

**MEETING SUMMARY**  
**PRESIDENT’S CANCER PANEL**  
**EMERGING OPPORTUNITIES TO STREAMLINE CANCER DRUG  
DEVELOPMENT**

December 9, 2016  
Arlington, VA

This workshop was the second in the President’s Cancer Panel’s (the Panel) 2016–2017 series on access to and cost of cancer drugs. The workshop brought together leaders and stakeholders in cancer research and drug development, including patients and patient advocates, oncologists, statisticians, and intellectual property specialists, as well as representatives from the biopharmaceutical industry, academic research institutions, the U.S. Food and Drug Administration (FDA), and other government agencies. Participants were encouraged to live-tweet at [#CancerRxValue](#) during the workshop. This meeting summary was prepared to satisfy requirements established by the Federal Advisory Committee Act. The summary provides an overview of presentations and discussions occurring during the workshop and does not necessarily reflect the views of Panel members.

***President’s Cancer Panel***

Barbara Rimer, DrPH, Chair  
Hill Harper, JD  
Owen Witte, MD

***National Cancer Institute, National Institutes of Health***

Abby Sandler, PhD, Executive Secretary, President’s Cancer Panel

***Meeting Co-Chair***

Gary Gilliland, MD, PhD, President and Director, Fred Hutchinson Cancer Research Center

***Participants***

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Kathleen A. Denis, PhD, Associate Vice President, The Rockefeller University  
Ann Geiger, PhD, MPH, Chief, Healthcare Assessment Research Branch, Healthcare Delivery Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute  
Clifford Hudis, MD, FACP, Chief Executive Officer, American Society of Clinical Oncology  
Suleika Jaouad, *New York Times* Columnist, Young Adult Cancer Advocate  
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Philip J. Stella, MD, Medical Director, Oncology Program, St. Joseph Mercy Hospital—Ann Arbor

James Zwiebel, MD, Chief, Investigational Drug Branch, Cancer Therapy Evaluation Program, National  
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## **WELCOME AND INTRODUCTIONS**

### **DRS. BARBARA RIMER AND OWEN WITTE**

Dr. Rimer welcomed invited participants and other attendees to the meeting on behalf of the Panel. She introduced Panel members, provided a brief overview of the history and purpose of the Panel, and described the aims of the current series of meetings. Dr. Rimer also thanked the workshop co-chair, Dr. Gary Gilliland, and introduced workshop facilitator Robert Mittman and Panel staff members.

Dr. Rimer stated that the issue of drug pricing and access transcends political party affiliation. The President-elect has expressed his intent to address the issue of high drug prices. The recent passage by the U.S. Senate of the 21<sup>st</sup> Century Cures Act illustrates bipartisan support for issues like cancer and Alzheimer's disease.

Dr. Witte noted that “value” is defined differently by different people depending on their circumstances and perspectives. For example, patients may define value differently than insurance companies or pharmaceutical companies. Value is not a dichotomous quality; a drug may be moderately or highly valuable.

Dr. Witte reported that the President's Cancer Panel Working Group on Connected Health and Cancer met on December 11, 2014, and on March 30, April 13, and July 9, 2015, to discuss policy, research, and program recommendations for the report to the President. Dr. Witte moved to accept all of the recommendations made by the Working Group on those dates. Dr. Rimer seconded the motion, and all three Panel members voted to accept the motion.

## **OPENING ROUNDTABLE**

The overarching goals of the workshop were to (1) review key scientific, regulatory, and clinical trial factors that affect how quickly high-value cancer drugs are brought to market and (2) identify actions that could optimize drug development processes, lower development costs, and ensure timely market entry of cancer drugs and drug combinations. Each participant was asked to identify a single change in the drug discovery and development process that would increase patients' access to high-value cancer drugs. Suggestions included:

- Ensure that patient voices are included in every step of drug discovery and drug development.
- Develop the science of patient input.

- Increase access to investigational drugs for preclinical research.
- Broaden clinical trial participation so that trial participants more closely resemble the general population.
- Increase comfort with and use of innovative statistical methods for clinical trials.
- Develop incentives and tools to increase collaboration among pharmaceutical companies to reduce redundancy and wastefulness in drug development.
- Increase access to clinical trial data, including data for trials with negative outcomes.
- Focus on development of drugs with unambiguously large benefits.
- Accelerate approval of potentially transformative drugs.
- Consider how higher regulatory standards might influence drug development.
- Ensure regulations do not unnecessarily impede clinical trials.
- Ensure that the prices of drugs reflect their value.
- Improve communication with patients and physicians about the value of products.
- Enable systematic evaluation of drugs after approval to learn more about safety and efficacy in real-world settings.
- Find ways to merge clinical practice and clinical research.
- Create a free and open market for healthcare and research data.

## **BRINGING DRUGS THAT ADD VALUE TO MARKET FASTER**

### **FDA ROLE IN ONCOLOGY DRUG DEVELOPMENT**

*Richard Pazdur, MD, Acting Director, Oncology Center of Excellence, U.S. Food and Drug Administration*

#### **Key Points**

- It is difficult to define and identify truly transformative therapies. FDA struggles with this issue when it considers whether a drug is a breakthrough therapy. What evidence is needed to categorize a drug as a breakthrough therapy? Is there a specific preliminary activity threshold that must be attained, or is a drug a breakthrough simply if it is better than currently available therapies?
- In the 1990s, FDA approval required two randomized clinical trials showing that a drug conferred a survival advantage. If this same criterion were in place today, the landscape of oncology drugs would be very different. The United States needs to find ways to create opportunities for oncology drug development without sacrificing standards.
- When Dr. Pazdur joined FDA in 1999, he pushed back against the idea that all drugs should be subject to the same standards. Oncology drugs are different than other drugs for many reasons:
  - Cancer is a life-threatening disease, which results in a different risk-benefit ratio than for many other drugs. Higher levels of risk or toxicity often are considered acceptable for oncology drugs. Higher levels of toxicity also are deemed acceptable for historical reasons—many of the anticancer drugs developed in the 1950s and 1960s were basically poisons.
  - Oncology drugs have a de facto restricted distribution. Unlike drugs that are prescribed by many in the medical community (e.g., general internists, emergency room physicians), oncology drugs are used by specialists who are experts in toxicity management and evaluation of these drugs.

