21st Century Cures: Modernizing Clinical Trials

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Good morning, Chairman Upton, Ranking Member Waxman, Subcommittee Chairman Pitts, Ranking Member Pallone, and Members of the sub-committee. Thank you for inviting me today to share my experience regarding innovative clinical trials for cancer patients. My name is Dr. Roy Herbst and I have been working on this problem for nearly 30 years having trained as both an MD and PhD in cancer medicine. I am currently the Ensign Professor of Medicine and Chief of Medical Oncology at the Yale Cancer Center where I am also the Associate Director for Translational research. In my role at Yale, I care for patients with lung cancer, conduct/collaborate on basic research, and work on clinical trials from phase I (first in human) to phase III. Over the last two years I have been working with the Friends of Cancer Research (founded and led by Ellen Sigal), the National Cancer Institute, SWOG, and FDA on an innovative public-private partnership approach to clinical trials- and am honored to be invited to participate in this important hearing today.

Cancer is the second most common cause of death in the US. According to the American Cancer Society, about 585,720 Americans are expected to die of cancer in 2014. Unfortunately many cancers that have spread or become metastatic are currently incurable. Lung cancer is one such incurable cancer and as a specialist in this area I often see patients with advanced disease and work to develop new therapies and cures. This disease is accompanied by much pain and suffering, loss of life and productivity. Twice in my career I personally have seen and been involved in the development of new agents for the treatment of lung cancer that have truly transformed the landscape. In 1997, we began to study drugs that target the epidermal growth factor receptor and noticed that 10-20% of patients experienced extraordinary benefit. However it was not until 2004 that researchers identified the biomarker and learned how to identify that small group of patients who would benefit from the treatment. Patients are still alive from

these initial studies. Today we have the advent of immunotherapies, that provide extraordinary benefits in melanoma, renal, lung and other tumor types, but we still do not know who benefits most. If we knew how to identify these patients in advance we could find ways to provide more effective, less toxic and more cost effective therapies that are tailored to best suit each patient.

Due to our country's investment in research, in 2014 we can now sequence every gene in a tumor including the 25,000 protein coding genes. This is amazing technology and science, but is limited because 1) it is only available to a minority of patients, 2) it is expensive and often not covered by insurance, 3) the informatics and data interpretation challenges are overwhelming, and most importantly 4) we still do not have the ability to translate the information into therapeutic benefit. The medical community remains limited on our abilities to match the right patient to the right drug at the right time. The challenges are multifold- and include issues such as limited knowledge of the distribution of a particular genetic alteration in the patient population as well as cost of trials. For example, I recently conducted a trial in lung cancer with an agent that targets FGFR (Fibroblast growth factor receptor), with a presumptive abnormality in 10-20% of patients. We screened 100 patients to find only 6 with the abnormality, which was much fewer than expected, and inevitably we were only able to enrolled 2 patients on the trial. This type of trial does not help enough patients and also is not conducive to productive research.

Clinical trials need to be modernized for the molecular age. Often clinical trials are limited by numerous challenges including the start-up time, accrual, expense, and the need to identify defined sub-populations of patients that makes trial enrollment difficult. Developing a potential therapy from the initial discovery stage through clinical testing and regulatory approval is a complicated, expensive, and often inefficient process that can take up to 15 years. Only by finding better ways to match drugs with patients and studying them in large and diverse populations can we help more patients with this disease

and get drugs approved. Modernizing this process with innovative approaches and new clinical trial designs is of high importance.

With this need in mind, the Lung-MAP: is an innovative, groundbreaking clinical trial designed to facilitate efficiencies and advance the development of targeted therapies for squamous cell cancer of the lung. It provides a mechanism to genomically screening large but homogeneous cancer populations and subsequently assigning and accruing patients simultaneously to a multi-sub-study "Master Protocol", resulting in a prospective, randomized phase II/III registration protocol. It addresses unmet medical needs for squamous cell lung cancer (commonly diagnosed in those with a history of smoking) and will provide answers to current questions across all of drug development, including how to develop drugs for uncommon-rare genotypes, how to apply broad-based next generation screening (NGS), and how to achieve acceptable turn-around times for molecular testing for therapy initiation?

