancer therapy, or continued accrual of risk after therapy?
  - What is the improvement in prognosis with cessation, for a given history of exposure?

Scientific questions (continued)

Does quitting smoking actually impact the outcome of cancer, or is the damage already done?

Peter Shields, Professor

The Ohio State University College of Medicine

Deputy Director, The Ohio State University Comprehensive Cancer Center (OSUCCC)

Scientific questions (continued)

Does tobacco use diminish treatment efficacy?

We need to understand the mechanisms by which tobacco could exacerbate the disease or dilute the efficacy of the treatment.

Vish Viswanath, Associate Professor
Harvard School of Public Health
and Department of Medical Oncology
Dana-Farber Cancer Institute

Scientific questions (continued)

"There are substantial opportunities to
identify better cancer therapeutics,
use smoking as a model of general therapeutic resistance, and
assess methods to improve outcomes."

Graham Warren, Associate Professor
Vice Chairman for Research in Radiation Oncology
Dept of Cell and Molecular Pharmacology and Experimental Therapeutics
Medical University of South Carolina
Alliance (Cooperative Group Prevention Committee)

Scientific questions (continued)

"Why does smoking affect virtually all disease sites for most treatment modalities?

Do we know of any other exposure that has this effect? If we can determine how tobacco causes these effects, we might have a spectacular opportunity to advance cancer treatment.

Costs of existing therapies are so high, maximizing the utility of these therapies could be a great investment."

K. Michael Cummings
Professor, Department of Psychiatry & Behavioral Sciences
Medical University of South Carolina

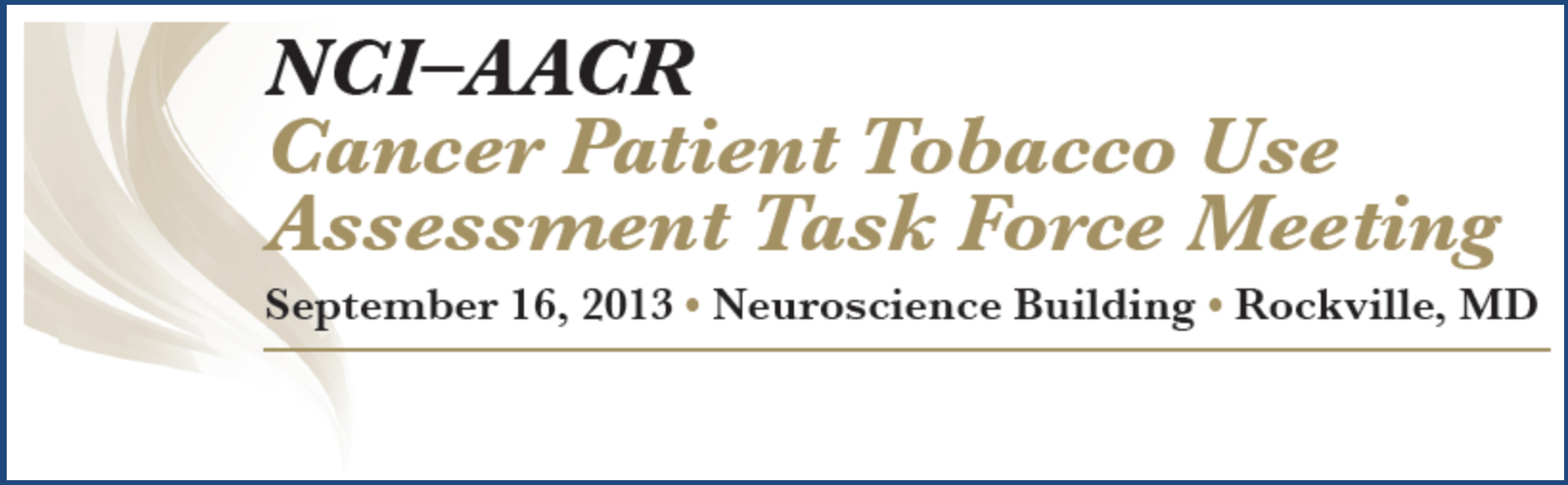
Scientific questions (continued)

- How does tobacco use affect tumor biology?
- Should cancer therapeutic agent dosing be modified for tobacco users?
- Optimal timing of cessation relative to therapy?
- What are the best approaches for cessation interventions in cancer patients?
- Can cessation improve adherence to cancer therapy?
- Can cessation improve quality of life?
- How does tobacco use interact with other behavioral and demographic factors?
- What is the clinical impact of other tobacco products?

Task Force Near Term Deliverables

- Recommended measures (online)
  - 3 tiers; Tier 1 is minimal set
- Protocol for tobacco use measurement (online)
  - Timing and procedures
- Research agenda (publication; see handout)

- June-present, 2013: Working groups and conference calls
- Sept 2013: In-person meeting facilitated by NCI Office of Science Planning and Assessment



Draft recommended measures Tier 1 (minimal) paraphrased

Baseline:

- Ever smoked 100+ cigarettes in lifetime?
- How long since smoked?
- How many years smoked?
- Average number of cigarettes per day?

Follow-up:

- How long since smoked?

Action Timeline

Next steps

- Finalize and promote measures and recommendations via scientific dialog
- Facilitate implementation of tobacco use assessment in National Clinical Trials Network
- Assessment in selected trials
- Develop NCI Guidance

Feedback

What are the barriers to incorporating tobacco use items in

- Selected clinical trials?
- All NCTN Phase III clinical trials?

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE (NCI)
AND
AMERICAN ASSOCIATION FOR CANCER RESEARCH (AACR)

NCI-AACR CANCER PATIENT TOBACCO USE ASSESSMENT TASK FORCE

The Task Force assigns highest priority to the following list of research endpoints and topics.

Defining the population: We suggest that high priority be given to research regarding cancer patients who continue to smoke cigarettes following diagnosis as well as those who recently quit (within 1 year prior to diagnosis).

Research Priorities:

1. Determine the effects of tobacco and other forms of nicotine use by cancer patients as well as the benefits of tobacco cessation (before diagnosis, during treatment, or during survivorship). Research in this area could include:
    a. Effects on medical outcomes
        i. Tumor response
        ii. Disease progression or recurrence
        iii. Second primary cancer
        iv. Survival and mortality
    b. Effects on cancer treatment efficacy
    c. Effects of tobacco/nicotine use and cessation on adverse effects and complications of cancer treatment; recovery from surgery and other cancer treatment
    d. Effects of tobacco/nicotine use and cessation on needed dose, duration and other characteristics of cancer treatment delivery
    e. Effects on symptoms, psychosocial outcomes and behavioral factors, including:
        i. Quality of life
        ii. Mental health
        iii. Adherence to cancer treatment and post-treatment procedures

2. Determine the effects of nicotine and other tobacco constituents in all forms of products (tobacco, nicotine replacement therapy, e-cigarettes and other electronic nicotine delivery systems) and the mechanisms of effects, on cancer biology
    a. Carcinogenesis
    b. Proliferation
    c. Angiogenesis
    d. Migration/invasion and metastasis
    e. Inflammation
    f. Immune modulation
    g. Tumor microenvironment
    h. Viral carcinogenesis and effects of viruses on cancer therapy (such as HPV)
    i. Metabolism of cancer therapeutic agent
    j. Chemotherapeutic resistance
    Note: these effects have implications for tumor vaccine development, as well as for the need to develop animal/in vivo models of tobacco and cancer treatment/biology, as opposed to cellular models.

3. Determine optimal strategies for implementing tobacco use cessation and prevention within the cancer setting
    a. Evaluate the most effective platforms to promote system wide identification of users of tobacco (and other forms of nicotine intake, such as e-cigarettes) and recent quitters using electronic health records and meaningful use criteria
    b. Evaluate the most effective means of delivering tobacco cessation treatment to all such individuals, including motivational approaches for the ambivalent tobacco user and telemedicine for patients who live at a distance. *Centralized tobacco dependence care can reduce provider burden and address barriers to treatment.*
    c. Evaluate the effects of potential cessation treatment moderators. Where appropriate, develop focused approaches to ameliorate those effects. Moderators may include:
        1. Psychiatric co-morbidities
        2. Genetics (pharmacogenetics)
    d. Assess role of biochemical verification
    e. Evaluate cost-effectiveness
    f. Determine the optimal cancer and cessation treatment timing. Should cessation treatment precede or even delay some forms of cancer care?
        1. Risk and benefit
        2. Optimal timing, duration and intensity of treatment
    g. Consider and inform provider behavior

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE (NCI)
AND
AMERICAN ASSOCIATION FOR CANCER RESEARCH (AACR)

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Medical University of South Carolina
Member, Alliance Prevention Committee

Incorporating Patient Reported Outcomes (PROs) in NCI- sponsored Clinical Trials (U10s)

Lori Minasian, MD, FACP
Deputy Director, DCP, NCI

Issues

- **Multiple Different NCI & NIH PRO Initiatives & Activities**
  - Each with Different Purposes
  - Each In Various Stages of Development
  - Each Requires Different Expertise
- **Need for Clarity in the Incorporation of PROs/HRQOL into NCI-sponsored Clinical Trials**

Key Initiatives & Activities

- **PRO Endpoints in NCI Clinical Trials**
  - Secondary Endpoints in Treatment Trials (PRO & HRQOL)
  - Primary Endpoints in Symptom Management Trials
- **Curation of HRQOL Tools for caDSR**
  - Common Data Elements
  - Different Approach for HRQOL (whole instrument)
  - Integration for Medidata Rave
- **PRO-CTCAE**
  - Symptomatic Toxicity Measurement System
- **PRO Core Domains**
  - Collection of Common PRO Domains Across Clinical Trials
  - Three Disease Specific Domains

PRO Endpoints in NCI Clinical Trials

- **Incorporate PROs into NCTN/NCORP Clinical Trials**
  - NCI Ensure the Hypothesis-driven Inclusion of PROs
    - Clinical Context, PRO Expertise, Statistical Analysis
    - Review Rationale for Inclusion and Analysis
    - Treatment Trials Different Issues than Symptom Management
- **Community Needs Clarity**
  - PROs for Symptoms, Toxicities, Functional Assessments & HRQOL
- **Framework Needed**
  - Overall Concept for Inclusion that Does Not Dictate, but Provides Guidance to Investigators, Reviewers on Use

Curation of HRQOL/PROs for caDSR

- **Users Put PRO Content into caDSR**
  - Often Multiple Data Elements Support One Measure
  - Tools Difficult to Find by Other Users
- **Numerous HRQOL/PRO Measures now in caDSR**
  - 30% PRO Content Curated Based Upon Best Practices
  - 70% PRO Content not Curated with Best Practices
  - Need Users to Review and Retire Redundant PRO Content
- **Common Data Elements Curation of HRQOL & PROs Started**
  - HRQOL Project Plan Developed
  - Call for Membership for HRQOL Curation Working Group
  - Facilitate Integration with Medidata Rave

PRO-CTCAE

- **Sandra Mitchell, PhD to Present**
- **Measurement System for Capturing Real Time Patient Reports of Symptomatic Toxicities**

