Facilitating Collaborations to Develop Combination Investigational Cancer Therapies: Workshop Summary

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Margie Patlak, Erin Balogh, and Sharyl J. Nass, Rapporteurs; National Cancer Policy Forum; Institute of Medicine

FACILITATING COLLABORATIONS TO DEVELOP COMBINATION INVESTIGATIONAL CANCER THERAPIES

WORKSHOP SUMMARY

Margie Patlak, Erin Balogh, and Sharyl J. Nass, *Rapporteurs*

National Cancer Policy Forum

Board on Health Care Services

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Ramzi Dagher, Vice President, Worldwide Regulatory Strategy and Regulatory Head, Oncology Business Unit, Pfizer, Inc., New London, CT

Beloo Mirakhur, Senior Director, R&D/Medical Affairs, Oncology N.A., GlaxoSmithKline, Collegeville, PA

Jane Perlmutter, Founder, Gemini Group, Ann Arbor, MI

Jeffrey Sosman, Professor of Medicine and Director, Melanoma & Tumor Immunotherapy Program, Vanderbilt-Ingram Cancer Center, Nashville, TN

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of this report. The review of this report was overseen by **Melvin**

Worth. Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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Introduction

Despite recent advances in deciphering the molecular pathways that trigger cancer and its progression, progress in developing therapies that effectively target those pathways has been hampered by their complexity. Researchers are finding that many cancer pathways have backup or bypass pathways that foster drug resistance. Consequently, targeted therapies that initially are quite effective in certain patients eventually stop working. In addition, many therapies appear to work best when they are used in combination with various treatment modalities.

Combining investigational cancer therapies early in their development is thought to be a promising strategy for identifying cancer treatments that will be effective in the long term, especially when a combination targets multiple pathways and byways in the development or progression of cancer, or more than one step in a pathway, potentially conferring greater benefit than a therapy directed at a single target. However, this approach to drug development presents several unique challenges, including developing and applying appropriate preclinical tests and clinical trial designs, prioritizing which combination therapies should be tested, avoiding toxicity of multiple agents, and overcoming legal and cultural barriers that impede collaboration among pharmaceutical companies, and between pharmaceutical companies and academic or government research institutions.

To help further the development of innovative combination cancer therapies, the National Cancer Policy Forum of the Institute of Medicine held a workshop entitled "Facilitating Collaborations to Develop

Combination Investigational Cancer Therapies" in Washington, DC, on June 13–14, 2011. The workshop agenda can be found in Appendix B of this report. The workshop convened experts to identify barriers that may be impeding the development of combination investigational cancer therapies as well as to offer ways to overcome those barriers. Workshop presentations and discussions included those that addressed:

- Scientific challenges and opportunities in the codevelopment of investigational therapies;
- Regulatory environment for codevelopment, including the recent Food and Drug Administration (FDA) draft guidance on this topic;
- Cultural and legal issues that affect collaboration;
- Lessons learned from codeveloping human immunodeficiency virus and cancer combination therapies; and
- Current examples that can serve as possible models of collaboration to develop combination cancer therapies.

A key goal of this workshop was to identify potential solutions to improve collaboration and accelerate the development of promising combination investigational cancer therapies. This document is a summary of the workshop. The views expressed in this summary are those of the speakers and discussants, as attributed to them, and are not the consensus views of the workshop participants, nor of the members of the National Cancer Policy Forum.

2

Why Combinations and Collaborations Are Necessary

Presenters highlighted several reasons for supporting combination strategies to develop more effective cancer therapies, including

- The current high failure and relapse rate for single-agent targeted therapies;
- The mounting evidence that combination targeted or immunotherapies will be more effective than single agents; and
- The need to counter the heterogeneity and evolution of tumors.

Participants also stressed the importance of collaboration to develop combination therapies because of the inability of a single drug company to have the resources to effectively and expediently counter the complex mechanisms by which cancer cells become resistant to treatment. Over the past decade, the scientific complexity and skyrocketing costs (Booth and Zemmel, 2004; Munos, 2009) of drug development have increased the incentives for more collaborative approaches. Dr. Bernard Munos, founder of the Innothink Center for Research in Biomedical Innovation, stressed the explosion of data on cancer due to the rise of genomics, metabolomics, proteomics, and the combinatorial expansion of treatment options. "It's bigger than we can handle in any single pharmaceutical company, in any single organization given our limited resources. We're running out of patients, money, and scientists. The only way to really make much progress is to join hands in order to be more effective," he said. Dr. Rachel Sherman, associate director for Medical Policy at the

FDA Center for Drug Evaluation and Research (CDER), agreed, adding, "Companies can no longer successfully develop groundbreaking therapy in isolation. The era of doing this solo is over."

Perhaps the most important reason for collaboration is to speed up the process of drug development so that effective treatments are delivered sooner to cancer patients, who may not have time on their sides. "Patients have a real sense of urgency. We can't wait," noted Dr. Jane Perlmutter, patient advocate and founder of the Gemini Group.

"We have been developing targeted agents for one pathway or target at a time, and that hasn't necessarily yielded the type of breakthrough therapies for patients that we are looking for," said Dr. Stuart Lutzker, vice president of Oncology Exploratory Clinical Development at Genentech. "From a sponsor's perspective, there has been an extremely high failure rate."