There are previous examples of this new approach to clinical trial design focused on testing driven by the presence of biomarkers in the study population. First, patients are screened for the presence of biomarkers and then are assigned to sub-studies with investigational drugs targeting the biomarkers. These targeted therapies hold promise for improved efficacy, but for traditional single component studies many patients may need to be screened before enough patients harboring the necessary genomic alteration are available for the trial to be completed. This new multi-component clinical trial design allows more efficient screening and facilitates the addition of new drugs and biomarkers into the protocol on a "rolling" basis.

Two types of studies follow this design: "Basket" studies which examine the effect of specific therapeutic agent(s) on a specific genetic or molecular biomarker regardless of the type or subtype of cancer in which it occurs. Patients with the different types of cancer are evaluated in separate sub-studies, or "baskets". This allows analysis of the responses to the therapy for each type of cancer

evaluated, as well as responses to the drug across cancer types. An example is the National Cancer Institute's Molecular Analysis for Therapy Choice (MATCH) trial. Lung-MAP is an example of the second type, "Umbrella" studies, which evaluate different therapy/biomarker combinations in a single type of cancer. Other examples are I-SPY 2 in breast cancer, Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) in non-small cell lung cancer (which I co-led while at The University of Texas MD Anderson Cancer Center and now we have BATTLE-2 as an National Cancer Institute [NCI] funded program at Yale in collaboration with my colleague Dr. Vassiliki Papadimitrakopoulou at The University of Texas MD Anderson Cancer Center), and FOCUS4 in colorectal cancer. The unique aspect of Lung-MAP is that it will build on the principles and approaches of the previously mentioned trials, but for the first time, it will be an "umbrella" study conducted in a late phase setting (phase II/III) allowing successful drug candidates to be immediately considered for approval. This model can provide system wide benefit because phase III trials are often the largest, longest, and most expensive to conduct. Another distinctive feature of Lung-MAP is the ability for a drug that is found to be effective in phase II to move directly into the phase III registration components, incorporating the patients from phase II. This unique statistical approach can save both time and the number of patients that would be needed to program compared to conducting separate phase II and phase III studies.

The concept of the Lung-MAP was developed at the 2012 Friends of Cancer Research/Brookings Conference on Clinical Cancer Research and was initiated and opened in a year and a half. The goal is to develop a biologically driven approach – building on the NCI funded Cancer Genome Atlas (TCGA) to identify targets. In February 2012 the NCI, including investigators of the Thoracic Malignancy Steering Committee (TMSC), the Food and Drug Administration (FDA), European Medicines Agency (EMA), and pharmaceutical companies met together on the subject of "Strategies for Integrating Biomarkers into Clinical Development of New Therapies for Lung Cancer". Following that meeting, a TMSC task force

was established to develop a series of Master Lung Cancer Protocols chaired by Dr. Fred Hirsch at the University of Colorado. Prior to this and simultaneously, the Friends of Cancer Research (FOCR), let by Drs. Ellen Sigal and Jeff Allen in conjunction with FDA and NCI, initiated a similar effort presented as part of the 5th Annual Friends of Cancer Research/Brookings Institution Conference on Clinical Cancer Research in November 2012, which they asked me to chair. We published a white paper which was the basis for this trial. Finally in March 2013, at a follow-up FOCR Forum, the decision was made to go forward with the study now known as Lung-MAP, which is a public-private partnership involving the NCI and its Cooperative Group/National Clinical Trials Network (NCTN) infrastructure, the FDA, multiple pharmaceutical companies, FOCR, and lung cancer non-profits and patient advocates. The study is being executed by the Foundation for the National Institutes of Health (FNIH) and coordinated by the Southwest Oncology Group (SWOG).

Benefits of Lung-Map approach include:

- Enrollment Efficiency: Grouping these studies under a single trial reduces the overall screen failure rate
- Operational Efficiency: A single master protocol can be amended as needed as drugs enter and exit the study
- Cost Efficiency: As a result of shared services, utilization of existing infrastructure, and avoiding redundancy of processes, this public-private partnership will be operated at a cost substantially less than operating individual trials
- Consistency: Every drug entered into the trial would be tested in the identical manner
- Predictability: If pre-specified efficacy and safety criteria are met, the drug and accompanying companion diagnostic will be approved

- Transparency: All study activities are vetted and approved by a multi-stakeholder governance structure including an Oversight Committee and Drug Selection Committee
- Patient Benefit: offers the advantage of bringing safe and effective drugs to patients sooner than they might otherwise be available