- After FDA approval, oncology drugs often are developed for multiple indications, combined with other drugs, and prescribed for off-label use. This means that evaluation of oncology drugs must be nimble and continue over time.
- Cancer drugs are administered to limited populations of patients, and these limited populations are getting smaller as genetic subpopulations are identified.
- FDA has increased its focus on the patient voice and patient-centric drug development. However, it is important to recognize that there is no single patient voice; rather, there is a litany of patient voices. Even among patients with the same disease, individuals have different perspectives and priorities.
- “Clinical benefit” and “benefit in the clinic” are two different concepts, and the difference has implications for patient-centered drug development. “Clinical benefit” is a regulatory construct that is defined by FDA as how a patient feels, functions, or survives. In oncology, this usually refers to survival. However, clinicians more often consider “benefit in the clinic,” which may include reduction in disease burden or disease stabilization, even in the absence of a survival benefit.
- Patients want endpoints that are clinically relevant to them and their experiences. They also want a regulatory agency that is focused on patients, not on the regulated industry. Currently, FDA is more focused on drug developers than on patients, though the Oncology Center of Excellence is helping enhance the focus on disease. Patients also want a regulatory agency that thinks about how drugs are used in the real world (e.g., sequentially or in combination with other drugs, off-label). Patients want FDA to *promote* American health in addition to *protecting* American health.
- Value is an ephemeral concept, impossible to define. Rational estimations of value require knowledge about the benefit of a drug, but it often is difficult to compare drugs even within the same disease because they have been evaluated using different endpoints.
- It is not a good idea to try to address drug pricing through the drug approval process. Drug approval and pricing are separate issues and should be addressed separately.
- FDA has several pathways for accelerating approval of drugs for serious and life-threatening diseases, including breakthrough designation, priority review, and accelerated approval. These pathways involve consideration of trial designs and endpoints used. FDA has recognized that although overall survival is the gold standard for oncology drugs, it cannot be used as an endpoint in all situations. Drug regulations are meant to serve the American people, and trials should be designed to meet the needs of patients, not rigid regulatory requirements.
- As part of the Cancer Moonshot, FDA is exploring ways to expedite drug development. One approach is the use of common controls wherein companies developing drugs for the same disease can use the same set of control participants for their trials. Other strategies include revisiting eligibility criteria and utilizing expanded seamless trial designs. Securing industry support for these types of strategies—which often depend on collaboration and communication among companies—is a major challenge.
- Resources needed for drug development—including financial resources and patients—are finite and must be invested judiciously.

## DISCUSSION

Participants were asked to discuss what makes drugs valuable to patients, physicians, and others, as well as whether the current oncology drug pipeline will add adequate value. It was noted that issues related to drug pricing and reimbursement will be discussed in depth at a future workshop.

## **Defining Value**

- It is difficult to define what patients value because patients are not a single entity. Patients have different sets of desires, and these desires change over time. Factors such as disease stage and age/stage of life may influence patients' definitions of value.
- It is difficult to define value for patients without taking price into consideration. If bevacizumab were free, most breast cancer patients would likely choose to take it to gain two weeks of progression-free survival. However, very few patients think this benefit is worth it when six months of treatment costs \$100,000.
- Ensuring that patients and physicians have access to information so they can have honest discussions about treatment options would be more useful than defining value. Patients want to know what their lives will be like if they decide to take a certain drug. Physicians need to have this information and be able to have these conversations with patients so each patient can make the decision that is right for him or her.
- Payers have a very different perspective on value and different paradigms for assigning value than do patients. Although it may be appropriate to keep regulatory systems separate from payment systems, there likely are going to be some points of intersection that need to be considered and discussed.
- Society places high value on new things—new drugs, new phones, new cars, etc. When a new therapy is developed, there is a sense that patients must have access to it. Physicians and patients view new therapies as new hope that they might provide increased benefit over other options.

## **Patient Needs and Considerations**

- Cancer care and research are not designed around patients. Physicians generally do a poor job of listening to and communicating with patients. Physicians need to ask the right kinds of questions and trust patients' responses.
- The high rate of bankruptcies among cancer patients is particularly disturbing in light of the fact that many patients receive little to no benefit from the costly drugs they are taking. Cancer patients who enter bankruptcy also have worse outcomes than those who do not enter bankruptcy.

## **Patient-Reported Outcomes**

- There is general agreement that patient-reported outcomes (PROs) are a good idea, but Cooperative Groups and pharmaceutical companies will not be enthusiastic about investing resources to collect these data unless they are convinced of their long-term value.
- In many cases, patients and doctors know a drug provides a quality-of-life benefit, but the benefit is not detected by existing PRO measures. PRO measures need to be expanded and validated so different types of benefits can be detected in reproducible and reliable ways.
- Collecting and deciphering patient-reported outcomes may be even more challenging for clinical trials that include patients with different disease presentations and experiences being treated with the same drug because of a common genetic mutation.
- When advising drug sponsors, FDA emphasizes the importance of developing and using appropriate PRO measures. For example, trials should make use of electronic tools that allow patients to record symptoms on a daily basis rather than depending on patient recall. PROs can be useful for assessing whether a treatment helps alleviate a disease symptom, but it is more challenging to make use of PROs when trial participants are asymptomatic. In these cases, PROs generally capture information on drug toxicities rather than the impact of the drug on the disease.
- In cancer research, quality-of-life questionnaires were first used in the context of clinical trials studying combined-modality treatment versus surgery. These questionnaires were very helpful for assessing functional outcomes that were relevant and important to patients, such as laryngeal

preservation in head and neck cancer, limb sparing in sarcoma, and mastectomy versus lumpectomy for breast cancer. These questionnaires are not as useful in the context of clinical trials comparing two different types of chemotherapy regimens. Different analyses are needed to understand the different toxicity profiles of various regimens and how these impact patients' quality of life.

- The National Cancer Institute's (NCI's) Molecular Analysis for Therapy Choice (MATCH) trial is evaluating patient experiences with undergoing biopsy and receiving genetic information.