Several speakers elaborated on that theme by pointing out different reasons why most patients do not respond or eventually become resistant to targeted therapies. Many of these treatments target a single biochemical pathway to inhibit the activity of a kinase enzyme that fuels tumor growth, but as Dr. Jeffrey Engelman, assistant professor of medicine at Harvard Medical School and director of Thoracic Oncology at Massachusetts General Hospital, noted, "Most cancers are not really that sensitive to a perturbation of a single kinase pathway." He described how certain breast and gastric cancers are "addicted" to receptor tyrosine kinases,[1] such as epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2/neu), and a kinase called MET.[2] In some cases, when these receptors are blocked with targeted therapies, tumor cells die and patients go into remission. Two major downstream signaling pathways emanate from these receptor tyrosine kinases—the PI3K (phosphatidylinositol 3-kinase)-AKT[3] pathway and the MAPK (mitogen-activated protein kinase) pathway. These pathways foster tumor growth by promoting cell division and inhibiting cell death. Consequently, when

[1] Kinases are a type of enzyme that can activate molecules in a cell, and some cancer treatments target certain kinases that are linked to cancer. Receptor tyrosine kinases are a type of cell-surface receptor important in normal cellular processes and the development and progression of certain types of cancer.

[2] EGFR binds to epidermal growth factor, causing cell division. In some cancers, EGFR is found at abnormally high levels on cells. The HER2/neu protein is a tyrosine kinase receptor involved in normal cell growth and is abnormally active in some types of cancer. MET is a tyrosine kinase receptor protein involved in wound repair that is abnormally activated in some cancers.

[3] AKT is a kinase that is involved in cell growth and proliferation, survival, and motility. It has been implicated as a major factor in many types of cancer.

drugs block the EGF, HER2/neu, or MET kinases, both these major downstream pathways that fuel tumor growth also are blunted (see Figure 2-1).

Research suggests that both the PI3K-AKT pathway and the MAPK pathway have to be blocked to counter a tumor's progression, and single-agent targeted therapies that only block one of these pathways are

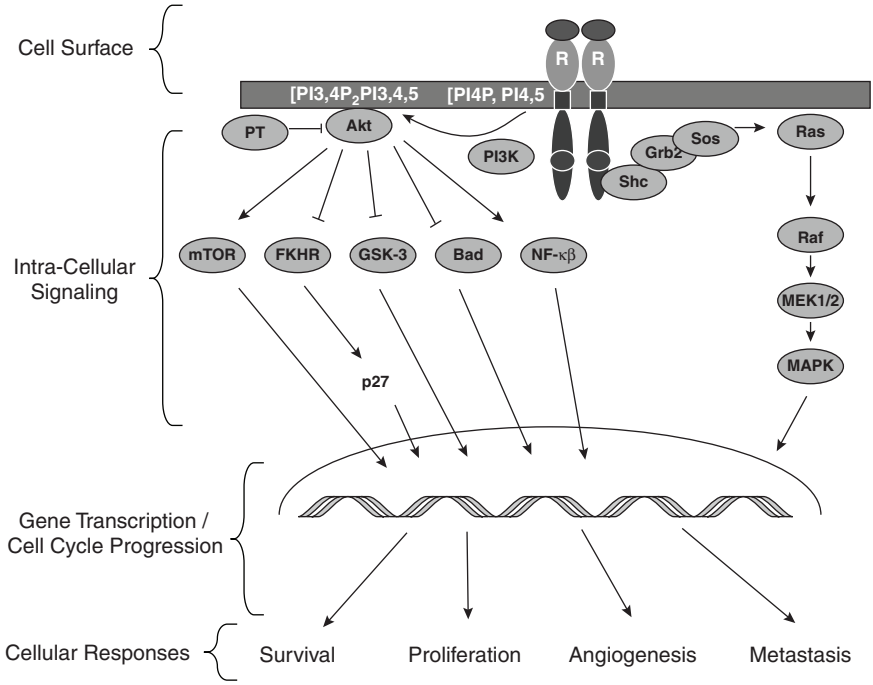

FIGURE 2-1 Growth factor receptor signal transduction pathways. Receptor tyrosine kinases, such as the epidermal growth factor receptor (EGFR) illustrated here, can be abnormally expressed and activated in many types of cancer. Two downstream signaling pathways of EGFR, the PI3K and MAPK pathways, can foster tumor growth by inhibiting cell death and promoting cell division. Thus, targeted therapies blocking receptor tyrosine kinases can block the downstream effects of these signaling pathways.

NOTE: FKHR = forkhead in human rhabdomyosarcoma; Grb2 = growth factor receptor-bound protein; GSK-3 = glycogen synthase kinase 3; MAPK = mitogen-activated protein kinase; MEK1/2 = MAPK kinase; mTOR = mammalian target of rapamycin; NF–κB = nuclear factor kappa B; PI3K = phosphatidylinositol 3-kinase; Sos = son of sevenless.