Patients with advanced-stage lung squamous cell carcinoma whose disease has progressed on first-line therapy are assigned to a sub-study and then randomized within that sub-study to biomarker-driven targeted or standard-of-care (SOC) therapy. Our goal is to accrue 625 patients per year and to run 4–7 sub-studies concurrently. Sub-studies are defined by a genotypic alteration (biomarker) in the tumor and a drug that targets this alteration. Patients bearing more than one relevant biomarker are assigned to a sub-study based upon a pre-defined algorithm that helps facilitate even enrollment across all sub-studies. The protocol also includes a "non-match" sub-study for screened eligible patients that do not qualify for any of the current biomarker-driven sub-studies. This sub-study will compare a non-match therapy (which in the first iteration of Lung-MAP is an immunotherapy not yet shown to be effective in a limited, biomarker defined population) to SOC. A non-match sub-study will be open to accrual throughout the trial. Each sub-study will function autonomously and will open and close independently of the other sub-studies. Each sub-study is independently powered for overall survival (OS) with an interim analysis for progression-free survival (PFS) to determine the "go-no go" decision to proceed from phase II into phase III. Along with the paired biomarker, agents that are successful at interim analysis in phase II based on PFS will continue enrollment to evaluate phase III endpoints which include clinically meaningful increased PFS and OS for potential registration of the drug. Candidate drugs are evaluated by a multidisciplinary drug selection committee using specific criteria, such as:

- Demonstrated biologic activity against the target associated with a proposed predictive biomarker(s)
- Well-understood mechanism of activity against the target

- Evidence of clinical activity in cancer, particularly in squamous cell cancer (*e.g.*, phase I responders)
- Manageable toxicity as a monotherapy and in combination with chemotherapy
- Practical dosage regimens that are acceptable to the patient and clinician

Currently, the study team has been looking at single agents, but will begin to explore combinations of targeted drugs. Candidate biomarkers defined primarily as genetic alterations (mutations, amplifications, fusions) detected on a commercially available next generation sequencing (NGS) platform—Foundation 1. In some cases, *e.g.*, where over-expression is key to defining presence of actionable target, sequence-based screening will be supplemented by immunohistochemical assays or other methodologies as appropriate, performed in a Clinical Laboratory Improvement Amendment (CLIA)-approved setting.

There are challenges to the Lung-MAP approach, and to cancer drug development generally, that we believe can be addressed and can be a model for future trials. For one, it requires large and rapid accrual with many sites near patients, which we believe can in part be addressed by the new NCI NCTN mechanism. The NCTN coordinates activities between different cooperative group research sites and their affiliates, which will allow Lung-MAP to be offered as a clinical trial option at hundreds of sites around the country. In order to try and accelerate access to as many sites as possible, Lung-MAP utilized the recently established NCI Centralized IRB. By doing so, individual research institutions that allow the Centralized IRB to replace institutional IRBs reduce administrative steps to activating the trial, while maintaining the safety of study participants. With hundreds of sites activating Lung-MAP, having one main IRB review as opposed to hundreds can greatly accelerate the time in which the trial becomes available to patients.

Another challenge is that Lung-MAP requires commitment by pharmaceutical partners and the FDA to ensure that trial provides a regulatory approval pathway. To support this, we have involved all partners NCI, FDA, pharmaceutical companies, academic leaders, FOCR, and FNIH in the design and development of study as whole and individual sub-studies. Furthermore, it is difficult to conduct randomized trials in setting where patients have multiple options for obtaining treatment with targeted agents. In order to reduce confusion and help patients reach the best decisions for their care, we have implemented a system to provide guidance to physicians and patients on evaluation of screening results. In some cases, exciting new drugs may have too little supporting clinical data for selection for Lung-MAP. To address this, we are looking to establish a mechanism (*via* phase I/IIa studies) to seamlessly develop needed data for a new candidate to become eligible for Lung-MAP.

Finally, in many clinical trials it may be difficult to discern differences in how patients are feeling as a result of drug therapy. As Lung-MAP proceeds, the study is already examining ways that patient reported outcomes (PROs) could be incorporated into the study so that important improvements to patients' health quality can also be measured in additional to analyzing each drug's anti-cancer potential. By using Lung-MAP as a venue to validate a lung cancer PRO, the resulting metrics will become available for future lung cancer trials without having to keep developing and validate new methods each time.