### **Research and Drug Development**

- There has been a shift in the drug development landscape in recent years. Pharmaceutical companies are doing less basic science research now than in the past. Many academic institutions are trying to move their drugs further through the pipeline with funding from government agencies and foundations.
- A [paper](#) by Dr. Kesselheim and colleagues in *Health Affairs* reports that the most transformative drugs developed in the United States over the past 25 years originated in government-funded laboratories, either within academic institutions or government agencies. It is likely that the most promising discoveries will continue to be made in these settings, so it is important that these labs are funded.
- A more in-depth understanding of cancer biology is needed to promote development of transformative drugs. When a drug against a novel target is tested in clinical trials, it is useful to have a biomarker that provides information on whether the drug has an impact on the target pathway and whether this translates to clinical benefit. The earlier a functional readout can be obtained, the better.
- Academic laboratories could increase the understanding of the biological effects of drugs if they could get access to these drugs earlier; however, it is currently very difficult for academic investigators to obtain new drugs for basic research.
- Longitudinal modeling is needed to determine how patients are affected by their therapies over time. This requires a deeper understanding of how therapies affect various aspects of disease.
- More efficient drug development processes are a worthy goal, but it is important that these improvements lead to drugs that are less expensive.
- Drugs for metastatic disease often are approved more rapidly, and this provides opportunity to explore these drugs in greater depth and enhance understanding of the risk-benefit profile in various therapeutic settings. Data from epidemiological studies, CancerLinQ, and Surveillance, Epidemiology, and End Results (SEER) can provide insight into how a drug works in different settings and populations, but more granularity can be gained through the common treatment protocols used in clinical trials.

### **Clinical Trials Infrastructure, Participation, and Design**

- There should be efforts to increase patient involvement in research and clinical trials. During the HIV epidemic in the 1980s, the patient community was instrumental in research. The field moved quickly because patients volunteered for research studies, encouraged other patients to volunteer, and helped communicate the benefits of the emerging treatments.
- A very high percentage of pediatric cancer patients participate in clinical trials, but participation rates for adults with cancer are only about 3 to 5 percent.
- The infrastructure for pediatric cancer care—and, by extension, the infrastructure for pediatric clinical research—is very different from the infrastructure for adult clinical care. For example, pediatric oncologists are financially supported; they do not need to bill and code for their interactions with patients in the same way adult oncologists do.

- Dr. Pazdur urged the group not to devote too much attention to clinical trial participation rates, which are somewhat arbitrary. The more important issue is that trials address the most important clinical questions for cancer and cancer patients. For patients, clinical research should not be about an individual drug, it should be about making progress in a disease area. The cancer community should think about what questions it wants patients to help address through trials. The best way to ensure that clinical trials address important questions is to involve patients in the trial design process.
- Mr. Simon asserted that fewer, rather than more, cancer clinical trials are needed. Patients are a valuable resource, and this resource is misused when patients are spread across too many trials.
- User-friendly tools are needed to help patients find clinical trials. As part of the Cancer Moonshot, a new interactive dashboard was created on [trials.cancer.gov](https://trials.cancer.gov) that allows people to find trials using common words and zip codes.
- Ms. Jaouad noted the importance of guiding patients so that they can determine for themselves whether a treatment or clinical trial is right for them. In addition to providing information about medical toxicities, the cancer community needs to help patients understand and deal with other factors that make treatment or clinical trial participation difficult. This includes things like transportation and financial issues. The practical problems facing patients often change, so it is important to touch base with them repeatedly over the course of their diseases and treatments. It also is important to make sure patients are aware of resources that can help them deal with the challenges they face.
- Many patients face geographic barriers to clinical trial participation. It is often physically difficult for patients to travel long distances, and the long trips are a burden on caregivers as well. Some major academic institutions are partnering with other sites so that patients can participate in trials while staying closer to home, but these programs are not available everywhere.
- NCI's National Clinical Trials Network and the NCI Community Oncology Research Program connect academic institutions and hospitals across the country, but there is still fragmentation in the ways trials are funded, organized, and conducted. A physician at one hospital may not be able to enroll patients onto a clinical trial that is open in another hospital in the same town because there are no mechanisms to distribute funding outside of an established network. This type of system does not serve patients well.
- There may be opportunities for pharmaceutical companies to utilize the NCI-supported clinical trials networks across the country.
- It would be beneficial to have good definitions of net health benefit that could be applied across multiple clinical trials.
- It often is difficult to show an increase in overall survival in a clinical trial. Real-world data are needed to assess the benefit of drugs in the clinic.
- From 2002 to 2014, 71 drugs were approved for treatment of solid tumors. The median improvement in progression-free survival was 2.3 months, and the median improvement in overall survival was 2.1 months. Most people would consider these to be marginal gains. The American Society of Clinical Oncology (ASCO) has created definitions of meaningful benefit for progression-free survival and overall survival, but very few drugs meet these benchmarks. Consideration should be given to whether any improvement in progression-free survival or overall survival should be enough to warrant regulatory approval.
- Two-thirds of oncology drugs are being approved on the basis of surrogate endpoints, such as tumor shrinkage or progression-free survival. There is some disagreement over whether progression-free survival necessarily constitutes clinical benefit. Dr. Prasad expressed his opinion that clinical benefit should be viewed as patients living longer or living better and should be measured using survival or quality of life. There is no large-scale empirical evidence correlating quality of life with progression-free survival.

- More transparency is needed regarding clinical trial results, particularly for trials with negative results. The Department of Health and Human Services recently issued the [final rule](#) on reporting requirements for clinical trial results.

### **Prioritizing Novel and Transformative Drugs**

- Most drug developers set out to create a transformative therapy, but it is exceedingly difficult to accomplish this. Although transformative results are usually the goal, incremental improvements can result in significant cumulative benefit over time and have been the bedrock of much progress in oncology.
- Drugs that have large effects can move through the regulatory review process very quickly. For example, first-in-human studies of pembrolizumab began in 2011, and the drug was approved in 2014 based on strong results in a phase IB expansion study. The emerging landscape of immunotherapies for cancer is very exciting, with potential for other transformative treatments.
- Dr. Pazdur asserted that it is a good thing to have more than one drug within the same class, but there is a point at which it becomes excessive to continue to develop drugs within the same class.
- Dr. Scangos acknowledged criticism of the pharmaceutical industry for developing multiple drugs with the same mechanism of action but pointed out that companies do not know which drugs will be effective until after clinical trials are completed. It would not be a good idea for multiple companies to pool resources and pursue only one drug because they may choose the wrong one.
- The suggestion was made that FDA should be given power to act as a gatekeeper and prevent companies from developing too many drugs within the same class (i.e., so-called me-too drugs). Dr. Pazdur responded that giving FDA this responsibility would be misguided, fraught with danger, and not in the best interest of patients. FDA is charged with evaluating drugs based on safety and efficacy and should continue to operate in that capacity. Dr. Pazdur also pointed out that pharmaceutical companies operate internationally and answer to multiple regulatory agencies around the world.
- The approval of multiple drugs with the same mechanism of action may provide downward pressure on the prices of these drugs. This has been observed for drugs recently approved for treatment of hepatitis C. However, this has not been the case for oncology drugs to date. For example, the prices of Bcr-Abl inhibitors has increased, not decreased, as new drugs in this class have been introduced.