SOURCE: Tabernero, J., T. Macarulla, F. J. Ramos, and J. Baselga. 2005. Novel targeted therapies in the treatment of gastric and esophageal cancer. *Annals of Oncology* 16(11):1740–1748, by permission of the European Society for Medical Oncology.

often not effective. Based on preclinical modeling that showed improved efficacy of concurrent administration of MAPK kinase (MEK) and PI3K inhibitors compared to either agent alone, a Phase I dose escalation study of the combination therapy was initiated in patients with solid tumors. Results from this study suggest that combination therapy of MEK and PI3K inhibitors demonstrated some antitumor activity and was generally well tolerated, with side effects similar to Phase I studies involving the single agents (Shapiro et al., 2011).

Combination targeted therapy can be beneficial even when the initial single-agent therapy is effective, Dr. Engelman added, because of the development of drug resistance. Such resistance usually comes in two types. One type is due to a mutation or genetic event affecting the target of the drug itself so that the kinase is still able to drive the growth of the tumor, despite the continued presence of the drug. Another type of resistance occurs when the cancer uses pathways that bypass the blocked kinase. These bypasses activate the same key downstream tumor growth-promoting signaling pathways so that the tumor no longer needs the kinase the drug inhibits in order to grow. Research suggests that most cancers have multiple drivers—multiple inputs into the PI3K-AKT and MAPK pathways that can serve as bypasses, according to Dr. Engelman. When researchers perturb one signaling pathway with a kinase inhibitor, it often causes rebound activation of these bypass backup pathways such that the effectiveness of the inhibitor is muted (Engelman et al., 2007; Hsieh and Moasser, 2007; Nagata et al., 2004; Zhang and Yu, 2010). Consequently, combination treatments are needed that target both the kinase and the bypass pathway the kinase inhibitor activates.

For example, if a compound inhibits mTORC1 (mammalian target of rapamycin complex-1), which is downstream from AKT, it triggers the activation of AKT by lifting the negative feedback on the insulin-like growth factor (IGF) receptor, which normally suppresses AKT activation. However, early phase clinical trials suggest that if both a TORC1 inhibitor and an IGF inhibitor are used in combination, the rebound activation of AKT is effectively blocked. Such an approach has shown impressive activity in estrogen receptor (ER)–positive breast cancers, said Dr. Engelman (Cosimo et al., 2010; Rathkopf et al., 2010).

Due to the emergence of bypass pathways or mutations in drug targets, "these great responses that make the cover of *Time* magazine are really modest because the time to progression, on average, is a year. When you are talking to a patient, that is not even close to being something to celebrate," Dr. Engelman said. "We now know that we are going to need to employ combination therapies to deal with this resistance that's emerging."

Combinations with immunotherapies are also needed to fully provide

the complexity of an antitumor immune response, and to make such a response more likely to be effective by combining it with chemotherapy or radiation, several participants pointed out. For example, several studies show that T cells that are removed from a patient's body and genetically engineered and/or treated with immune stimulants to boost their numbers and/or tumor-killing abilities will be more likely to shrink the patient's tumor if, prior to receiving that treatment, the patient receives "host conditioning" with chemotherapy or radiation, said Dr. Carl June, professor of pathology and laboratory medicine at University of Pennsylvania School of Medicine and director of Translational Research at Abramson Cancer Center (see Figure 2-2).

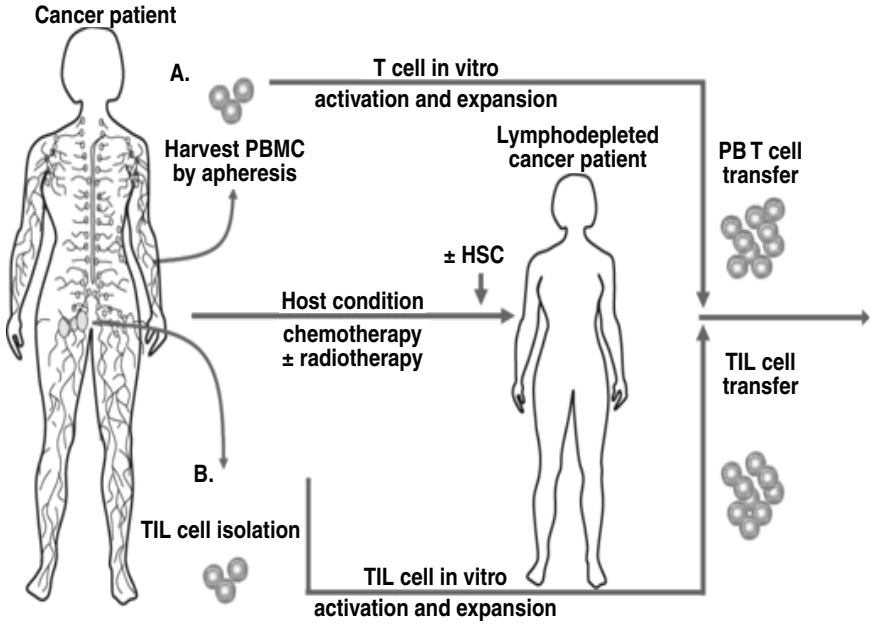

FIGURE 2-2 Adoptive cellular therapy. T cells or tumor infiltrating lymphocytes are removed from a cancer patient and activated and expanded. These activated T cells and tumor infiltrating lymphocytes are then returned to the patient after patient treatment with chemotherapy, and in some cases radiotherapy, and/or hematopoietic stem cell transplantation.
NOTE: HSC = hematopoietic stem cells; PBMC = peripheral blood mononuclear cell; TIL = tumor infiltrating lymphocytes.
SOURCES: June presentation (June 13, 2011) and Grupp and June, 2011. With kind permission from Springer Science+Business Media: Cancer Immunology and Immunotherapy, Adoptive cellular therapy, 2011, 151, S. A. Grupp and C. H. June, Figure 1.