Core Set of PRO Domains For Trials

- **Consensus Development of PRO Core Domains**
  - Common, Consistent, Clinically Relevant Symptoms Across Cancer Sites
  - Use Across Studies to Facilitate Treatment Effect & Cross Trial Comparison
- **Disease Specific Domains**
  - Ovarian Cancer, Head & Neck Cancer, Prostate Cancer
  - Multi-Modality Therapy with Symptomatic Toxicities
- **Presented March 2013 CTAC**

Existing Working Group & Committee

- **SxQOL Steering Committee**
  - Review of Symptom Management Trials
  - Liaisons to Disease Steering Committees for PRO & HRQOL Review on Treatment Trials

- **NIH/FDA Outcomes Assessment Working Group**
  - Coordination Activities Between NIH ICs & FDA
  - Development of Tools for Outcomes in Clinical Trials
  - Patient Reported, Clinician Reported, Observer Reported

New Coordination Activities (To Be Formed)

- **Internal NCI Patient Reported Outcomes Working Group For NCTN/NCORP Clinical Trials**
  - Coordinate & Formalize the Internal NCI ad hoc Discussions
  - Build on Success of Coordination of PRO-CTCAE

- **New Working Group with External PRO Investigators & NCI**
  - Develop Framework for Inclusion of Different PRO Assessments Across NCTN/NCORP Clinical Trials.
  - Short-term (12-18 months)
    - Primarily through Conference Calls, In-person Meeting
    - Membership from QOL Experts in Groups, SxQOL, Liaisons to Disease SCs

- Questions?
- Discussion

National Cancer Institute

Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events

PRO-CTCAE

Sandra A. Mitchell, PhD, CRNP
Outcomes Research Branch
Division of Cancer Control and Population Sciences
National Cancer Institute

mitchlls@mail.nih.gov

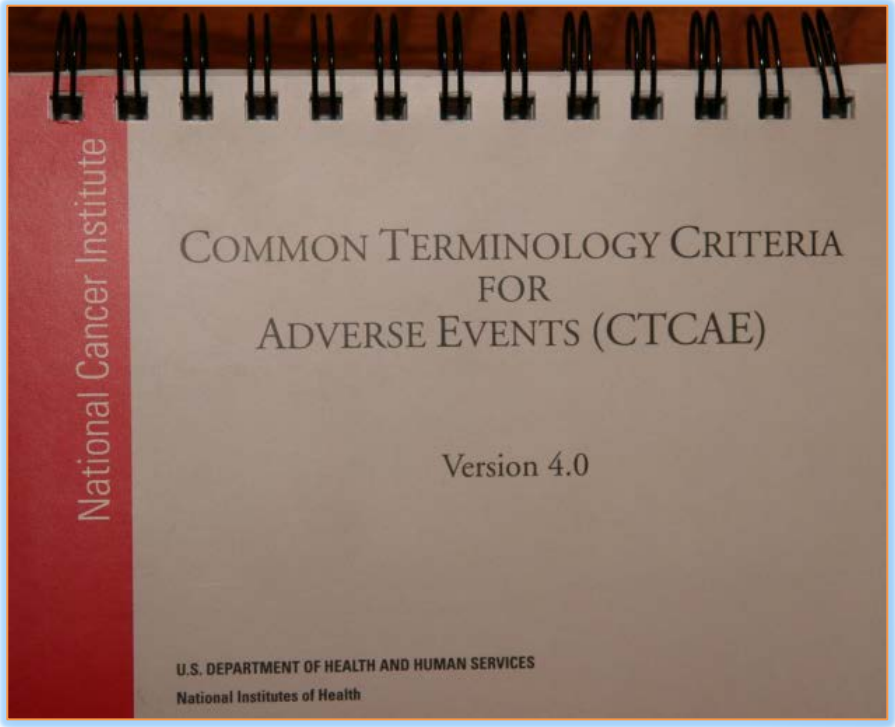
Presentation to Clinical Trials Advisory Committee: November 6, 2013

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

PRO-CTCAE

Patient-Reported Outcomes version of Common Terminology Criteria for Adverse Events

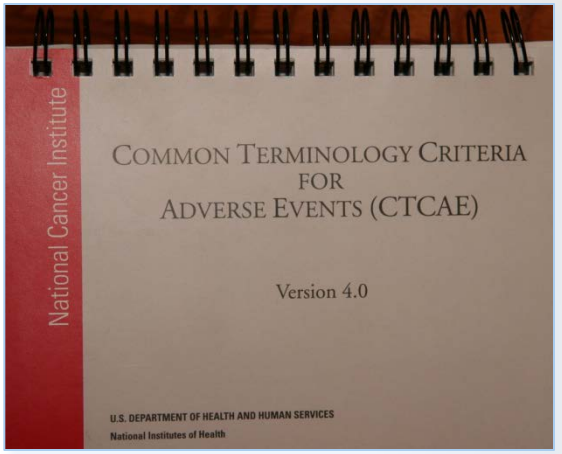
- Treatment-related toxicity (safety and tolerability)
  - Fundamental outcome when drawing conclusions about therapeutic effectiveness, including comparative effectiveness
  - Currently evaluated by clinicians using **C**ommon **T**erminology **C**riteria for **A**dverse **E**vents (***CTCAE***)

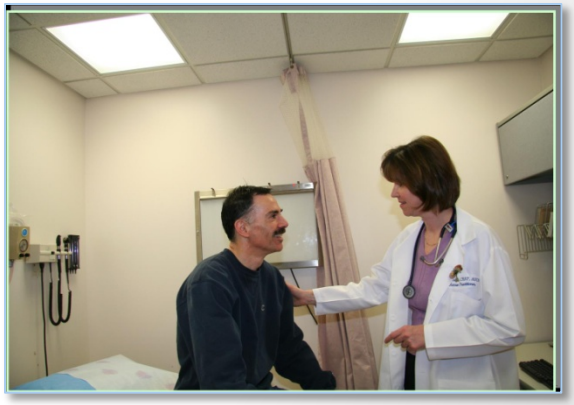


PRO-CTCAE

Patient-Reported Outcomes version of Common Terminology Criteria for Adverse Events

- 1 of 8 of the adverse events listed in CTCAE is a symptom outcome
  - Validity of reporting symptom outcomes is eroded when those reports are filtered through research staff and clinicians[1]
  - Staff-based adverse event reporting occurs at clinic visits; adverse events that occur between visits may be missed
- Real-time ascertainment of symptomatic adverse events using PROs could improve the precision and reproducibility of adverse event reporting
- PRO reporting of symptomatic toxicities is valued by trialists[2]





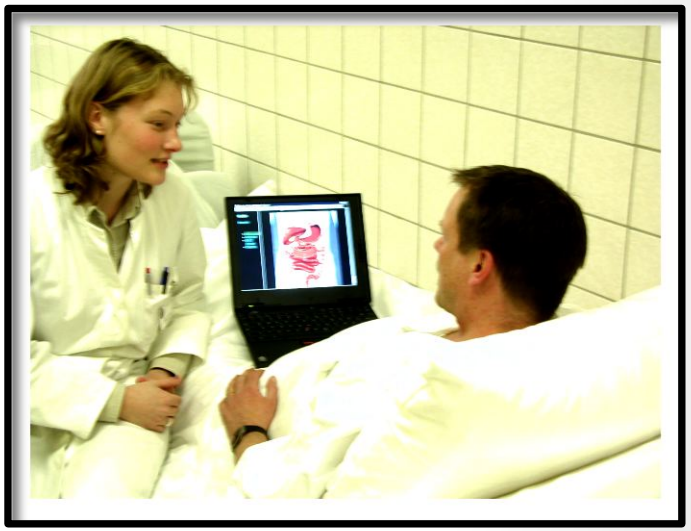
[1]Xiao et al. (2013). Comparison between patient-reported and clinician-observed symptoms in oncology. *Cancer Nurs.*,36(6):E1-E16

[2]Bruner et al. (2011). Stakeholder Perspectives on Implementing the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *Translational Behavioral Medicine: Practice, Policy, Research*, 1 (1), 110-122.

PRO-CTCAE

Patient-Reported Outcomes version of Common Terminology Criteria for Adverse Events

- **PRO-CTCAE** is a patient-reported outcome (PRO) measure that ascertains in real time the presence, severity and interference of symptoms experienced by patients participating in cancer clinical trials
- Co-funding and Strategic Oversight
  - DCCPS
  - DCP
  - DCTD
  - CBIIT
- Contracts awarded to Memorial Sloan-Kettering Cancer Center: Ethan Basch, PI



NCI PRO-CTCAE Study Group

Supported through NCI contracts HHSN261200800043C and HHSN261201000063C

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	Cori Couture	Edward Korn	Lauren Rogak
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Deborah Bruner	Maria Gonzalez	Hannah O'Gorman	Diane St. Germain
Laurie Burke	Mehul Gulati	Ann O'Mara	Ann Marie Trentascosti
Kate Castro	Gaurav Gupta	Diane Paul	Ted Trimble
David Cella	Jennifer Hay	John Payne	Andy Trotti
Alice Chen	Madeline Hernandez-Krause	Frank Penedo	Andrea Vinard
Ram Chilukuri	Jessica Hess	Barbara Perez	Vish Viswanath
Steven Clauser	Lori Hudson	Richard Piekarz	Gordon Willis
Charles Cleeland	Norval Johnson	Liora Pollick	Jennifer Wind

- Organizational Affiliations: NCI Community Cancer Centers Program (NCCCP), RTOG, Alliance, FDA
- We gratefully acknowledge our study participants and patient representatives!

PRO-CTCAE Measurement System

1. Symptom Library	2. System for Survey Administration
• 78 symptomatic adverse events drawn from CTCAE • PRO-CTCAE questions evaluate symptom occurrence, frequency, severity, and interference	• Web-based system to customize surveys and manage survey administration • Patient responds to surveys using web, tablet or interactive voice response (IVRS) telephone system • Conditional branching (skip patterns) • Write-ins with automatic mapping to standardized terminology