### **Need for Collaboration**

- Collaboration among industry, academia, and nonprofit organizations is essential for making drug development more efficient. Each of these stakeholders needs to do its part to address barriers to collaboration. Lack of collaboration within the pharmaceutical industry is a big problem.
- Pharmaceutical companies often are hesitant to collaborate with one another. For example, if a company wants to test one of its drugs in combination with a PD-1 inhibitor, the company may develop its own PD-1 inhibitor rather than use an existing PD-1 inhibitor owned by a different company. This is an inefficient use of money and patients, but companies may think it is worthwhile because it gives them more control over the pricing of the PD-1 agent.
- The NCI Cancer Therapy Evaluation Program (CTEP) negotiates agreements with pharmaceutical companies to facilitate collaboration and access to drugs for research. A large proportion of trials of cancer drug combinations are run through CTEP. The key to this type of collaborative structure is an overarching framework to guide negotiations on issues such as intellectual property and data sharing.

## Potential Recommendations

- Mechanisms or a federal agency should be created to support platform trials, which are studies simultaneously investigating multiple treatments, for cancer and/or other diseases (similar to the European Prevention of Alzheimer’s Dementia trial funded by the Innovative Medicines Initiative). Trials should be attractive to pharmaceutical companies. Dr. Zwiebel acknowledged that NCI performs this role to some extent, but not all companies want to work with NCI.
- Cancer patients across the country should be surveyed about what they want from their treatments. There should be particular effort to collect information from patients who are not involved in formal advocacy activities. Dr. Hudis suggested that the *CancerCare* survey may accomplish this goal.
- Methodologies to assess patient-reported outcomes and net health benefit from patients’ perspectives should be improved.
- Regulatory issues that contribute to fragmentation in the ways clinical trials are funded, organized, and conducted should be addressed so that trials can be completed more quickly, efficiently, and collaboratively.
- The burden of clinical trial participation should be reduced for patients. Patients should be fully reimbursed for their participation, including per diem for loss of work, travel costs, etc. In addition, patients should be able to stay close to home when participating in trials. This will require use of standard nomenclatures and procedures across multiple institutions (e.g., standards for obtaining biological materials, pathology, lab results).
- Incentives should be created for oncologists to record and share patient-level data on treatments and outcomes in standard formats. To do this, efforts are needed to prospectively define what information should be collected. Incentives could include reimbursement or membership in professional societies. Information sharing should become the default in healthcare. Informed consent processes should be structured to facilitate information sharing.

## ACCELERATING THROUGHPUT AND LEARNING FROM CLINICAL TRIALS

### ACTIVITIES OF THE FDA CENTER FOR DRUG EVALUATION AND RESEARCH OFFICE OF BIOSTATISTICS

*Lisa LaVange, PhD, Director, Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration*

#### Key Points

- In rare disease settings, e.g. cystic fibrosis, patients are recognized as a scarce commodity, so there are efforts to ensure that clinical trials are of high value before they begin recruiting participants. In some cases, a foundation or patient advocacy group screens protocols before recruitment begins to be sure that the trials are really worth doing. Should that be considered in cancer?.
- The FDA’s Office of Biostatistics does more than evaluate submissions for drug approval. It also evaluates protocols and interacts with sponsors regarding study design. The goal is to use statistical tools to make drug development more efficient (e.g., identify ineffective or unsafe drugs more quickly, making better use of patients). Areas of focus and research by the Office include:
  - Multiregional clinical trials—Dr. LaVange is working with an International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) working group to develop guidance for the planning and design of multiregional clinical trials. A draft report available on the ICH website includes discussion of statistical tools that can be used to interpret regional variation in trial results (e.g., help determine whether regional

variation in response is due to things like genotype variation, regional differences in use of other drugs, or other factors).

- Subgroup analysis—This is becoming increasingly important due to efforts to broaden eligibility criteria for clinical trial participation, which introduces heterogeneity into patient populations. Heterogeneity creates challenges for data interpretation, but there are statistical tools that can help perform better subgroup analyses to identify populations in which a drug has benefit.
- Surrogate endpoints—Data are being used to identify intermediate endpoints that can be used for accelerated approval or, in some cases, full approval. For example, pathological complete response has been used to support accelerated approval. Minimal residual disease currently is being evaluated as a surrogate endpoint for acute lymphoblastic leukemia. The trajectories of tumor growth and tumor shrinkage also are being evaluated as endpoints for immunotherapy trials.
- Patient-reported outcomes—There is a need to validate PROs. It is possible to gather information on patient experiences through clinical trials, but it would be helpful to gather patient-reported data that could contribute to quantitative assessment of a drug's benefit. FDA has a good clinical outcomes assessment group and is hoping to hire doctoral-level statisticians with a focus on measurement, quantitative measurement, and validation to work in this area.
- Sequential randomization trials—This work focuses on how to interpret overall survival data when patients are moving between treatments, as is the case with sequential multiple-assignment randomized trials (SMART). When patients are treated with multiple drugs, it is difficult to determine the drug(s) to which benefit should be attributed.
- Sequential parallel comparison trials—In these trials, placebo nonresponders are re-randomized partway through the trial. These trials are mainly being used to evaluate antipsychotic drugs, not cancer drugs.
- ICH Good Clinical Practice—The ICH E6 guideline, which focuses on good clinical practice, was recently revised. Previously, the document defined clinical trials very narrowly (i.e., traditional clinical trials). FDA proposed a renovation of E6 to expand the definition of “clinical trial” to include pragmatic trials in real-world settings. The proposal was adopted.
- Other areas of work include master protocols, adaptive designs, shrinkage estimators, dynamic treatment regimes, quantitative methods for risk assessment, biomarker qualification, and restricted mean survival time for nonproportional hazards.
- Many in the pharmaceutical industry think that innovative trial designs will not be acceptable to FDA, but this is a misconception. For statisticians, the biggest clinical trial failure is completing a trial and being unable to interpret the results because of poor trial design (e.g., critical data not collected, clear endpoints not established). This is a waste of patients' time.