Studies also suggest that patients treated with such T cell therapy and a tumor vaccine will have a greater response than either alone, Dr. June added. "There are a number of studies that show these immunotherapies can be synergistic, in terms of serologic antibody responses and cellular immune responses," he said. Dr. Renzo Canetta, vice president of Oncology Global Clinical Research at Bristol-Myers Squibb, and Dr. Jeffrey Schlom, chief of the Laboratory of Tumor Immunology and Biology and head of the Immunotherapeutics Group at the National Cancer Institute (NCI), added that many immunotherapies are cocktails of immune stimulants, costimulatory molecules, immune checkpoint suppressors, and other effectors of the immune system that singly are not effective, but in concert have a synergistic antitumor effect, as shown in studies, including some clinical studies.

Dr. Schlom stressed that vaccines used in combination with standard chemotherapy, radiation, or hormonal therapy induce minimal added toxicity and can act independently of concomitant therapy. Certain chemotherapeutic agents or radiation can alter tumor cells so they are more susceptible to killing by T cells, his preclinical models show, and these T cells can continue to inhibit tumor growth even after the tumor has become resistant to the chemotherapy used. This may explain why, in a study of a tumor vaccine combined with docetaxel in metastatic breast cancer patients, preliminary analyses suggest that those patients who received docetaxel alone had a median time to progression of 84 days, whereas those who received the vaccine combined with docetaxel had a time to progression of 265 days (NCI, 2011b). "We firmly believe that vaccines should be part of an immune-oncology platform," Dr. Schlom said.

Dr. Canetta and Dr. Keith Flaherty, associate professor of medicine and director of Developmental Therapeutics at the Massachusetts General Hospital Cancer Center, also noted several studies showing that various immunotherapies combined with targeted cancer therapies can be more effective than either modality used alone. Dr. Flaherty cautioned that there can be antagonistic effects with some targeted therapies and immunotherapies, however. MEK inhibitors, for example, appear to also inhibit T cell proliferation, unlike BRAF (rapidly accelerated fibrosarcoma (B family)) inhibitors, which appear to increase the influx of CD8 T cells into tumors, he said. Dr. Canetta added that not all cytotoxic agents may affect the immune system equally, and those interactions need to be studied more.

Another reason combination cancer therapies are needed is because of the heterogeneity of the cancer cells within individual patients, particularly in advanced tumors, in which the genetic instability of tumor cells fosters the emergence of multiple metastatic clones, each with a different genetic profile and varying sensitivity to specific treatments. As Dr. Michael Barrett, associate professor and head of the Oncogenom-

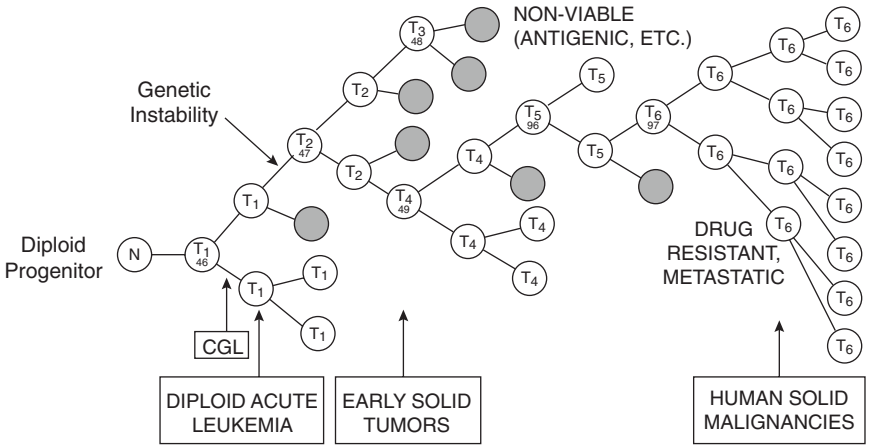

FIGURE 2-3 Clonal evolution of human neoplasia. The instability of tumor cells and the associated selection process result in a heterogeneity of tumor cells within an individual patient. These genetically distinct cancer cells may have different sensitivities to specific treatments, which may require treatment with combination therapies.
NOTE: CGL = chronic granulocytic leukemia; N = normal cell; T = tumor cell.
SOURCE: Barrett presentation (June 13, 2011). From Nowell, P. C. 1976. The clonal evolution of tumor cell populations. *Science* 194(4260):23–28. Reprinted with permission from AAAS.

ics Laboratory at the Translational Genomics Research Institute, pointed out, such sensitivity will vary over time because a specific treatment applies selective pressure on some genetic subtypes of cancer cells, such that those lacking the genetic variant the treatment targets will expand in number (see Figure 2-3).