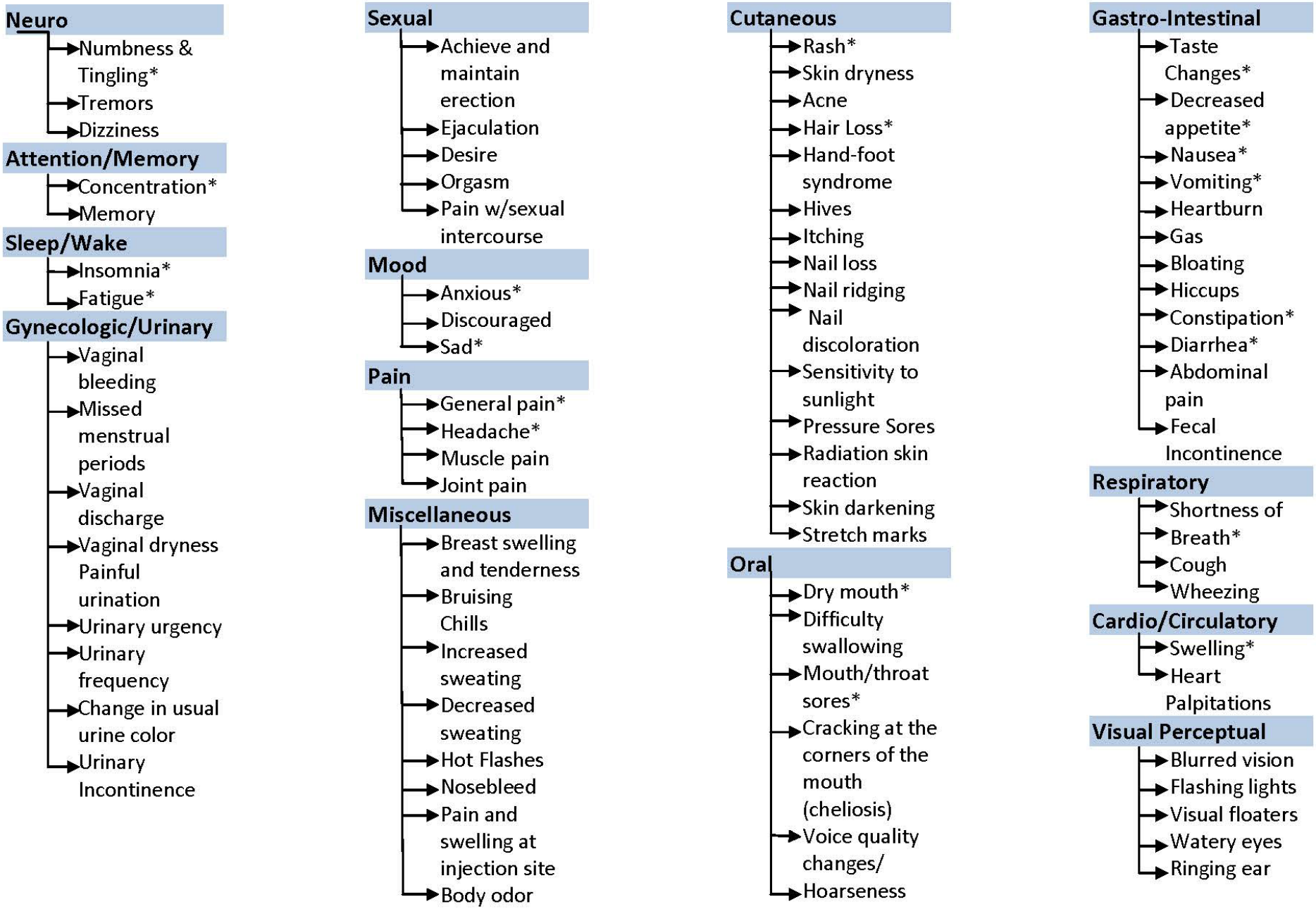


CTCAE vs. PRO-CTCAE Item Structures

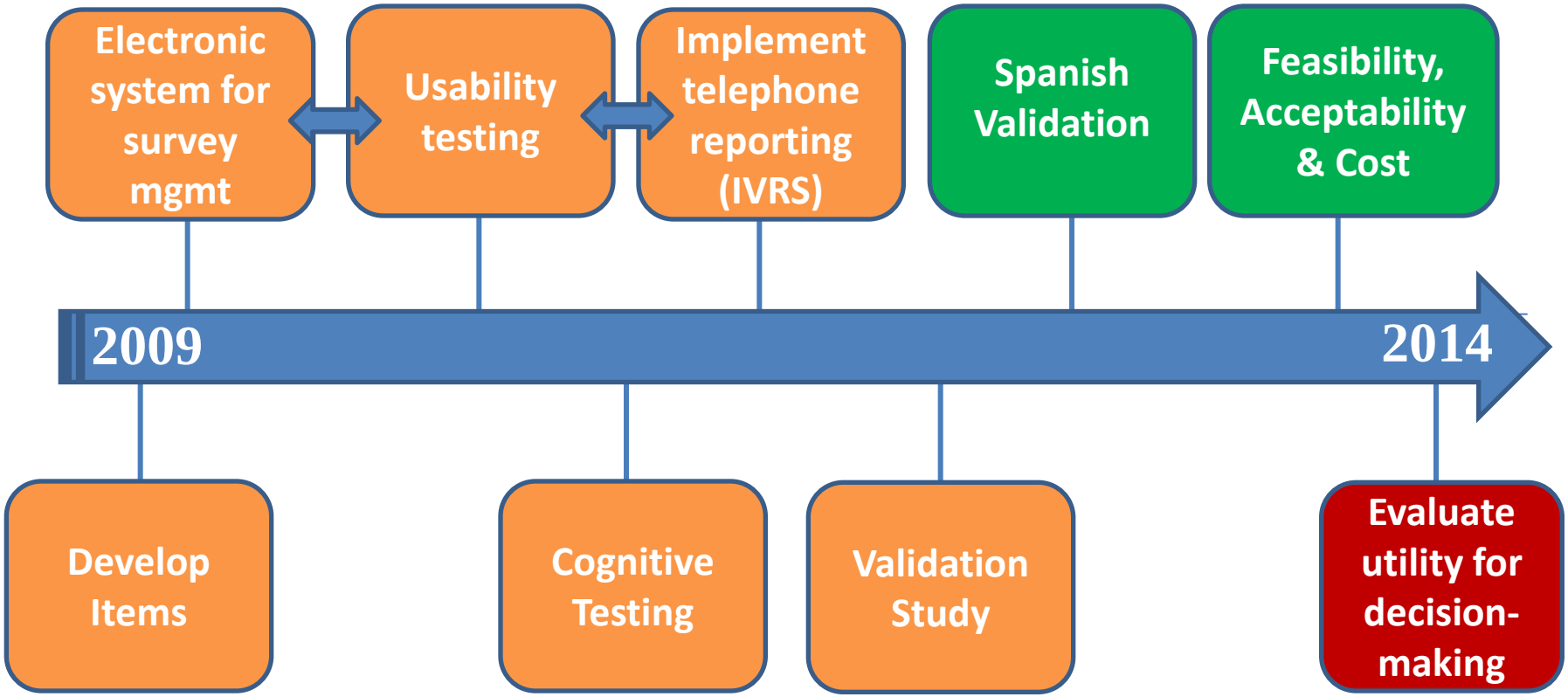
CTCAE					
Adverse Event	Grade				
	1	2	3	4	5
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	-

PRO-CTCAE
Please think back over the past 7 days:
What was the severity of your MOUTH OR THROAT SORES at their WORST? None / Mild / Moderate / Severe / Very severe
How much did MOUTH OR THROAT SORES interfere with your usual or daily activities? Not at all / A little bit / Somewhat / Quite a bit / Very much

PRO-CTCAE Symptom Library



- Psychometrically robust library of items
- Electronic system fits data collection smoothly into trials workflow and offers favorable user-experience
- Accommodate patients with limited English proficiency/digital literacy
- Supply meaningful data to improve understanding of symptomatic AEs



PRO-CTCAE: Evidence for Reliability and Validity[1-3]

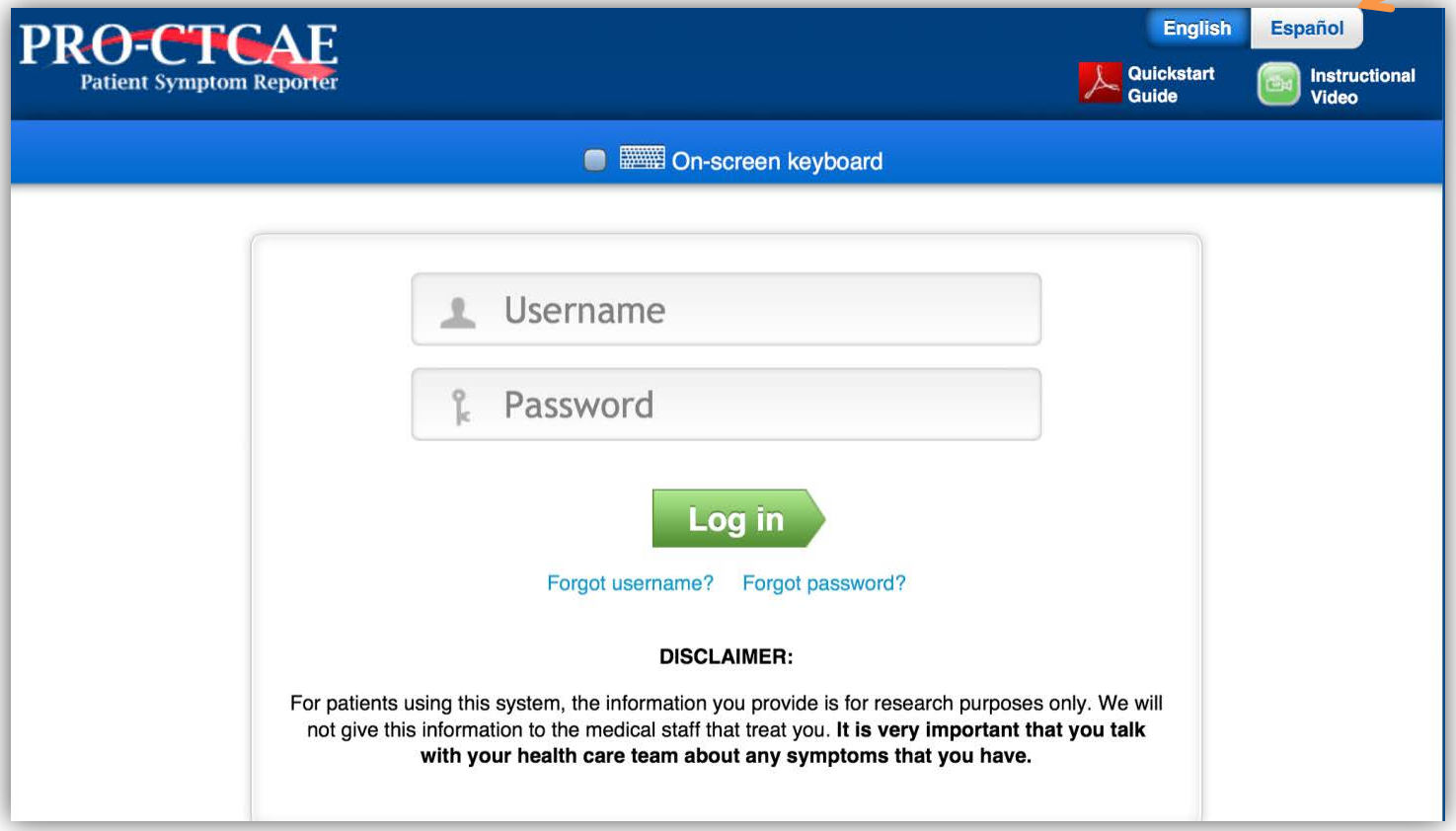
- Studies conducted in diverse samples all of whom were receiving cancer-directed therapy;
- Samples enriched for lower educational attainment, racial/ethnic diversity, and lower performance status
  - Item development: rigorous process mapping out of the CTCAE and building phrasing from legacy PRO measures
  - Cognitive interviewing to establish content validity
  - Psychometric validation
    - Almost all items met one or more a priori criteria for validity
    - Majority of items distinguished subgroups based on PS, disease site, and/or treatment characteristics