## **ACCELERATING THROUGHPUT AND LEARNING FROM CLINICAL TRIALS**

*James Zwiebel, MD, Chief, Investigational Drug Branch, Cancer Therapy Evaluation Program, National Cancer Institute*

### **Key Points**

- The CTEP mission is to improve the lives of cancer patients by finding better ways to treat, control, and cure cancer. CTEP sponsors clinical trials to evaluate agents from both industry and academia, with a particular emphasis on investigating drug combinations, identifying molecular targets, and elucidating mechanisms of drug effects.
- CTEP currently has clinical agreements with industry and academic collaborators regarding 99 agents and holds 140 Investigational New Drug Applications (INDs). Nearly 3,000 institutions in the United

States and internationally participate in CTEP studies. There are between 700 and 800 active CTEP protocols at any given time, and about 140 new CTEP protocols are initiated each year. Approximately 20,000 patients enroll in CTEP trials each year. CTEP is the largest sponsor of cancer-related combination studies in the world. Approximately two-thirds of all combination studies listed in [clinicaltrials.gov](http://clinicaltrials.gov) are CTEP-sponsored studies.

- NCI sponsors several precision medicine trials, including MATCH, MPACT (Molecular Profiling-Based Assignment), Exceptional Responders, Lung-MAP (Lung Cancer Master Protocol), and ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial).
- The overarching goal of NCI's precision medicine trials is to use more precisely defined and limited molecular subgroups to enable more rapid discovery of therapeutic signals and more expeditious transitions from early-phase trials to definitive trials. Precision medicine trials have a number of unique features:
  - They require screening of large numbers of cancer patients to find those with the appropriate molecular abnormality.
  - They demand sophisticated high-throughput testing with rapid turnaround.
  - They are logistically challenging for sites because of the inclusion of multiple treatment arms.
- The MATCH trial is under the leadership of the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) Cooperative Group. Patients undergo genetic sequencing. If they are found to have an actionable mutation, they are assigned to a study arm with a particular study agent. If they exhibit stable disease or a response, they continue on the study. If patients' diseases progress, their initial genetic screens are reviewed to see whether there is a second actionable mutation. If there is, patients may be assigned to another treatment arm. Patients may also undergo a repeat biopsy to see whether any new actionable genetic abnormalities have emerged.
- The MATCH trial opened in August 2015 with ten treatment arms. It was temporarily closed in November 2015 for a planned interim analysis. During this timeframe, nearly 800 patients were screened, far more than were expected. More than 900 sites are approved to enroll patients. To date, 192 sites have enrolled at least one patient; of these, two-thirds are community-based and one-third are academic institutions.
- The MATCH trial recommenced in May 2016 with 24 treatment arms. Some of these arms are testing a specific drug matched to a genetic mutation, and a few are testing drug combinations. Currently, more than 100 patients are screened each week. As of October 23, 2016, there were 2,141 patients enrolled, with 311 patients assigned to one of the 24 treatment arms. More than three-quarters of those assigned to an arm enrolled on that arm. Two arms have completed enrollment already, and it is expected that 11–12 arms will complete accrual by the time 5,000–6,000 patients are screened. Six arms are awaiting activation, and four additional arms are in development.
- The MATCH trial has been very popular, with enrollment exceeding expectations. As of early December, more than 3,000 patients had been enrolled on the study. The match rate for successful biopsies is 23 percent, which is in line with what was predicted. Large-scale screening is needed to detect rare genetic variants and mutations. Some mutations are present in only 2 percent of patients screened. Laboratory testing for MATCH is going well; about 93 percent of biopsies have been successful in determining whether an actionable mutation is present.
- Although MATCH was designed to be nimble, it can take several months to add arms. Negotiations with companies, regulatory issues, and trial design efforts can take considerable time.
- NCI is working to address the issue of clinical trial development timelines. About nine years ago, NCI commissioned an efficiency expert to evaluate the steps involved in opening a clinical trial. The results—which were published in a *Journal of Clinical Oncology* [article](#) in 2009 and a *Clinical*

*Cancer Research* [article](#) in 2010—revealed that clinical trials are a complex process, which results in long timelines. For a phase III trial, the median time from concept submission to activation—a process involving several hundred steps—was over 600 days (range of 454–861 days). The evaluation also showed that trials with longer activation times were less likely to meet their accrual goals. This is likely in part because a study may become less interesting or relevant after two years.

- NCI convened the Operational Efficiency Working Group (OEWG) in 2010. Members include representatives from industry, academia, NCI, and FDA, as well as patient advocates. The most important recommendation from OEWG has been to improve the timeline to activation for NCI-sponsored trials. Target timelines and absolute deadlines were created for studies to go from initial concept review to activation. For phase I and II studies, the target timeline was 210 days, with an absolute deadline of 540 days. For phase III studies, the target timeline was 300 days, with an absolute deadline of 730 days. Absolute deadlines have since been changed to 450 days for phase I and II trials and 540 days for phase III trials. Trials that do not meet the absolute deadline are liable to be disapproved.
- There has been a significant reduction in clinical trial activation times since 2010. Between 2006 and 2008, only about 40 percent of NCI-sponsored phase III trials were activated within two years of concept submission. In 2014–2016, 97 percent of phase III trials were activated in less than two years. A similar pattern was observed for phase II trials.
- NCI has instituted Corrective Action Plans (CAPs) for trials that are accruing slowly. Principal investigators for early-phase trials that are accruing at less than 50 percent of their projected accrual rate by the end of Quarter 2 are asked to identify barriers and possible actions for increasing accrual. An analysis of this program found that CAPs were associated with improvements in accrual rates for about three-quarters of trials. Reasons provided by investigators for slow accrual included safety, toxicity, strict eligibility criteria, and protocol design concerns for phase I trials. For phase III trials, reasons for delay were Institutional Review Board (IRB) and site activation delays, strict eligibility criteria, and protocol design. Interestingly, about half of proposed action plans were not aligned with the identified barriers to accrual.
- NCI has a number of systematic steps for addressing clinical trial accrual. One is the Accrual Core Team, which includes representatives from the National Clinical Trials Network (NCTN), NCI Community Oncology Program (NCORP), NCTN Lead Academic Participating Sites, patient advocates, and NCI. This group meets monthly to identify and discuss slow-accruing trials and address strategies for improvement. NCI also has promoted trials via a number of outlets, including network-wide webinars, social media (e.g., Twitter), surveys, and patient-friendly materials. One pilot program currently uses social media principles to increase consideration of participating in multiple myeloma trials among African-American patients.

## DISCUSSION

Participants discussed ways to make clinical trials more efficient and effective.

### Clinical Trial Design

- ASCO and the Association of American Cancer Institutes (AACI) recently partnered to develop standards for improving clinical trials. The resulting [paper](#) by Julie Vose and colleagues describes standards for contracts and reimbursement policies, among other things. ASCO also has called for relaxation of certain noncritical aspects of trial design. For example, exclusion criteria only are acceptable if they limit potential harm to participants. ASCO has adhered to these standards in the design of its Targeted Agent and Profiling Utilization Registry (TAPUR) Study. The Panel could consider endorsing these standards.