Despite these challenges that will be addressed as the study progresses, there are many key benefits of the trial including;

- Grouping biomarker driven targeted drug studies under a single arm will reduce screen failure rate, making the screening worthwhile for both patients and physicians

- Operational and protocol development efficiencies of having a master protocol
- Consistency of applying a master protocol—every drug for the disease would be tested in the identical manner
- Regulatory approval pathway for drugs and companion diagnostic biomarker provided
- Shared infrastructure for screening, database, enrollment, *etc.* less costly than individual studies
- Improvement in overall efficiency of drug development in a specific disease setting, bringing safe and effective drugs to patients sooner than they might otherwise be available

In summary, we believe that Lung MAP, this unique public-private partnership, is a unique vehicle to both benefit patients and support accelerated research and drug approval. This has been a team effort with FOCR (led by Ellen Sigal and Jeff Allen), NCI (Jeff Abrams); SWOG (Vali Papadimitrakopoulou, David Gandara, Charles Blanke, Fred Hirsch, Mary Redman), FDA, and the private industry.

The potential of studies like Lung-MAP and other similar efforts is built on several key components that we believe this committee can consider as the 21st Century Cures Initiative advances:

- Biomarkers: Lung-MAP is systematically evaluating multiple genotypic markers within the same study to assess their impact in lung cancer and beyond. Studies that incorporate Biomarker evaluation are frequently far more expensive than traditional clinical trials. The 21st Century Cures Initiative could establish an increased rate of per patient reimbursement to support and incentivize these types of trials.

- Diagnostics: A framework is needed to help coordinate the development, validation, regulation, reimbursement, and implementation for advanced diagnostics. This is no small challenge. For

example, the NIH voluntary registry for genetic testing contains 19,000 tests for 4500 conditions. Lung-MAP will help provide a case study - but this is just one approach. This committee should consider developing a framework of policies governing advanced diagnostics, including the pre-market and post-market authorities for data generation and requirements and rates for reimbursement.

- Partnerships: Lung-MAP is an example of a multi-stakeholder partnership that has already been able to accelerate clinical trial processes and we are committed to continue to do so in many other ways as the study now moves forward. In order for more of these types of partnerships to occur, this committee could examine incentive structures and processes to facilitate data generation/sharing and collaboration. This could include the review of current administrative practices for establishing and implementing large scale trials to standardize approaches so future partnerships are building on past successes and not starting over.

- Resources: We do need to ask for more resources and funding to do more such projects. The NCI budget is flat at best and it is difficult to bring new drugs and profiling to patients. We therefore ask for sustained funding for NIH and FDA with a diminution of the constraints on education, travel and paper work that make these projects even more complicated.

Lung-MAP is a public-private collaboration where each sector has committed to committed to do business differently. Together we believe that Lung-MAP can demonstrate a new model for high-quality drug development in less time, at less cost, for more people, and most importantly, improve the lives of patients with lung cancer. The shared goal of accelerating the pace in which new drugs are developed is

the driving force behind this partnership. We know that this Committee shares that goal, and so we thank you for taking on this important 21st Century Cures Initiative.

Appendix – Lung-MAP Leadership & Committees:

Study Co-Principal Investigators

David Gandara, Director, Thoracic Oncology Program, UC Davis

Roy Herbst, Chief of Medical Oncology, Yale Cancer Center

Fred Hirsch, Professor of Medicine and Pathology & Associate Director for International Programs University of Colorado Cancer Center

Philip Mack, Assistant Adjunct Professor, Co-Leader Molecular Pharmacology, UC Davis Comprehensive Cancer Center

Vali Papadimitrakopoulou, Professor, Department of Thoracic/Head and Neck Medical Oncology, MD Anderson

Mary Redman, SWOG Statistical Center in Seattle & Fred Hutchinson Cancer Research Center

Lawrence Schwartz, Chair of Radiology, Columbia University & Chair of SWOG Imaging Committee

Lung-MAP Trial Oversight Committee

Roy Herbst, Chief of Medical Oncology, Yale Cancer Center (Co-Chair)

Ellen Sigal, Chairperson and Founder, Friends of Cancer Research (Co-Chair)

Jeff Abrams, Associate Director, NCI-CTEP

Charles Blanke, Group Chair, SWOG

Tony Coles, Former CEO, Onyx Pharmaceuticals

Gwen Fyfe, Former Vice President, Oncology Department, Genentech

David Gandara, Chair, Lung Committee, SWOG-UC Davis

Gary Gilliland, Dean and VP, Precision Medicine, University of Pennsylvania

Fred Hirsch, Professor of Medicine and Pathology & Associate Director for International Programs
University of Colorado Cancer Center