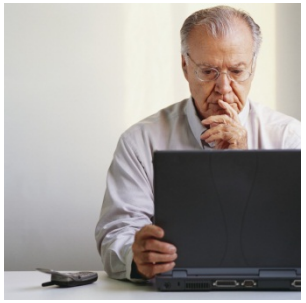
[1]*Hay et al (2013).* Cognitive interviewing of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) to support content validity. *Quality of Life Research July 20 2013 [Epub ahead of print]*

[2]*Dueck et al.* Validity and reliability of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Manuscript in preparation for Journal of Clinical Oncology

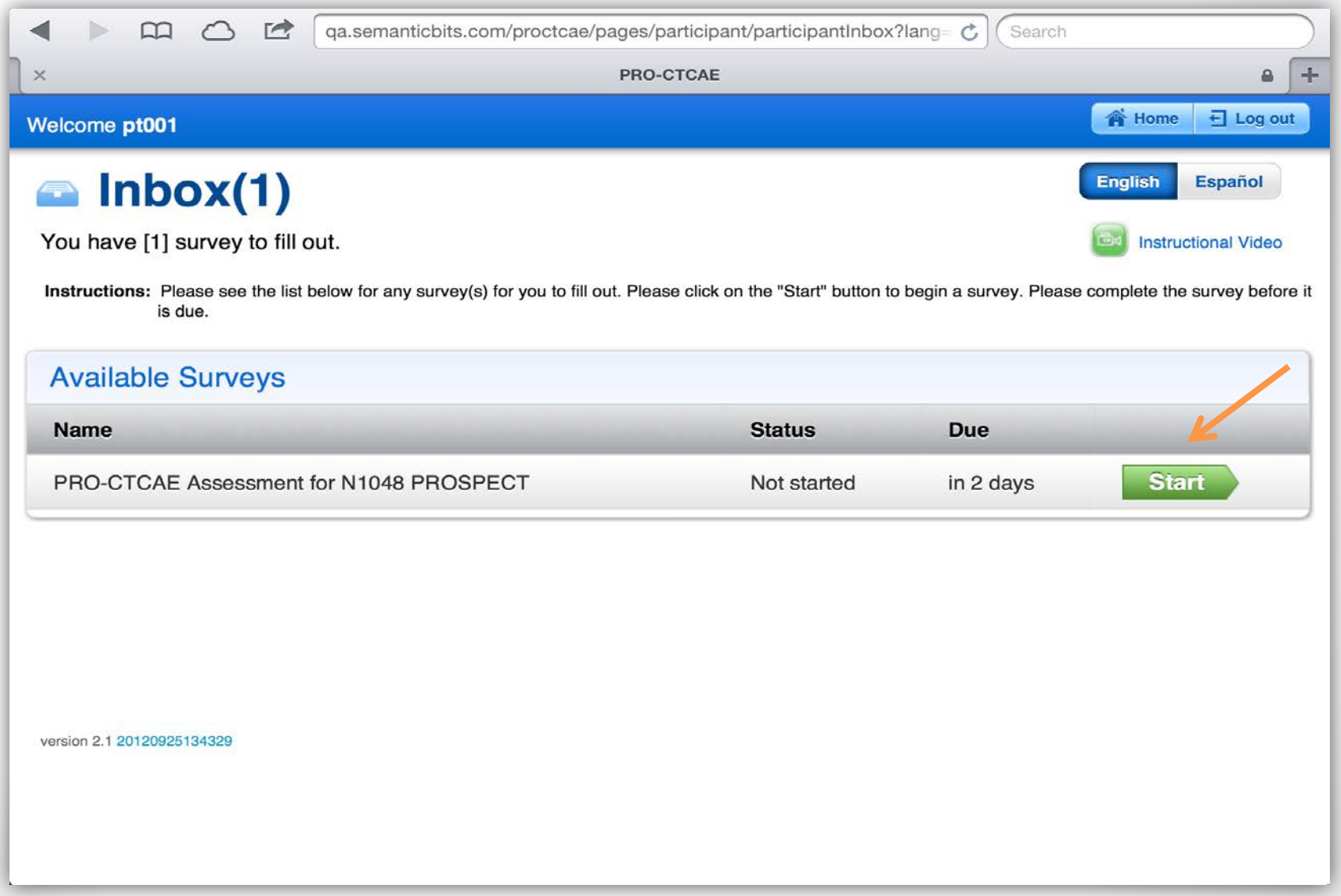
[3]*Basch et al.* Development of the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Manuscript under review at JNCI.