- In order for guidelines related to eligibility factors and other criteria to be widely adopted, they will need to be embraced by pharmaceutical companies. However, expanding eligibility criteria and other strategies to make trials better reflect real-world clinical settings may increase risk of failure for drug companies.
- FDA has written on the topic of eligibility criteria. One suggestion put forth by FDA is to analyze drug efficacy using a standard population while assessing safety in an expanded population. This approach would make trials more expensive but may also make them more efficient.
- Cancer drug development is unpredictable. While it is important to standardize when possible, it also is important to recognize that tailored approaches will be needed and should be used when appropriate.
- Adaptive clinical trial designs and seamless drug development (i.e., without distinct clinical trial phases) are options that may improve the efficiency of oncology drug development. Seamless development processes may be particularly useful for drugs that have large treatment effects. Adaptive trial designs allow investigators to modify protocols during the course of a trial based on data. These designs must include statistical plans to guide modifications.
- Dr. Pazdur stated that FDA is open to adaptive trial designs and soon will be releasing a guidance document on this topic. Innovative clinical trial methodologies also increasingly are being recognized by policy makers (e.g., 21<sup>st</sup> Century Cures Act, Prescription Drug User Fee Act [PDUFA] VI).
- Physicians and patients should be educated about innovative trial designs so the results of these trials are viewed as meaningful and reliable. Physicians may be hesitant to change the way they practice without evidence from traditional randomized clinical trials.
- Representatives from pharmaceutical companies were asked to comment on the challenges of adaptive trial designs. Dr. Scangos reported that Biogen has done some adaptive trials that have worked reasonably well, but he noted that it is important to establish appropriate endpoints. Dr. Rothenberg noted that it can be difficult to convince upper management to undertake an adaptive approach because there is less certainty about cost and time to completion of these studies. Dr. Berry reported that many pharmaceutical companies have been open to adaptive designs.
- Clinical trials should follow patients over a long period of time to help shed light on the natural history of their cancers. This long-term view is now possible for many cancers because there are more treatment options available than in the past.

### **Real-World Data**

- Real-world data can refer to pragmatic randomized clinical trials or the use of observational data (not collected as part of a prospective research study). There is documented discordance between observational data and the results of randomized controlled trials. This is likely due to several factors, including the fact that clinical trial participants are usually younger and have fewer comorbidities than the general population.
- Dr. Prasad noted that it is difficult to use observational real-world data for the initial demonstration of a drug's efficacy because there are so many confounding factors. However, Dr. Pazdur maintained that performance of a drug in real-world settings is the most meaningful outcome. FDA has a strong interest in ensuring that drugs are safe and effective when used in real-world settings, which is why it has promoted less-restrictive exclusion criteria for clinical trials. Dr. Pazdur stated that real-world data would be considered as part of the body of evidence for a drug. In some cases, it may be possible to use observational data in combination with other data to establish efficacy. It also is possible that FDA would update a drug's label based on its performance in real-world settings.

## Collaboration

- Dr. Zweibel reported that very few of the drugs being studied through CTEP are new molecular entities; most have been approved for at least one indication. In general, pharmaceutical companies conduct their own registration studies. Dr. Zweibel suggested this may be, in part, because companies think they can complete these studies more quickly on their own. Dr. Pazdur also pointed out that virtually every trial conducted by drug companies is international in scope. NCI supports a limited number of clinical trial sites in other countries, but these are not sufficient to meet the needs of pharmaceutical companies. In some cases, NCI has worked with pharmaceutical companies to combine data collected in the United States with data collected in other countries, but it is logistically difficult and expensive to do this.
- TransCelerate is a group of about 17 pharmaceutical companies working together to address challenges in clinical trials. One of the biggest challenges identified by the group relates to antitrust issues. TransCelerate meets with FDA and the European Medicines Agency once or twice a year.
- Dr. Baynes reported that the pharmaceutical industry has had discussions about the value of shared data platforms as a way to facilitate collaboration on clinical trials. Currently, each company has its own investigator portal; a shared investigator portal with common provisioning would reduce investigator burden. Standard and interoperable electronic PRO and data capture formats also would be helpful.
- Pharma is interested in making the clinical trial experience more appealing to investigators because investigators facilitate access to patients.

## FDA and Government Role in Drug Development

- Several participants emphasized that FDA is a leading force in the use of innovative approaches to get better oncology drugs to patients more quickly and efficiently. This view is reinforced by results of a FasterCures survey of 150 stakeholders from different areas of biomedical research conducted to inform recommendations for the new administration. Respondents cited FDA as an asset and called for increased support for the agency (e.g., better hiring authority, funding).
- FasterCures' report for the new administration, which is available on its [website](#), includes seven recommendations that address areas such as big data and clinical trials. There has been concern that people with big data expertise will not be willing to work with the federal government because of the onerous paperwork and processes involved. There may be opportunities to work with the new administration to reduce this burden.
- The United States has a free enterprise economy, so it is not possible for any agency or body to dictate what drugs should be developed by pharmaceutical companies. The FDA is legally prohibited from doing this.
- Dr. Pazdur stated that “carrots” always work better than “sticks” when trying to change behavior. If FDA attempted to restrict what pharmaceutical companies can do, there would be massive litigation, which is not productive. Development of collaborative strategies viewed as positive by all parties is a much more effective approach.
- The goal of curing cancer was compared with the goal of going to the moon. One important difference between these two efforts is that landing on the moon was an engineering challenge, while curing cancer is a basic science challenge.

## PUBLIC COMMENT

- Srinikrishnamoorthy stated that it would be useful if a quantitative score of net health benefit could be calculated based on trial results and the perspectives of various stakeholders, including patients, drug companies, investigators, and others. The federal government, as a representative of the people,

should weigh in on drug prices. The federal government invests a lot of money in research that drug companies can use to inform drug development. The American public should receive some value for this investment. The federal voice on drug pricing does not need to be FDA; it could be another agency.