As Dr. David Stern, professor of pathology at Yale Medical School and associate director of the Shared Resources for the Yale Comprehensive Cancer Center, summarized, "There are rapid routes through genetic and epigenetic plasticity, through on-target and bypass mutations, and through tumor cell population heterogeneity. This is the landscape we're all working in." Such a landscape is too complex for one company to tackle alone, said Dr. Munos. "The challenges are too big because the science is very complex," he said. "I've been in meetings in industry where people sat around the table and looked at a cluster of pathways and tried to pick targets. You can do that, but figuring out what will happen once you modulate those targets is basically next to impossible, because you cannot grasp the network effects that lie outside this cluster you're looking at."

3

Scientific Challenges in Developing Investigational Combination Therapies

Participants identified numerous scientific challenges to developing investigational combination therapies, including the need for:

- Better animal models and validated preclinical tests;
- Better dosing and treatment schedules to avoid toxicity, yet be effective;
- Better benchmarks, endpoints, and clinical trial designs for combination therapies;
- A way to prioritize which combinations to test;
- A way to select patients most likely to respond to combinations; and
- More basic research on the molecular mechanisms that underpin cancer and how they interact.

IMPROVING PRECLINICAL DEVELOPMENT OF INVESTIGATIONAL COMBINATION THERAPIES

Standard preclinical development of drugs involves assessing the effects of varying concentrations of experimental compounds in in vitro or animal models and using those results to determine initial doses to test in clinical trials. Such preclinical development presents numerous challenges that may be exacerbated in the development of combination therapies, including cell lines or animal models that do not adequately mimic the tumor, tumor microenvironment, or the propensity to develop

resistance, and a lack of biomarkers for efficacy. In addition, many animal models do not adequately mimic the immune response to tumors, so it is difficult to assess how immunotherapies are working in those models. There are also challenges that are unique to the development of combinations. For example, animal models appropriate for one therapeutic class might not be appropriate for another class with which they are being combined. These challenges were discussed at the workshop, as well as ways to address them.

Key Suggestions for Improving Preclinical Development of Combinations from Various Workshop Participants

- Funds to develop novel animal models that better mimic human cancer
- Use of non-cancer animal models (e.g., as autoimmune or infectious disease models) as surrogate efficacy models for anticancer immunotherapies
- Strategies to ensure target engagement and inhibition
- Innovative approaches to maximize dose and schedule of combinations
- Better ways to distinguish on-target versus off-target toxicities
- Greater use of animal models to identify resistance mechanisms
- Greater use of statistical modeling

Inadequate Models of Human Tumors and Tumor Microenvironment

Dr. Lewis Cantley, professor of medicine at Harvard Medical School and director of the Beth Israel Deaconess Hospital Cancer Center, noted that cell lines do not adequately model the diversity of tumor types, but rather those tumor cells that can grow in a petri dish or under other common laboratory conditions. "Once you establish these cell lines, they have been selected for and evolved to grow on plastic and they are not selected to grow in vivo. They have clearly evolved away from the original tumor from which they arose and do not represent what you see in the disease," he said. Consequently, he suggested that the most appropriate models in which to test cancer therapies are mouse explant models in which the tumor cells are growing within the animal, which ideally should be

a "humanized" mouse.[1] Alternatively, he suggested researchers mutate the same targets that are altered in the human cancer in the same tissue at the same time of development in the animal model. "Both of these are more powerful approaches than what we currently do," Dr. Cantley said.

But Dr. Kurt Bachman, Head of Translational Medicine and Biology for the Cancer Metabolism discovery unit at GlaxoSmithKline (GSK), pointed out that multiple tumor explants are needed to capture the diversity of tumor types. The tumor cells available for explants may not have the tumor subtype likely to respond to the combination therapy being tested preclinically. "We want to target K-ras mutant lung cancer, but those explants may not have K-ras mutations," said Dr. Bachman. It is also more expensive to test therapies in explant animal models than in numerous cell lines, Dr. Stern added. Dr. James Zwiebel, chief of the Investigational Drug Branch in the NCI Cancer Therapy Evaluation Program (CTEP), noted that NCI recently launched the Center for Advanced Preclinical Research, which will serve as a national resource for comprehensive preclinical testing of anti-tumor efficacy and selectivity, biodistribution, and metabolism in early-stage candidate drugs using genetically engineered mouse models (NCI, 2011a). "That's an approach that hopefully will gain traction," he said, and added that Dr. Terry Van Dyke is coordinating this effort and looking for interested parties to participate in it.

Dr. Bachman stressed that understanding how the tumor microenvironment affects growth of the tumor is crucial to improving cancer therapy and pointed out that his laboratory is starting to grow tumor cell lines in different microenvironments to see how that influences the action of inhibitors they've developed. He noted that effects seen in cell lines grown in three-dimensional cultures are different from when they are grown in standard culture conditions. "We are doing a lot of experiments to see if our culture conditions shift anything so the cell line looks more like a primary tumor that we can use to better predict what we are going to see in the clinic," he said.