System for Electronic Data Capture

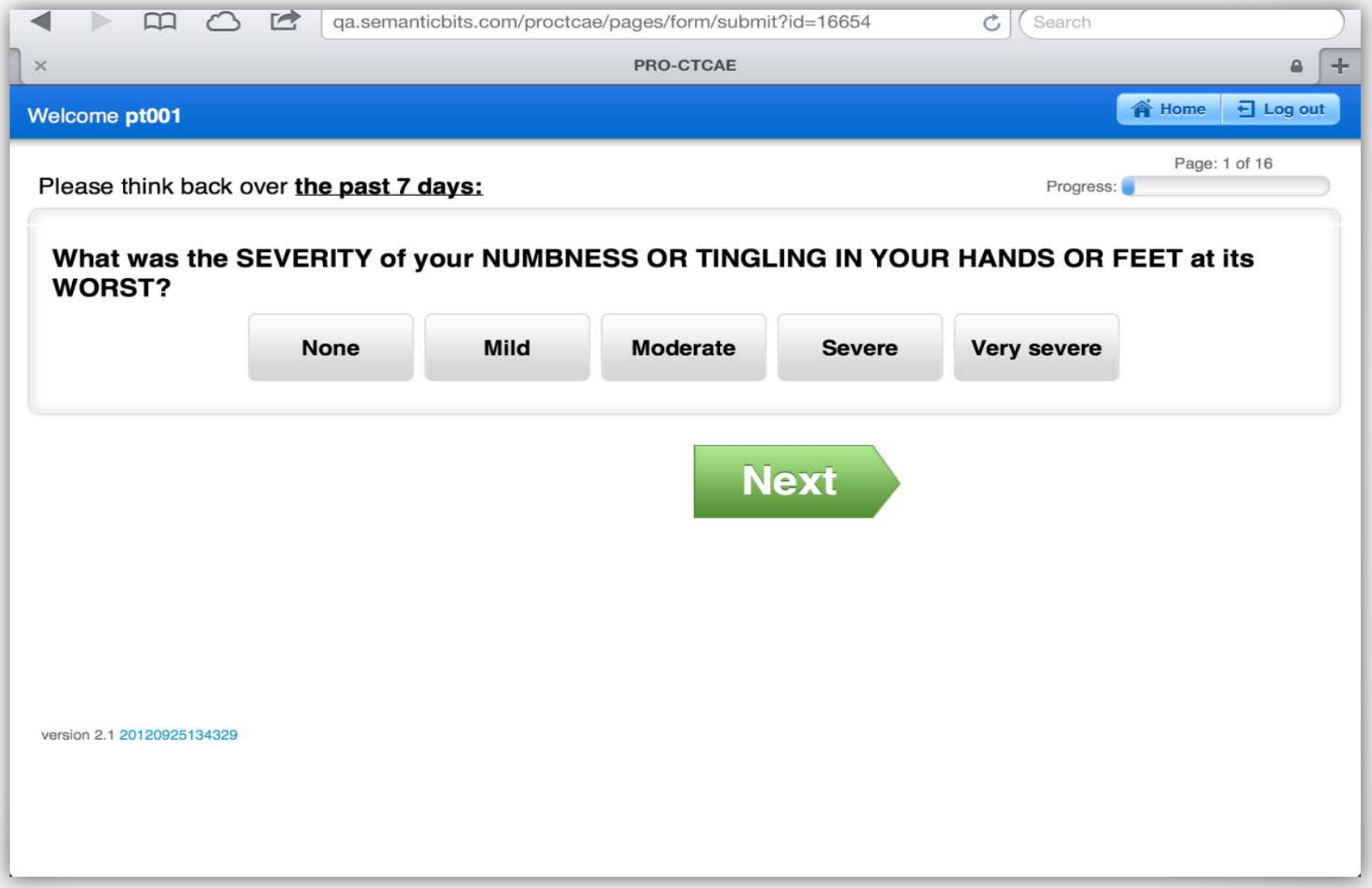




E-Mail Notification



Conditional Branching



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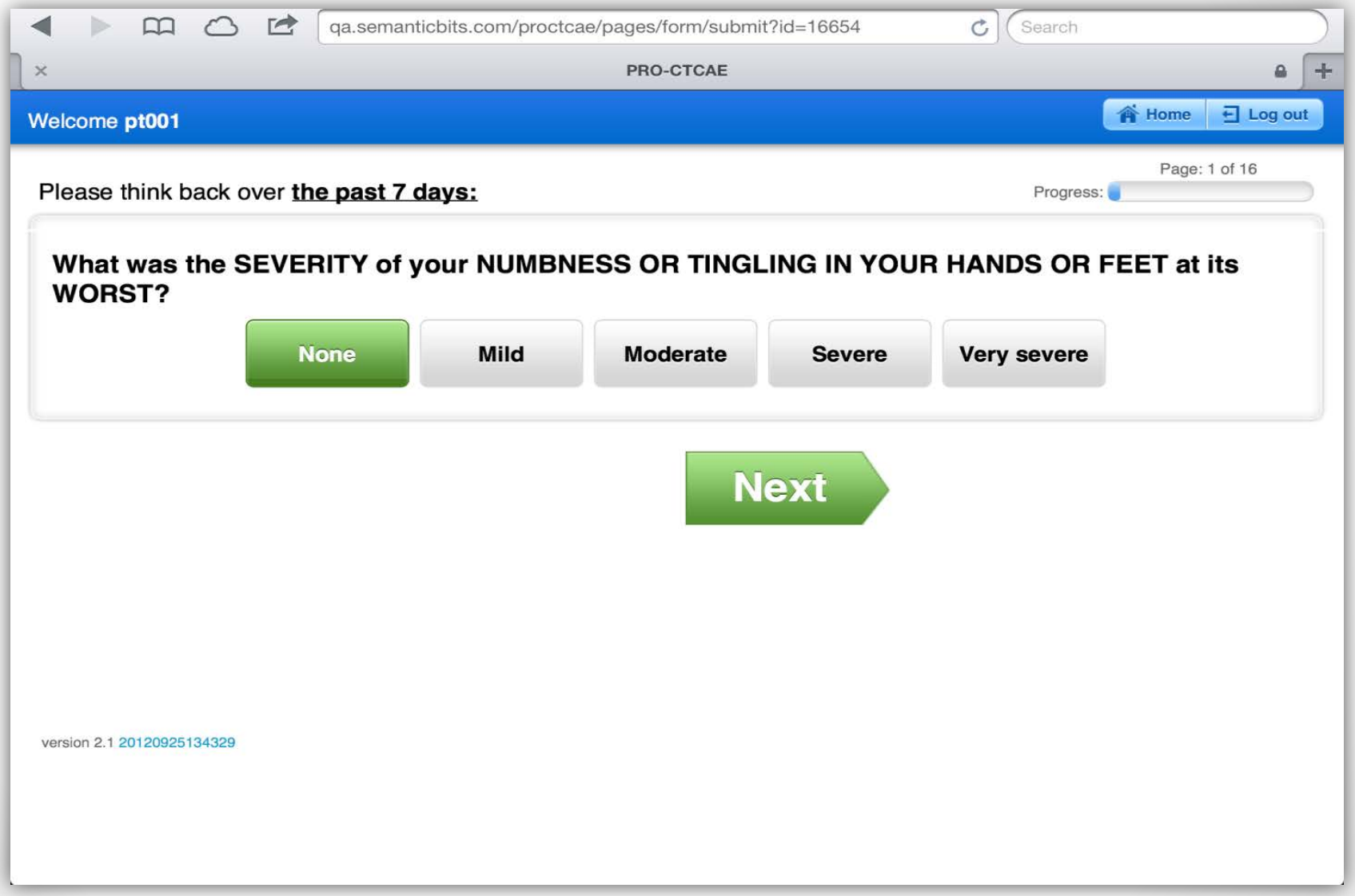
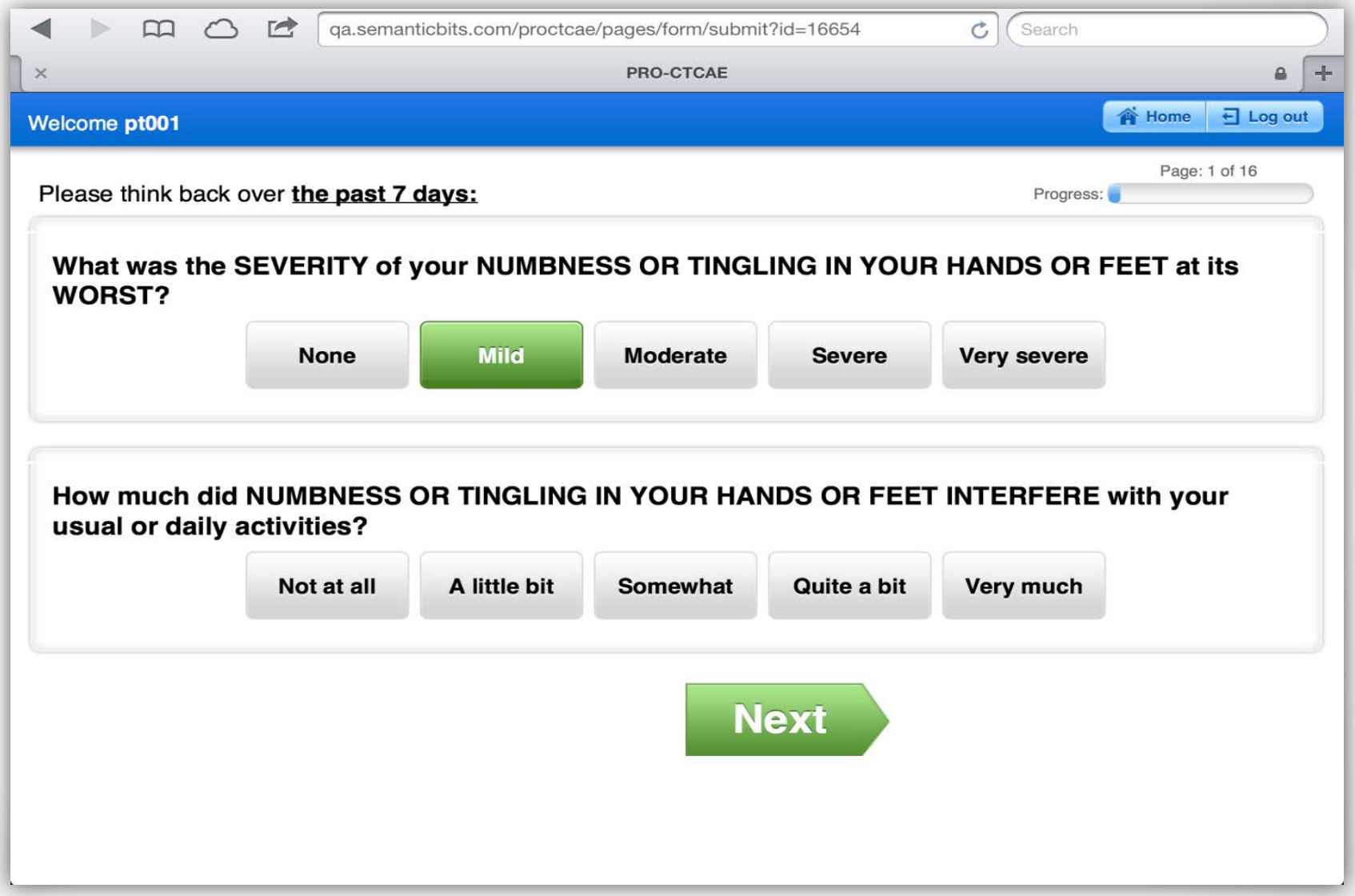
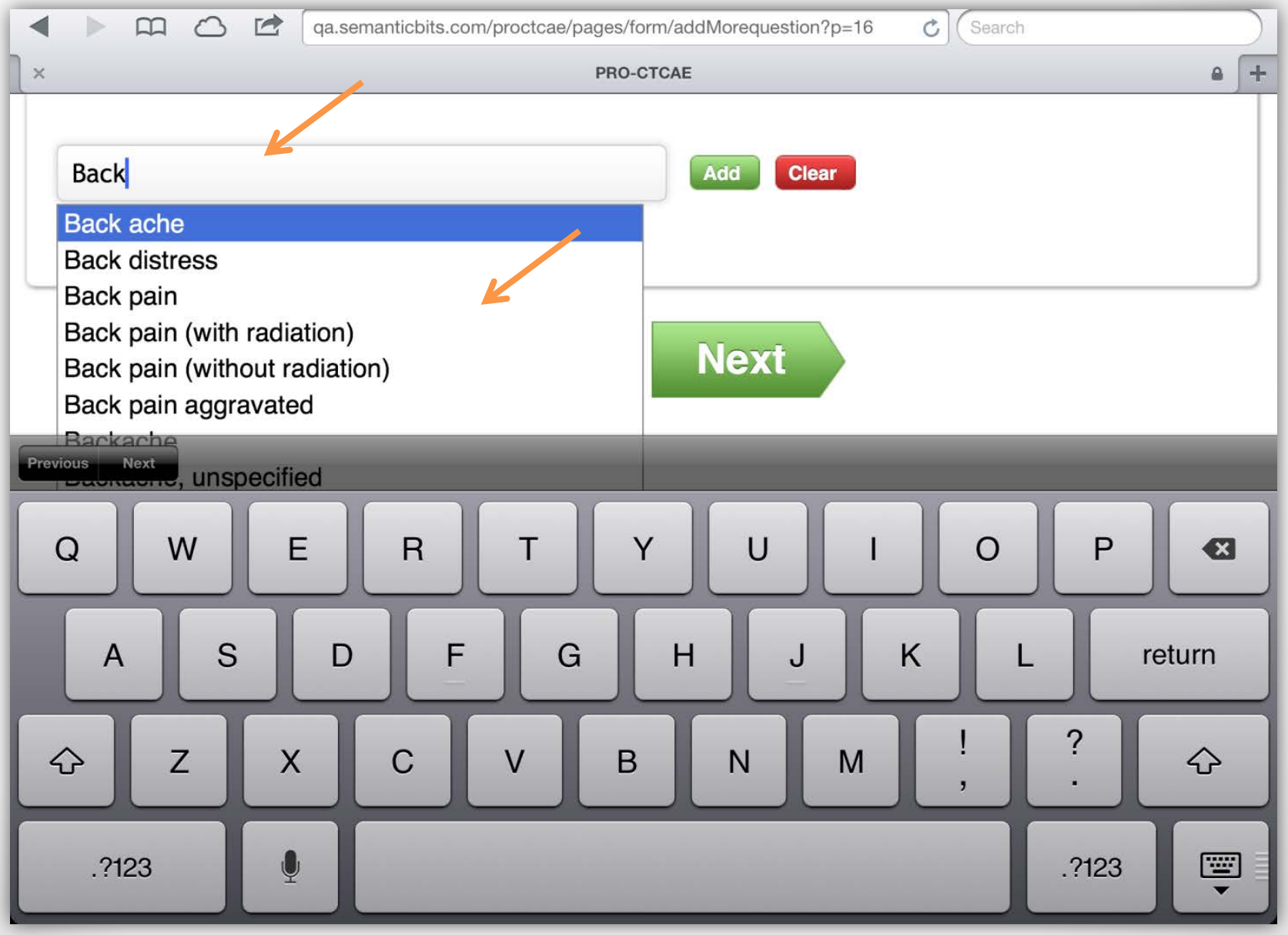


Conditional Branching



Write Ins for Additional Symptoms



PRO-CTCAE Implementation

Use in 2 cooperative group trials

- Feasibility and acceptability
- Data quality
- Resource requirements and cost
- Measurement characteristics/interpretability:
  - Responsiveness to change
  - Sensitivity to detect differences between treatment groups

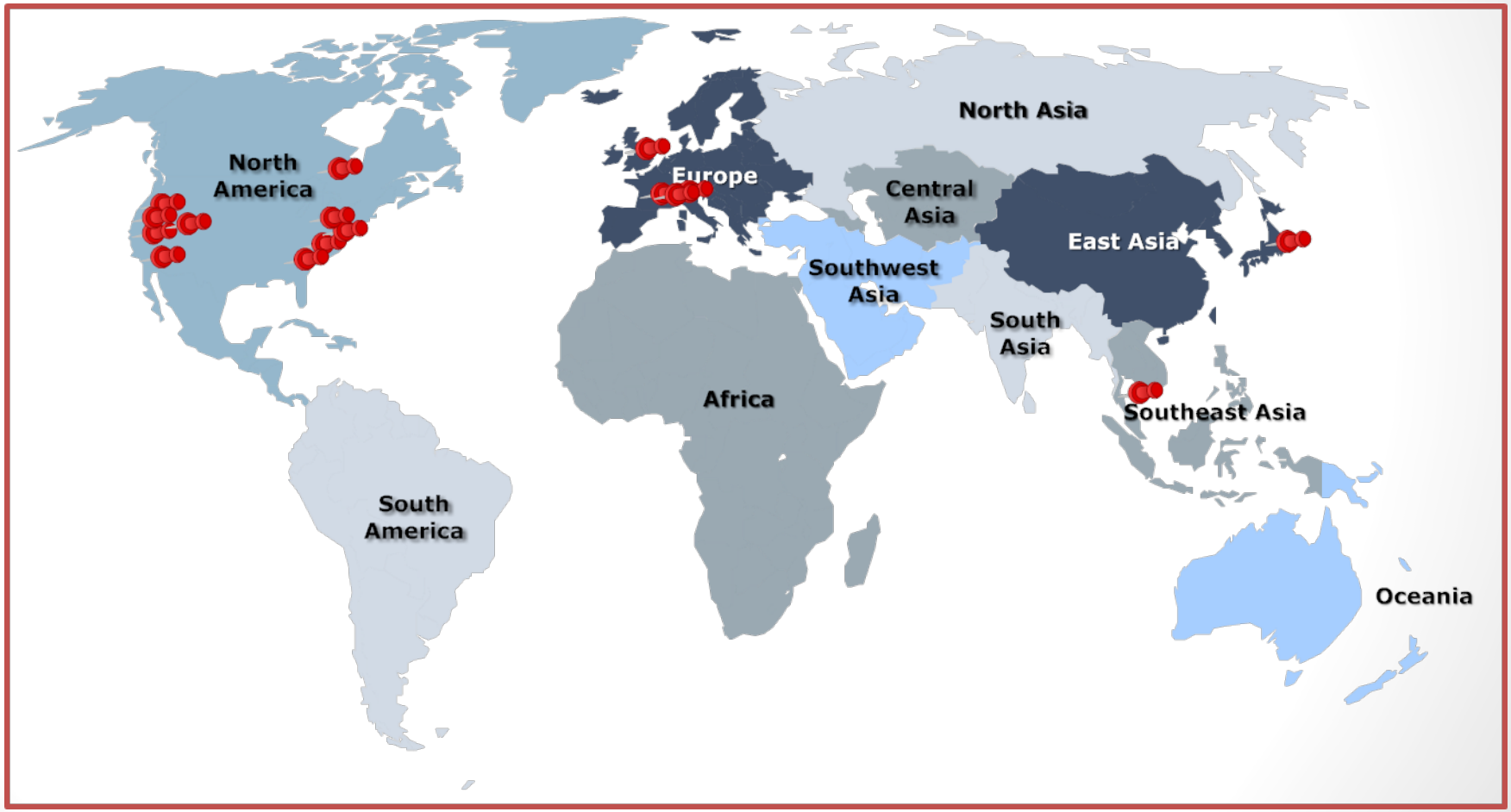
RTOG 1012: Phase II Randomized Trial of Prophylactic Manuka Honey for the Reduction of Chemoradiation Therapy Induced Esophagitis-Related Pain During the Treatment of Lung Cancer