## **EVALUATING AND APPROVING COMBINATION THERAPIES**

### **CHALLENGES IN DEVELOPMENT OF COMBINATION THERAPIES**

*Gary Gilliland, MD, PhD, President and Director, Fred Hutchinson Cancer Research Center*

#### **Key Points**

- Some new anticancer agents—including some new immunomodulatory agents—have potential to be highly effective, perhaps even curative, as monotherapies. However, primary and acquired resistance is a challenge for most anticancer drugs, which provides a rationale for pursuing combination therapies.
- Oncology drug development is extremely difficult. Approximately 90 percent of oncology drugs tested in humans ultimately fail to be approved. Investigating drug combinations will be even more challenging. One drug sponsor stated that there are at least 4,000 combinations that could be considered for one drug being developed, far too many to test empirically.
- Challenges related to the development of combination therapies include:
  - Preclinical testing—It is difficult to identify and develop appropriate preclinical models that reflect the genetics, immune factors, and microenvironments that will be present in patients.
  - Toxicities—Combination therapies may cause toxicities not observed when either drug is used as a monotherapy. In one case, combination therapy with a tyrosine kinase inhibitor and an immunomodulatory agent—neither of which were known to cause hepatic toxicity on their own—resulted in hepatic necrosis in a small number of patients.
  - Dosing and schedule—Issues related to pharmacokinetics and mechanisms of drug action need to be taken into account when making decisions about the order in which drugs should be given, as well as the timing and dose.
  - Biomarkers and companion diagnostics—Co-development of biomarkers and companion diagnostics is challenging for single agents, and there will be added complexity for combinations. It also is possible that the best biomarkers and companion diagnostics for combination therapies may be different than those used for individual agents.
  - Clinical trial design and regulatory issues—Early and frequent engagement with FDA is needed to obtain guidance on clinical trial design and determine what types of data are needed for approval (e.g., Does the combination need to have superior efficacy and safety compared with either monotherapy?).
  - Collaboration—Intellectual property and legal issues need to be addressed when combinations include drugs developed by different companies. Companies also need to work out how risk-sharing and profit-sharing will be done. It seems that pharmaceutical companies are more willing to collaborate now than in the past. These collaborations must be smart business decisions.
  - Pricing—Combinations pose challenges related to pricing, particularly if each drug is expensive. It is not economically feasible to charge for two drugs individually if both are more than \$100,000 per year. However, high prices would be more acceptable for high-value drugs; for example, patients and payers likely would be willing to pay more if a treatment regimen is curative or if patients with a high likelihood of benefit could be identified. Value-based reimbursement models in which pharmaceutical companies are paid in full only when patients

respond are being considered. Pricing challenges are less daunting when both or all of the drugs used in the combination are being developed by the same company and when generic drugs are used.

- Industry-academia-government collaborations are needed to overcome challenges in the development of combination therapies for cancer.

## **DEVELOPMENT OF KEYTRUDA AS A COMBINATION THERAPY**

*Roy Baynes, MD, PhD, Senior Vice President and Head of Global Clinical Development and Chief Medical Officer, Merck Research Laboratories, Merck & Co., Inc.*

### **Key Points**

- Merck is developing immune-oncology agents targeting three areas: (1) T-cell priming and trafficking to the tumor, (2) the immunosuppressive tumor microenvironment, and (3) direct tumor cell killing.
- Most patients who respond to Keytruda (pembrolizumab)—Merck’s immunotherapy that is approved for melanoma and lung cancer—have gene expression profiles that indicate T-cell inflammation. However, there are some patients whose tumors have T-cell inflammation but do not respond to Keytruda. Merck is trying to identify genes or patterns of genes that are associated with Keytruda resistance in these patients. Merck also is trying to find ways to modulate the immune environment in nonresponding patients who do not have a T-cell inflammation gene expression profile to increase responsiveness to Keytruda.
- Merck’s goal for Keytruda is to improve long-term disease control and survival across a wide range of cancers. Strategies for accomplishing this goal are to establish Keytruda as a foundation for cancer treatment, identify patients most likely to benefit from Keytruda, and improve upon the efficacy of monotherapy by combining Keytruda with other agents.
- Keytruda was the first PD-1 inhibitor approved by FDA. The drug received a number of accelerated approvals, some of which have transitioned to full approvals. Keytruda is approved for use in melanoma, lung cancer, and head and neck cancer. It is under review for use in Hodgkin’s lymphoma and microsatellite instability-high (MSI-H) cancers, and positive outcomes also have been observed for bladder cancer. Merck has worked closely with FDA throughout the development process. A number of the accelerated approvals were based on results of a fluid design trial.
- Merck is pursuing a data-driven approach to identifying combination partners for Keytruda. Standard therapies, immunomodulators, targeted therapies, and novel vaccines are being pursued. Merck currently has over 200 collaborative clinical trials involving Keytruda combinations. Some examples include combination with standard chemotherapies in lung, head and neck, gastric, and breast cancers; combination with a CTLA-4 inhibitor in melanoma and lung cancer; combination with an IDO (indoleamine 2,3 dioxygenase) inhibitor in melanoma and head and neck cancer; combination with VEGF/TKI in renal cell carcinoma; and combination with T-VEC in melanoma and head and neck cancer.
- Merck is conducting a registration trial of Keytruda in combination with platinum chemotherapy based on evidence of synergy in preclinical models and platinum activation of the innate immune system. Early-phase trials indicated manageable toxicity with the combination. In a randomized phase II trial in untreated nonsquamous non-small cell lung cancer patients, the objective response rate in patients who received chemotherapy and Keytruda was nearly twice that observed in patients who received only chemotherapy. The combination also was associated with a 47 percent reduction in risk of disease progression. A phase III trial of Keytruda in combination with chemotherapy is under way, with results expected in 2017.
- Merck is conducting multiple phase III trials of Keytruda in combination with immunomodulatory drugs (lenalidomide or pomalidomide) and dexamethasone in multiple myeloma patients. Although

Keytruda is not very effective as a monotherapy for multiple myeloma, dramatic responses were observed when patients who were refractory to immunomodulatory drugs were treated with Keytruda, an immunomodulatory drug, and dexamethasone.

- In melanoma, Keytruda is being combined with IDO1 inhibitor epacadostat. A phase II trial showed strong and durable responses in melanoma with minimal additional toxicity. A phase III study is being planned.
- In renal cell carcinoma, early-phase trials showed a high level of antitumor activity and acceptable toxicity when Keytruda was combined with axitinib, Pfizer's VEGFR/TKI. Two phase III trials are under way to further investigate this combination in renal cell carcinoma patients.
- Keytruda is being studied in combination with Amgen's oncolytic virus, T-VEC, which is injected locally into tumors. Based on exploratory trial results, phase III trials are being pursued in melanoma and head and neck cancers.
- The work on Keytruda combinations has been informed by biology, although understanding of the biology of these cancers and drugs is incomplete.
- The success of Merck's work with Keytruda illustrates the value of breakthrough designation for drugs, as well as the importance of sponsor interaction with FDA throughout the drug development process. Collaborations among companies also are very important.