Gary Kelloff, Special Advisor, NCI-DCTD

Liz Mansfield, Director, Personalized Medicine, CDRH, FDA

Vali Papadimitrakopoulou, Professor, Department of Thoracic/Head and Neck Medical Oncology, SWOG-MD Anderson

David Wholley, Executive Director, The Biomarkers Consortium, FNIH

Janet Woodcock, Director, CDER, FDA

Lung-MAP Drug Selection Committee

Roy Herbst, Associate Director, Translational Research, Yale (Chair)

David Gandara, Director, Thoracic Oncology Program, UC Davis

David Rimm, Professor of Pathology and Medicine, Yale

Everett Vokes, Chair, Dept. of Medicine, University of Chicago

Fred Hirsch, Professor of Medicine and Pathology, University of Colorado Cancer Center

Garry Kelloff, Advisor to Associate Director, NCI

Glenwood Goss, Head, Division of Medical Oncology, University of Ottawa

Gwen Fyfe, Former Vice President, Oncology Department, Genentech

Ignacio Wistuba, Chair, Department of Translational Molecular Pathology, MD Anderson

Jack Welch, Head of Gastrointestinal and Nueroendocrine Cancers Therapeutics, NCI-CTEP

Jeff Bradley, Department of Radiation Oncology, Washington University in St. Louis

Kapil Dhingra, Managing Member, KAPital Consulting LLC

Kathy Albain, Professor of Medicine, Loyola

Mark Socinski, Director, Lung Cancer Section, UPMC

Pasi Janne, Scientific Director, Dana Farber Cancer Center

Peter Ho, Founder, Metastagen

Suresh Ramalingham, Chief of Thoracic Oncology, Emory

Vali Papadimitrakopoulou, Professor, Department of Thoracic/Head and Neck Medical Oncology, MD Anderson

Jamie Zwiebel, Chief, Investigational Drug Branch, NCI-CTEP

Mary Redman, Biostatistics, SWOG, Fred Hutchinson Cancer Center

Dana Sparks, Director of Operations and Protocols, SWOG

Naoko Takebe, Senior Investigator, NCI-CTEP

Shakun Malik, Head, Thoracic, and Head and Neck Cancer Therapeutics, NCI-CTEP

Ellen Sigal, Chair and Founder, Friends of Cancer Research

Jeff Allen, Executive Director, Friends of Cancer Research

David Wholley, Executive Director, The Biomarkers Consortium, FNIH

Sonia Pearson-White, Scientific Program Manager, Oncology, FNIH

Caroline Sigman, President, CEO, CCS Associates

Vince Miller, Chief Medical Officer, Foundation Medicine

Matt Hawryluk, Director of Business Development, Foundation Medicine

Roman Yelensky, Director, Clinical Genomic Analysis, Foundation Medicine

Lung-MAP Public Affairs Committee

Ryan Hohman, JD, Managing Director, Policy & Public Affairs, Friends of Cancer Research (Chair)

Frank DeSanto, Communications Manager, SWOG (Vice Chair)

Richard Folkers, Director of Communications, FNIH

Alison Hendrie, Senior Vice President, Rubenstein Communications (on behalf of FNIH)

Alex Sturm, Account Executive, Rubenstein Communications (on behalf of FNIH)

Mary Pat Lancelotta, MBA, Vice President, Strategic Marketing, Foundation Medicine

Vikki Christian, Corporate Affairs, Amgen

Ayesha Bharmal, Global Media Relations Director, AstraZeneca

Jennifer Mills, PhD, MSW, MPH, Advocacy Relations, Genentech

Tracy Rossin, Director, External Communications, MedImmune

Katherine Reuter, Senior Manager, External Communications, Pfizer

NIH/NCI

Mike Miller, Senior Science Writer, NCI

Lynn Cave, Scientific Program Analyst, NCI-CTEP

Holly Massett, PhD, Senior Behavioral Science Analyst, NCI-CTEP

Lung-MAP Advocate Advisors

Holli Kawadler, PhD, Acting Co-Executive Director, Uniting Against Lung Cancer

Laurie Fenton-Ambrose, President & CEO, Lung Cancer Alliance

Andrea Stern Ferris, President and Chairman, LUNGevity

David LeDuc, CFRE, Program Director, Free to Breathe

David Simpkins, MS, Vice President, Strategic Communications Planning, American Cancer Society

Scott Santarella, President and CEO, Addario Lung Cancer Foundation