NCCTG 1048: A Phase II/III trial of Neoadjuvant FOLFOX, with Selective Use of Combined Modality Chemoradiation versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision

Early Adopters

- 35 Early adopters in academic settings and in industry are testing PRO-CTCAE in trials and observational studies
- Collaboration agreements (35) established with these investigators:
  - Stimulate efficient and coordinated testing of PRO-CTCAE in clinical trials
  - Allow for sharing of data and collaborative analysis
  - Generate evidence about best approaches for particular study contexts and patient populations

Collaboration Agreements Established with Investigators in 8 Countries



Where Are We Heading Next?

- Standard analytic validation for a patient-reported outcome measure completed
- PRO-CTCAE can be used for descriptive information
- Understanding of clinical validity, interpretation, and clinical utility is evolving

Key Issues

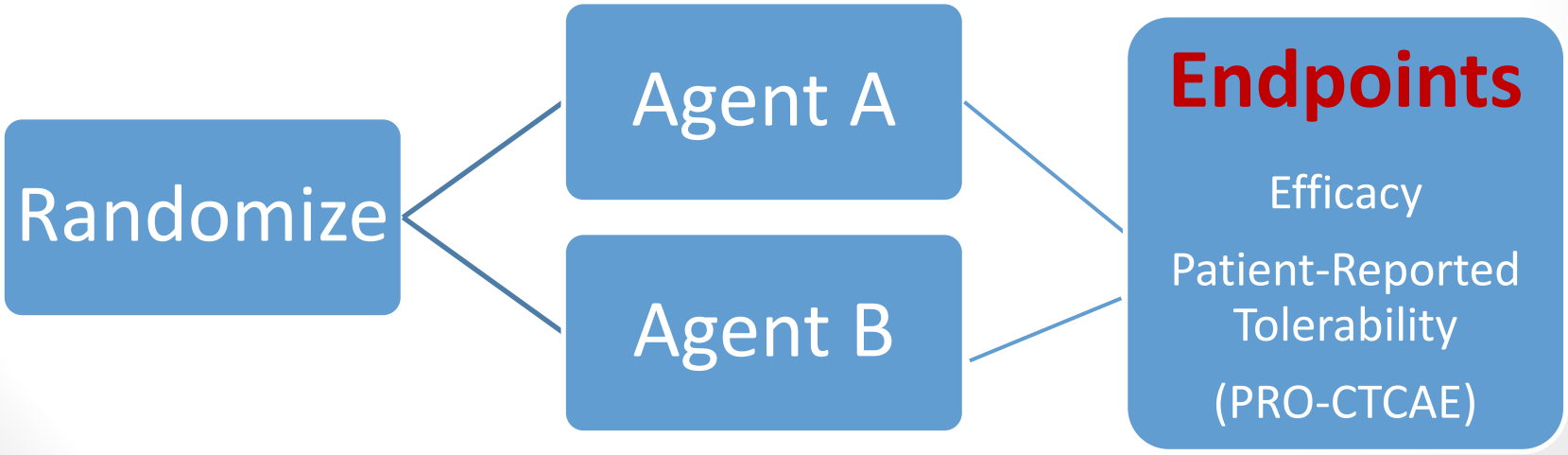
- Identify trial contexts and investigational therapies where PRO-CTCAE will be particularly useful
- Interpret PRO-CTCAE scores to assign a grade
- Delineate principles for design and interpretation of trials that incorporate patient self-reporting of adverse effects and yield interpretable and meaningful information

Utility of PRO-CTCAE

- **Phase I:** Exploratory
  - Gauge side effects relative to dose escalation; refine measurement approaches (items, timing) for later phase studies
- **Phase II:** Describe Toxicity in Depth
  - Assess tolerablility of the recommended phase II dosing
  - Identify chronic symptomatic toxicities that may impair adherence
  - Explore approaches (schedule/dosing, supportive care) to reduce symptomatic adverse effects
- **Phase III:** Assess Overall Benefit/Risk for Regimen
  - Evaluate efficacy and tolerability on a wider scale
  - Assess impact of dosing modifications to reduce chronic symptomatic toxicities on overall benefit/risk
- **Phase IV:** Efficacy → Effectiveness
  - Optimize tolerability
  - Tailor regimens for vulnerable sub-populations (comorbidities, frail, older adults)

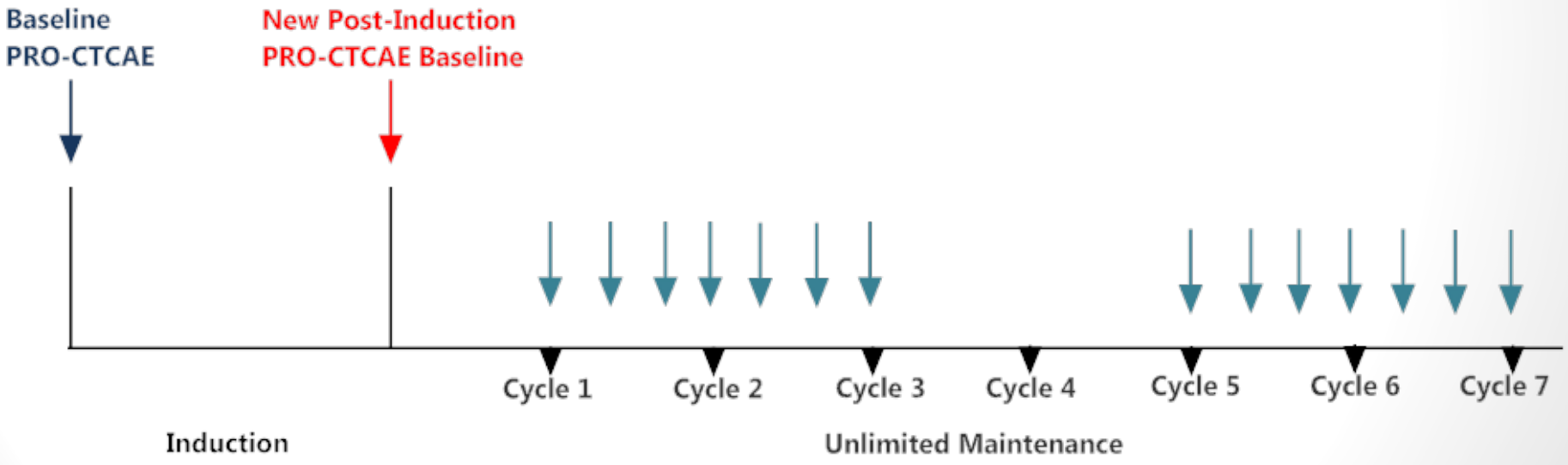
Phase 2 B Comparative Tolerability

- Two oral agents with comparable efficacy and clinician-rated toxicity in Phase II trials
  - Research Question: Are there subtle tolerability differences between the two agents that might become important in Phase III and which can be detected with inclusion of PROs in Phase II?
- Randomized phase II B study with efficacy and patient-reported tolerability as the primary endpoints



Tolerability of Maintenance Therapy

Research Question: What is the chronic tolerability of unlimited bortezomib maintenance therapy in multiple myeloma in remission after induction?



Scaling Towards Implementation

- **Increase accessibility for pediatrics**
- **Incorporate into CTCAE**
  - Demonstrate clinical validity/interpretability and utility across trial designs and populations so that integration into CTCAE is empirically-driven
- **Ongoing efforts to embed PRO-CTCAE into existing clinical trials**
  - Understand how reporting could influence dose modifications
  - Efficiently incorporate into trial design to yield information that is interpretable and useful for decision-making (individual and trial-level)
- **Integrate PRO-CTCAE into Medidata Rave (NCI's Remote Data Capture System)**

Discussion with CTAC Members

- What are the trial populations, study designs, and therapeutic contexts in which PRO-CTCAE will be particularly useful?
- As key stakeholders in NCI ‘s clinical trials system, we need in your engagement and perspectives about:
  - Consensus-based and data-driven approaches to mapping PRO-CTCAE responses into CTCAE grading
  - Best practices for aggregate reporting of PRO-CTCAE outcomes
  - Best practices for integration of PRO tolerability data into real-time monitoring and analysis/interpretation of trial level outcomes

Appendices: Supplementary Material

Appendix A:
Cognitive Interviewing Study

- Aim: Evaluate comprehension/interpretation of PRO-CTCAE terminologies and response options
- Methods: 3 rounds of cognitive interviews
- Sample: 127 patients with advanced cancer receiving active treatment at 4 cancer centers
  - 35% <high school; 28% non-white; 59% female
- Results:
  - 63/80 symptom terms generated no cognitive difficulties
  - 17 terms (e.g. diarrhea, insomnia, wheezing) modified and retested with no further difficulties
  - Distinction among frequency, severity, and interference understood

Hay et al (2013) . Quality of Life Research July 20 2013 [Epub ahead of print]

Appendix B:
Validation Study Aims and Methods

Aim: Examine validity and reliability

Methods:

- Convergent validity: associations with EORTC QLQ C30 scores
- Known-groups validity: groups based on disease site, clinical characteristics, and ECOG PS
- Test-retest reliability: assessed on consecutive days in a subsample

Sample: 975 patients who had received cancer-directed therapy in the prior two weeks

- 59 years (range 19-91); 28% non-White; 32%< high school; 35% lung/head and neck; 28% breast; 18% GU/Gyn; 17% PS 2-4

Appendix B:
Validation Study Results

- **PRO-CTCAE demonstrates favorable validity and reliability in a large, heterogeneous sample of patients undergoing cancer treatment**
  - Most PRO-CTCAE items (116/124) were shown to be valid across one or more validity criteria ($p<.05$)
    - 8 items (rare events with low endorsement) could not be meaningfully validated in this sample
  - All PRO-CTCAE items correlated with EORTC QLQ-C30
  - 96/124 PRO-CTCAE items distinguished subgroups based on PS, disease site, and/or treatment characteristics
  - Acceptable test-retest reliability across tested items (Median ICC 0.77)

Dueck et al. Manuscript in preparation for JNCI

Appendix C:
Ongoing Validation Analyses

- Mode equivalence
  - Comparison of paper, web, and telephone administration on the same day
- Recall Period
  - Comparison of 28 daily ratings to 1-, 2-, 3-, and 4-week recalled ratings
- Interpretability
  - Relationships among symptom attributes (frequency, interference, severity)
  - Cut scores

National Cancer Institute

Clinical Trials Reporting Program (CTRP): 2013 Update

Presented to CTAC
November 6, 2013

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for CCCT and CBIIT

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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NCI's Clinical Trials Reporting Program

- Overview
- Progress since last report to CTAC (July, 2011)
- Future considerations for CTRP data capture and reporting
- CTAC Clinical Trials Informatics Subcommittee: addressing future considerations and unresolved policy issues

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What is CTRP?