### Questions

- Dr. Witte asked about the inclusion of dexamethasone, a steroid, in the clinical trial of Keytruda in combination with lenalidomide in multiple myeloma patients. Dr. Baynes acknowledged that this seems counterintuitive since dexamethasone is anti-inflammatory, but he reported that patients on immunotherapies do not appear to do worse when treated with steroids. More research is needed to understand the biology underlying this observation.
- Dr. Stella asked about the possibility that drugs given in combination with Keytruda would increase expression of PD-L1. Dr. Baynes responded that PD-L1 is likely a relatively nonspecific inflammatory marker rather than mechanistically important for Keytruda action. The significance of PD-L1 upregulation with respect to Keytruda activity is unknown.

### DISCUSSION

Participants discussed challenges related to development and testing of drug combinations for cancer treatment.

#### Challenges with Collaboration

- Merck has devoted extensive resources to investigating combinations including Keytruda because they believe Keytruda has significant potential. There was early skepticism within Merck about the possibility of collaborating with other companies, but most companies have been eager to participate. There has been agreement about intellectual property (IP) issues because all partners retain their own IP. In general, broad-based collaboration has not been a problem.
- Dr. Rothenberg pointed out that one challenge to collaborating with other companies is that the partnering company's commitment to their molecule is uncertain (e.g., in the case of an adverse event). For its Keytruda studies, Merck is primarily pursuing partnerships involving stable, reliable molecules and companies. The risks are greater in cases in which there is little or no information on the drug's activity as a single agent. Dr. Baynes stated that Merck requires that partnering companies commit to providing their drug for phase III trials, which helps protect against the risk that a drug will be deprioritized when a company undergoes a merger, acquisition, or reorganization.

- Merck is exploring Keytruda in combination with both approved and investigational drugs. Some of the nonapproved drugs are designed to act on novel targets. It is important to evaluate safety for all combinations, but it is particularly important to do this for combinations that include a nonapproved drug for which there are minimal data on safety.
- When NCI develops agreements with pharmaceutical companies for use of a drug, terms for use of the drug in a combination are always included, even if the drug initially will be used as a single agent. This has allowed fast initiation of combination studies when the opportunity arises.
- Academic researchers could help elucidate biological mechanisms of drugs and drug combinations. However, some companies, particularly small companies, are reluctant to share their drugs with academic researchers. One reason is that they are concerned that adverse events will negatively affect the drug's chances of approval.

### **Biomarkers**

- Identifying and developing biomarkers for cancer drugs is challenging. Biomarkers are most important for drugs that work in only a subset of patients. They are less important for drugs like Keytruda that invoke a strong response in the general patient population.
- Merck has used gene signatures as a way to gain insight into the biology of a drug's activity, but these do not necessarily lead to identification of a biomarker.
- For drug developers, it is challenging to commit to a biomarker for a clinical trial that will last several years because there is a good chance that the “best” biomarker will change based on new knowledge.
- Dr. Berry stated that adaptive trial designs can be used to plan for and implement changes in biomarkers during the course of a clinical trial. This was done for the I-SPY 2 trial. It also is possible to plan trials that will identify the biomarker threshold that identifies patients in which a treatment is most likely to be effective.
- Dr. Pazdur reported that sponsors usually use a straightforward statistical principle—allocation of alpha with co-primary endpoints—to evaluate whether their drug works in the general population and/or a marker-positive population. FDA has reviewed drugs for which there is a companion biomarker, which means the biomarker is essential for safe and effective use of the drug, as well as those for which there is a complementary biomarker that is not essential but identifies a population in which the drug has higher activity.
- Quantitative biomarker data may help inform decisions about doses of various drugs included in a combination.
- NCI CTEP is working to add value in the area of biomarkers. Biomarkers can help elucidate mechanisms of action in addition to providing clinical value. It is risky for companies to invest in biomarker development because there is a small likelihood of success.

### **Challenges in Modern Cancer Drug Development**

- The use of combination therapy was pioneered within the oncology field in the 1970s. The reasons for these successes should be considered. There are, however, several differences in the current landscape that impact drug development.
- Reimbursement practices have changed over the past several decades—insurance companies generally did not question oncologists' treatment decisions in the 1970s, but physicians do not have as much flexibility now. Payers are less likely to reimburse for off-label use of a drug, which means that sponsors must seek approval for combinations.
- Standards for safety are higher now than in the past, in part because patients are living longer after their cancer diagnoses.

- Knowledge of the genetic basis of cancer has created new opportunities for cancer therapies, but rational design of drugs and treatment regimens can be more complicated than the empirical approaches of the past.

### **Potential Recommendations**

- The Panel should recommend removal or minimization of barriers to access to investigational agents for early-stage development.

## **CONCLUSIONS AND CROSS-CUTTING RECOMMENDATIONS**

Participants were asked to suggest additional potential recommendations and identify high-priority topics that should be addressed by the Panel.

- The need for coordination was emphasized throughout the workshop. It may be useful to have coordinating centers focused on various topics related to clinical trials (e.g., PROs, clinical trial data availability, biomarkers).
- Collaboration is needed to accelerate progress. Stakeholders need to agree on a common vision and work toward accomplishing it.
- The Panel should consider modifications to the Affordable Care Act (ACA) that may be made by the next administration. One possibility would be to recommend that any new healthcare law include the ACA requirement that standard care in the context of a clinical trial be covered by insurance.
- The value of randomized trials needs to be considered. Randomized trials can provide important information, but there are many people questioning whether randomization is necessary. For example, a New York Academy of Sciences meeting entitled *The Need to Accelerate Therapeutic Development—Must Randomized Controlled Trials Give Way?* is planned for March 2017. In many cases, small patient populations may preclude conduct of traditional randomized trials. A possible recommendation would be to formalize the use of observational and other data to supplement randomized trials.
- The importance of investing in basic science research and technology development was emphasized.

### **PUBLIC COMMENT**

- There was no comment from the public.

### **CLOSING REMARKS**

Panel members thanked participants, the co-chair, staff members, the facilitator, and the graphic recorder for their contributions to the workshop. They urged participants to send any additional comments to the Panel office and expressed hope that participants will be willing to provide additional information and insights as the report is developed.

## **CERTIFICATION OF MEETING SUMMARY**

I certify that this summary of the President's Cancer Panel meeting, *Emerging Opportunities to Streamline Cancer Drug Development*, held December 9, 2016, is accurate and complete.

Certified by:

Date:

February 28, 2017

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Barbara K. Rimer, DrPH  
Chair  
President's Cancer Panel