Inadequate Models of Human Immune Responses to Cancer

Dr. Nils Lonberg, senior vice president of Biologics Discovery at Bristol-Myers Squibb, noted that immunotherapy combinations cannot be tested in standard tumor models in which tumors are grafted onto immunodeficient mice. Dr. Haleh Saber, supervisory pharmacologist in the FDA Office of Oncology Drug Products, concurred, adding that she

[1] Humanized mice have become an important research tool for the in vivo study of human cells and tissues. Humanized mice are immunodeficient mice engrafted with human hematopoietic cells or tissues, or mice that transgenically express human genes.

wanted to test a treatment for leukemia that combined genetically modified human immune cells with a small molecule that was designed to activate a particular gene in the cells. "There was no in vivo model so we couldn't do the animal pharmacology and toxicology studies," she noted. In addition, models appropriate for one type of therapy—a vaccine, for example—might not work for another type, such as a small molecule, noted Dr. Ramzi Dagher, vice president for Worldwide Regulatory Strategy and regulatory head for the Oncology Business Unit at Pfizer, Inc. Thus, finding the appropriate model in which to test their combination can be challenging.

Dr. Lonberg added that animal cancer models tend to be limited in how well they mimic the full spectrum of interactions between the host and the tumor that are key to assessing how well combination immunotherapies are working. He suggested using surrogate efficacy models, such as autoimmune or infectious disease models, to assess the effects of combinations of agents in immunotherapy. For example, the NOD[2] autoimmune mouse model can show synergy between immune system molecules by revealing a heightened autoimmune response, such as diabetes, when both molecules are combined compared to when they are given singly. Some researchers, such as Dr. Rafi Ahmed at Emory University, have also used chronic viral infection models, particularly the LCMV[3] mouse model, to reveal interaction between various components in the host immune system and the effects of that interaction on the viral load of infected cells (Kim and Ahmed, 2010). Alternatively, researchers, such as Dr. James Allison at Memorial Sloan Kettering Cancer Center, have tested combination immunotherapies preclinically by creating animal versions of the human antibodies or other immunotherapies that have been developed, and testing those in animals with intact immune systems.

But even these animal models may not fully mimic how the human immune system interacts with the tumor, according to Dr. Lonberg. He pointed out that the initial immune response to a tumor is an elimination phase in which the host immune system attacks the tumor. But then an equilibrium ensues. During this equilibrium phase, tumor cells express immunoevasion molecules that enable them to survive in equilibrium with the host immune system, with occasional tumor cells escaping immune defenses.

[2] Non-obese diabetic (NOD) mice exhibit a susceptibility to spontaneous development of autoimmune insulin-dependent diabetes mellitus.

[3] Lymphocytic choriomeningitis virus (LCMV): This mouse model has been useful for examining mechanisms of viral persistence and the basic concepts of virus-induced immunity and immunopathology.

Dr. Allison's animal model only mimics the initial elimination phase of an immune response. "You don't have time in a tumor model like that to look at equilibrium and escape," Dr. Lonberg said. So any advantages or disadvantages a combination immunotherapy might have in that regard cannot be predicted in preclinical testing in such animal models, he said.

One participant stressed that it is critical that the therapeutic mechanism targeted by a treatment is present in the animal model in which it is tested, and is relevant to human disease. For example, immunotherapy that acts as a CTLA-4[4] blockade does not work in a lot of animal models, he said, although ipilimumab, a monoclonal antibody targeting CTLA-4, has recently been approved by the FDA[5] for patients with advanced melanoma in first- and second-line treatment.

Dr. Cantley suggested using well-designed mouse models in which researchers can verify that each drug had adequately hit its target and had the desired downstream effects, that is, blocked the pathways that foster tumor growth. Evidence of those blocked pathways can then be gathered from the repeat biopsies taken from patients being clinically tested with the drug combination.

Given current deficiencies, Dr. Stern suggested that there be better access to animal models for combination therapies or funds to develop them. "For wet bench investigators, the bottleneck is often moving from cell biology to animals," he said.

Combined Toxicity

"Sometimes [drug] synergy is going to take us in the direction of enhanced toxicity," Dr. Flaherty noted. For example, Dr. Engelman described a combination therapy that was highly effective when tested in vitro, but when he gave the maximum tolerated dose of each of those drugs to mice simultaneously, they killed every mouse tested. "You want to shut down these pathways [in tumors], but these are very important pathways for lots of cellular processes. It was only when we started playing with different schedules and doses that we were able to find the sweet spot where the mice lived and the tumors shrank," he said.

Dr. Engelman suggested being more creative and innovative in how combination therapies are scheduled and dosed. "Lots of these thera-

[4] CTLA-4 (Cytotoxic T-Lymphocyte Antigen 4) is a protein that plays an important regulatory role in the immune system. It is a member of the immunoglobulin superfamily, which is expressed on the surface of Helper T cells and transmits an inhibitory signal to T cells.

[5] See http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm1193237.htm (accessed December 14, 2011).

pies are going to require three or four drugs, and a patient cannot be on all of them ad infinitum. They have to be pulsed or sequenced—we can't just give them everything every day and only dose-reduce when they experience too much toxicity." One regimen he suggested testing was giving monotherapy with periodic pulses of an additional treatment aimed at killing off those tumor cells that have become resistant to the monotherapy.