- Comprehensive database containing regularly updated information on all NCI supported clinical trials, including accrual
- Central repository of trials with information collected using standardized data elements
- System designed to support NCI's clinical trials portfolio management

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Added Value of CTRP to NCI

- Collects information not available in ClinicalTrials.gov that enhances NCI's clinical trials portfolio management; including:
  - Patient and site accrual data
  - Biomarkers: assay type, purpose, tissue specimen type and collection method
  - Protocol document for abstraction (except industrial trials)
  - Data needed to create Cancer Center Support Grant (CCSG) Data Table 4 (e.g., funding category, funding sponsor, anatomic site)
- Search of trial data enhanced by consistent terminology including disease terms, interventions and biomarkers
- Enhances ClinicalTrials.gov compliance
  - Facilitates ClinicalTrials.gov submissions, avoiding duplicate data entry by NCI awardees.
  - Supports management of NCI's ClinicalTrials.gov account and compliance with the FDA Amendment Act of 2007 for NCI sponsored trials.

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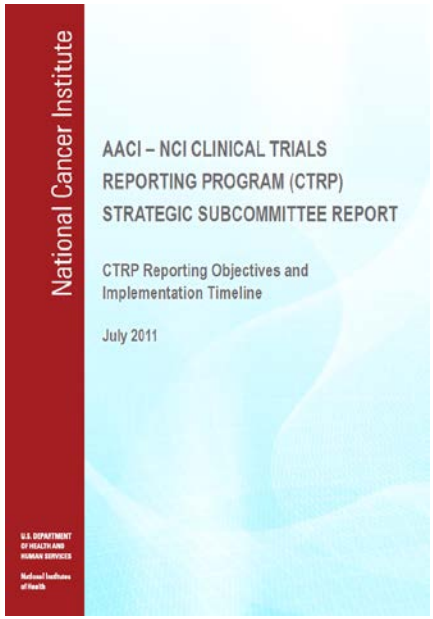
AACI* – NCI CTRP Strategic Subcommittee July 2011



- CTRP Reporting Requirements
  - Registration
  - Amendments
  - Updates/status changes
  - Accrual
  - Outcome reporting
- Timelines

*Association of American Cancer Institutes (AACI)

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Timelines*: AACI – NCI CTRP Strategic Subcommittee Report, July 2011

- Initial registration of interventional trials open to accrual on or after January 1, 2009 to be completed by September 2011
- Ongoing registration of new trials beginning September 2011
- Submit trial amendments and updates beginning March 2012
- Submit subject accrual reporting, with quarterly updates, beginning September 2012
- Defer observational trials and outcome data reporting for 3 to 5 years

*Timelines for NCI-Designated Cancer Centers

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Progress: Trial Registration

- Initial registration of interventional trials open as of January 1, 2009 has been completed by NCI-Designated Cancer Centers, CTEP, DCP, and CCR
- Registration of new trials is ongoing
- Registration of non-interventional (i.e., observational/ancillary/correlative) trials is accepted
- Registration of trials by other NCI awardees has not consistently begun

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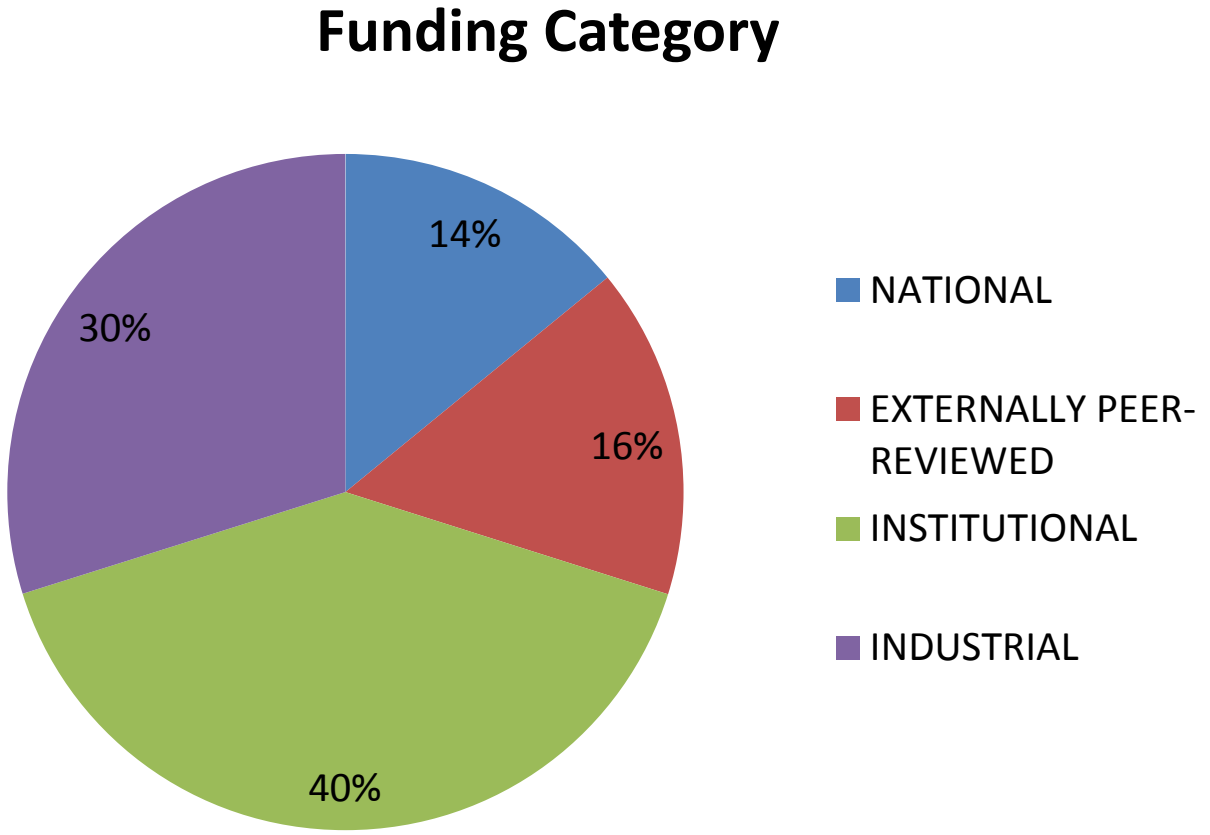
Registered Trials by Funding Category

10,257 Trials Registered and Abstracted (November 2013)



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Progress: Amendments and Updates

- NCI-Designated Cancer Centers are reporting amendments, updates, and status changes
- Timing of submissions:
  - Amendments: within 20 days of IRB approval
  - Status changes: within 30 days of the change
  - Updates: annually
- CTRP will implement an automated process for a yearly reminder to facilitate update reporting

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Accrual Reporting – Work in Progress

- Import of accrual data on NCI managed trials (CTEP, DCP, CCR) underway
- Cancer Centers reporting patient level accrual on institutional trials where they are the lead organization is in progress
- Cancer Centers report summary accrual count on Industrial trials where they are participating is in progress

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Progress: CCSG Data Table 4

- Initial CTRP automated CCSG Data Table 4 reports developed

- Beginning in January 2014, initial CTRP-generated Data Table 4 reports will be reviewed with each NCI-Designated Cancer Center to ensure:
  - The list of registered trials is accurate and complete
  - Accrual is complete and correctly reported for the Cancer Center and its affiliates

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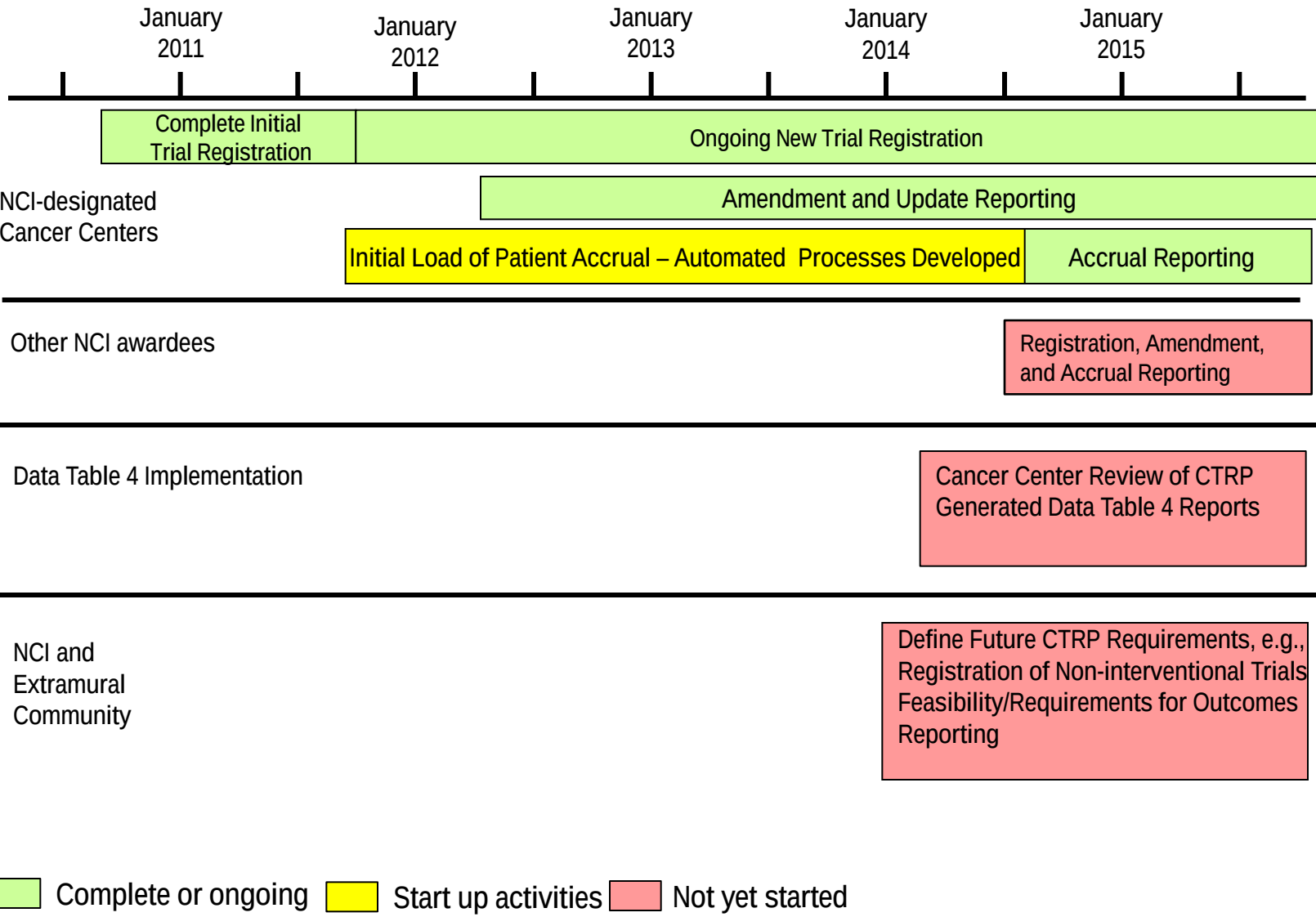
CTRP Timeline as of October 2013



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CTRP - A Collaborative Effort Within the NIH/NCI

- Collaborative effort within NCI
  - Involved many groups within NCI (CTEP, DCP, OCC, CCR, DCCPS) to initiate data transfer and integration activities
- Collaborative effort with NIH/NLM
  - Regular meetings to facilitate NCI and extramural community compliance with FDAAA reporting requirements to ClinicalTrials.gov
  - Developed and implemented “Upload from CTRP” function which allows sponsors to retrieve CTRP data for trial registration for upload to ClinicalTrials.gov
  - CTRP registration and amendment timelines make data available for upload well within timelines defined by ClinicalTrials.gov

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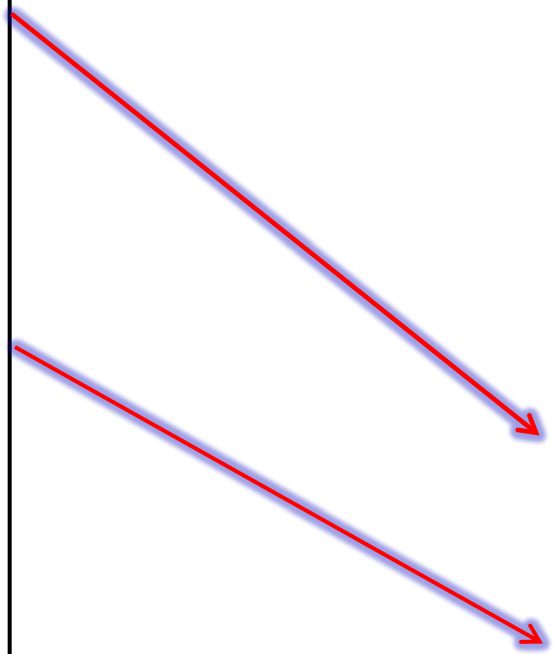
"Upload from CTRP" and ClinicalTrials.gov

- CTRP-ClinicalTrials.gov Upload function allows trial sponsors to register and maintain trial information in ClinicalTrials.gov from CTRP data
  - NCI-sponsored Trials: NCI ClinicalTrials.gov account for NCI sponsored trials
  - Other-sponsored Trials: Sponsors can upload CTRP data directly into their ClinicalTrials.gov account from CTRP via the Upload Service
- CTRP imports Industrial trial data from ClinicalTrials.gov for trials that Cancer Centers have indicated participation
  - The CTRP Clinical Trials Reporting Office (CTRO) performs scientific abstraction for cancer disease and interventions on Industrial trials to enable search and reporting across all trial categories

Main Menu

XML Upload

Upload from NCI CTRP



ClinicalTrials.gov
Protocol Registration System

Send message to ClinicalTrials.gov PRS

Help us improve: PRS Survey

Main Menu

Standard Functions

Protocol Records
- Create
- Modify
- View
- **QA Review Comments**
- **Problems: ncictro Records**
- Undelete

User Account
- Change password
- Modify Information
- PRS Administrator(s)

Help
- **Quick Start Guide**
- Frequently Asked Questions (FAQ)
- Responsible Party FAQ
- What's New **Jan 24, 2013**
- User's Guide

- Protocol Data Element Definitions
- Protocol Review Criteria

- Results Data Element Definitions
- Results Review Criteria
- Simple Results Templates
- About Results Data Entry

- FDAAA 801 Requirements
- FDAMA 113 Requirements

XML Upload
- Upload protocol records
- Check upload status
- Protocol XML Schema
- Results XML Schema
- Results Pick-list Normalization
- External Upload API
- Upload from NCI CTRP

Session
- Logout

Administrative Functions

Protocol Records
- **Problems: NCI Records**
- Validate all records
- Release all records
- Check release status
- Change owner
- Publication Report
- Transfer NIH Record (NIH)

User Accounts
- Create
- Modify
- Enable/disable

Organization Account
- Modify
- Groups
- Email Addresses
- Product Information

Help
- **Admin Quick Reference**

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CTRP: Future Considerations

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CTRP: Future Considerations

- Should the scope of trials required for reporting to CTRP be expanded to include submission of non-interventional trials?
  - CTRP currently accepts observational and ancillary/correlative studies but submission is not required
  - Current CCSG Data Table 4 format requires observational and ancillary/correlative studies; is this necessary going forward?
    - What data elements and accrual should be reported for these trials if CTRP required submission?
- The AACI/NCI 2011 report recommended deferral of outcome reporting to CTRP for 3-5 years
  - Is outcome reporting feasible and of value to NCI and the oncology community?

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CTRP: Reporting Requirements

- CTRP trial information is designed for NCI portfolio analysis on a number of data dimensions:
  - Cancer Center
  - Disease and Intervention
  - Biomarkers
  - Target and Actual Accrual
- Initial reporting focus has been on Data Table 4
- Need stakeholder input for future reporting requirements (within NCI and extramural)
- Policies for information access and corresponding user privileges needs to be established

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CTAC Clinical Trials Informatics Subcommittee Responsibilities

- Review progress on the implementation of CTWG and other clinical trials informatics initiatives
- Provide advice on CTRP topics needing additional consideration such as:
  - CCSG Data Table 4 report design
  - Reporting non-interventional trials in CTRP
  - Assessment of whether additional data elements should be captured in CTRP (e.g. outcome data)
- Working groups may be formed to accomplish specific tasks

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Data Elements/Definitions

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Trial Categorization: Definitions
NCI Office of Cancer Centers - Data Table 4

- **National:** NCI National Clinical Trials Network (NCTN) and other NIH-supported National Trial Networks

- **Externally Peer-Reviewed:** R01s, SPORES, U01s, U10s, P01s, CTEP, or any other clinical research study mechanism supported by the NIH or an approved peer-reviewed funding organization

- **Institutional:** In-house clinical research studies authored or co-authored by Cancer Center investigators and undergoing scientific peer-review solely by the Protocol Review and Monitoring System of the Cancer Center. The Cancer Center investigator has primary responsibility for conceptualizing, designing and implementing the clinical research study and reporting results
  - It is acceptable for industry and other entities to provide support (*e.g.,* drug, device, other funding) but the trial should clearly be the intellectual product of the center investigator.
  - This category may also include:
    - Institutional studies authored and implemented by investigators at another Center
    - Multi-Institutional studies authored and implemented by investigators at your Center

- **Industrial:** The design and implementation of these clinical research studies is controlled by the pharmaceutical company

http://cancercenters.cancer.gov/grants_funding/index.html

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AACI – NCI CTRP Strategic Subcommittee Amendments and Updates

- Amendments are changes that:
  1. Substantively alter the treatment administered; and/or
  2. The study design; and/or
  3. The sites in which patients are being enrolled on the trial

- Status changes: changes in overall status of the trial (e.g., a change from active to closed to accrual).

- Updates: Other changes to the protocol.

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Registration Data Elements
National, Peer-Reviewed, Institutional Trials

Registration Data Elements	Mandatory =M Optional = O Conditional = C
Lead Organization	M
NCT Number	O
Other Identifiers	O
Title	M
Phase	M
Trial Type	M
Purpose	M
Principal Investigator	M
Sponsor and Responsible Party	C (Mandatory if XML is requested)
Trial Submission Category	M
Summary 4 Funding Sponsor	M
Program Code	O
NIH Grant Information	O
Current Trial Status and Status Dates	M
IND/IDE Information	O
Protocol Document	M
IRB Approval	M
List of Participating Sites	O
Informed Consent Document	M
Regulatory Information	C (Mandatory if XML is requested)

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Registration Data Elements Industrial Trials

Registration Data Elements	Mandatory =M Optional = O Conditional = C
Lead Organization	M
NCT Number	O
Lead Org Trial Identifier Number	M
Title	M
Submitting Organization Name	M
Submitting Organization Local Trial Identifier	M
Phase	M
Trial Type	M
Purpose	M
Site Principal Investigator	M
Confirmation that Trial Submission Category is Industrial	M
Summary 4 Funding Sponsor Type	M
Site Specific Program Code	O
Current Site Specific Trial Status	M
Date Reporting Site Open to Accrual	C (M when date known)
Date Reporting Site Closed to Accrual	C (M when date known)
Trial related documents	O

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Accrual Data Elements
National, Peer-Reviewed, Institutional Trials

Protocol Administrative Data Elements	Mandatory =M Optional = O Conditional = C
NCI Protocol Number	M
CTEP/DCP Protocol Number	C (Mandatory if CTEP/DCP PIO managed trial)
Date Report Submitted	M
Cut-Off Date for Data	M
Current Protocol Status	M
Submitter Name and Contact Information	O
Patient Demographic Information	Mandatory =M Optional = O Conditional = C
Patient ID	M
Patient Zip Code	C (Mandatory if US)
Patient Country Code	C (Mandatory if not US)
Patient Birth Date (Month/Year)	M
Patient Gender	M
Patient Ethnicity	M
Patient Method of Payment	O
Date of Patient Entry	M
Patient Disease Code	C (Mandatory for all trials except DCP PIO trials registered in CTRP by NCI
Patient Race	M

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Accrual Data Elements
Industrial Trials

Protocol Administrative Data Elements	Mandatory =M Optional = O Conditional = C
NCI Protocol Number	M
CTEP/DCP Protocol Number	C (Mandatory if CTEP/DCP PIO managed trial)
Date Report Submitted	M
Cut-Off Date for Data	M
Current Protocol Status	M
Submitter Name and Contact Information	O
Accrual during reporting period	Mandatory =M Optional = O Conditional = C
Number of patients accrued at site	M