Divergent Effects Depending on Dose or Sequence

Dr. Patricia LoRusso, professor of internal medicine at Wayne State University Medical School and director of the Center for Experimental Therapeutics at Karmanos Cancer Institute, and Dr. Lutzker gave an example of the extensive preclinical testing of combination targeted cancer therapies done by Genentech. This preclinical testing of an MEK inhibitor combined with a PI3K inhibitor, which took about a year, not only assessed additivity versus synergy in various genetically diverse cancer cell lines, but also tested a wide range of daily dosing versus intermittent dosing in animal models that aided subsequent clinical trial design. "Genentech did an excellent job in trying to figure out how best to dose escalate. In a first-in-patient study [Shapiro et al., 2011], we were able to conduct multiple arms simultaneously so that we could more efficiently define the combination of each of the drugs leading the pack, which has helped us in the final outcome of this study," Dr. LoRusso said. "It is important when you get in the clinic to make sure you have drugs that can actually achieve the types of pharmacodynamic effects that you want or you hope to see in patients," Dr. Lutzker added.

For combinations that include immunotherapies, dose scheduling is key, Dr. Schlom pointed out. He noted that studies have found that tumor vaccines given after chemotherapy regimens are not as effective as those given prior to chemotherapy. Dr. Lonberg added that in one of his studies of two immunotherapy drugs, he found that when the drugs were given sequentially, there was a much more modest effect than when they were given together.

Finding the appropriate dose of an immunotherapy is also critical, Dr. Schlom added, because many immune modulators have dual functionality, depending on dose, including many immune stimulants that have no effect at high doses. He noted that these potential therapeutics have been shelved merely because they showed no effects and were toxic at the maximum tolerated dose in Phase I studies, but they might have some useful effects at lower doses and in combination with other treatments. "It's not only a matter of drug interaction, but it's also a matter of

what biologically makes sense in terms of sequencing and combining," summed up Dr. Canetta.

Differing Pharmacokinetics and Pharmacodynamics Between Mice and People

Dr. Cantley stressed that the pharmacokinetics and pharmacodynamics of drugs are dramatically different in mice and in humans. "We need to get beyond this fear that if a combination kills mice it's therefore going to stop a clinical trial, because those mice data don't mean anything," he asserted. Dr. Saber added that all oncology drugs are toxic and "the question is, can you monitor those toxicities? Most of the time we can and we adjust the dose so you're good to go."

But Dr. Engelman noted that although pharmacokinetic and pharmacodynamic data do not directly transfer from the mouse to human, they can suggest a framework for how to reduce dosing to counter toxicity. For example, researchers can use the mouse to test the effects of reducing both drugs on both targeting and toxicity versus reducing the dose of just one drug, or keeping the dose of both drugs, but increasing the duration between doses.

Dr. Donald Berry, professor of biostatistics at the MD Anderson Cancer Center, suggested going from bench to bedside and back to the bench by doing Bayesian statistical modeling of mouse preclinical test results the same way one would do for a clinical trial. "If there is no relationship between the mouse results and the human results, then we will just focus on the clinical aspects," he said, "but there is a tremendous opportunity to augment the one with the other. You can do it with a statistical model."

Dr. LoRusso stressed that "we need to have much higher standards as to what we are considering effective combinations preclinically. I don't know that the models have failed us. I think the way we are interpreting the models is what's really failing us." Dr. Engelman added that seeing a treatment response that is greater than a control response in preclinical tests does not necessarily mean that the treatment will cause clinical responses, but rather that the treatment has a biological effect. It is more important that the treatment causes significant tumor shrinkage in preclinical tests, he said. "If we can't see tumor regressions in a simple 200 mm cubed tumor—which is the most homogeneous sensitive model—than what's the likelihood that Mr. Jones, who has a huge amount of cancer that is heterogeneous, is going to benefit?" he said.

But Dr. Lutzker countered that most human tumors do not grow as fast as tumors in mice. "I'm not prepared to give up on a combination just

because in a xenograft[6] it didn't shrink the tumor," he said. Dr. Engelman agreed and said he would view a lack of tumor growth in a xenograft model as a positive indicator, but added that "maybe as a community, we have been too accepting of seeing a biological effect and assuming that would translate into a therapeutic benefit in the clinic."

On-Target Versus Off-Target Effects

Dr. Cantley suggested determining whether the limiting toxicity seen in animal models stems from how the combination affects the target, or alternatively whether it is due to how one or both drugs affect something other than the target. "If it's on-target combined toxicity, then you have done the best you can. If it's off-target, that means you try another combination, another PI3K or MEK inhibitor, for example. Fortunately, we have 18 of one and 7 of the other, so the probability that all combinations are going to have the same toxicity is unlikely," he said. He noted that often doses of the combination hit the targets hard enough before toxicity is seen either in the mouse or the human. "Sometimes you don't need to reach the mean toxicity because the toxicity is not on target," he said.

Dr. Saber suggested basing dose selection on data, when available, from Phase I clinical trials with the single agents that researchers plan to use in combination. Often sponsors will test a few doses of the single agents in people before combining them. But Dr. Roy Herbst, professor of medicine and chief of the Medical Oncology Section at Yale Comprehensive Cancer Center, said it is possible that lower doses of the two drugs combined might be more effective than the same dose of either agent used singly.

Identifying Resistance Mechanisms

Dr. Cantley described in his presentation how he often goes back and forth from bench to bedside. He uses animal models to determine what causes resistance to targeted treatments, and thus what treatments should be combined. He does this by doing a mutational analysis of the tumors removed from drug-resistant mice. For example, through this procedure he has discovered that resistance to a PI3K inhibitor can occur through amplification of MET. Armed with this information, he biopsies patients who have not responded to a PI3K inhibitor to see if their tumors also have MET amplification or produce high levels of MET protein. If that is

[6] A xenograft is a surgical graft of tissue from one species (in this case, a human) to an unlike species (in this case, a mouse).

the case, he will consider entering these patients into a trial that tests a combination of a MET inhibitor with a PI3K inhibitor.

PRIORITIZING COMBINATIONS TO TEST

Strategies for Prioritizing Which Combinations to Test in the Clinic as Suggested by Various Workshop Participants

- Using stricter preclinical benchmarks for effectiveness, such as tumor shrinkage, and demonstrating consistent effects in multiple animal models
- Demonstrating adequate pharmacokinetics and evidence of target activity at clinically relevant doses
- Doing high-throughput in vitro screening of drug combinations to detect synergy
- Subprioritizing so there is testing of the best drugs of each class
- Using genetic analyses and response biomarkers
- Testing combinations that optimize the benefit of already approved drugs

The growing number of targeted therapies that could be tested in combination, as well as the limited government and industry resources for such testing and the finite number of patients in whom combinations can be tested, suggests the need for a better way to prioritize which combinations get tested in clinical trials, several participants pointed out. Such prioritizing is key to developing a focus for patient advocates, federal agencies, and pharmaceutical chief executive officers (CEOs), said Dr. Michaele Christian, former NCI CTEP director, so everyone knows what the high-priority combinations are. But such prioritization can be challenging. As Dr. June noted, even in restricting combination therapy to combinations of immunotherapies, there is "a menu that is much too large to test in a combinatorial approach without some way of prioritization." Dr. Engelman added, "We are going to have more combinations than we have patients."

Dr. Engelman suggested using stricter preclinical benchmarks for effectiveness when deciding which combinations to test in the clinic. One of those benchmarks should be seeing tumors shrink in animals, as opposed to blocking tumors from forming or from growing. "Lots of times we get excited about a biological effect, yet the tumor still grows slowly or the cells still grow slowly and that does not predict for efficacy in the clinic," he said. Dr. Engelman added that he would prefer to see

synergy versus additivity in preclinical tests, but the most important effect is seeing the tumor shrink, regardless of whether it is caused by synergy or additivity. He also noted that he has been impressed with a web-based system[7] that Drs. William Pao and Mia Levy at Vanderbilt University have built to disseminate information on patients' tumor mutations and responses to various therapies to enable a genetically-informed approach to cancer medicine. The My Cancer Genome website is an international collaboration of contributing physicians and physician scientists that compiles information on the mutations influencing cancer progression and growth, potential therapies that may be effective against specific mutations, and available clinical trials that target specific mutations. These data can be used to prioritize which combinations of targeted cancer therapies should be tested in the clinic, and can inform clinicians at the point of care about tumor mutations and possible targeted therapies.

Dr. Bachman said that when testing combinations in cell lines, he also aims for finding synergistic, not just additive, results.

Dr. James Doroshow, deputy director for Clinical and Translational Research at NCI, suggested that combinations be tested clinically only if they work in at least three xenografts, and that they be based on a biological mechanism for which there is an assay. Before testing a combination clinically, Dr. Helen Chen, associate branch chief of the Investigational Drug Branch at NCI, said that the agents in the combination should have already demonstrated adequate pharmacokinetics and some evidence of activity or target engagement at clinically relevant doses and exposures. Ideally the individual targets should be validated, and priority should be given for combinations that have shown a higher degree of efficacy, such as those that have converted growth inhibition to a tumor cell kill, she said.

Dr. Cantley pointed out that sometimes agents used singly do not have a significant effect because they are not tested at high enough doses, and subsequent combination therapies using those same agents do show an effect. "We have learned that you really have to hit these targets hard," he said. In addition, some immunotherapeutic agents only work in combination and not singly, several experts in this field pointed out.

Dr. Chen also suggested assessing whether the synergism of the combination is seen consistently across all preclinical models, and if not, whether a predictive marker can be identified to choose those patients likely to respond to the synergistic interaction. Dr. Lutzker added that "in order to do small clinical trials, it is critical to try to understand which patient you want to test the combination in," and suggested not doing any clinical testing unless there is a biomarker test that can be done simulta-

[7] See www.mycancergenome.org (accessed December 14, 2011).

neously to assess which types of patients respond or do not respond to the treatment.

To systematically assess which combinations should be tested clinically, Dr. Stern is collaborating with Dr. Marcus Bosenberg to conduct high-throughput screening of 40 compounds at 3 concentrations on 30 tumor cell lines that model common human combinations of mutations. The tested drugs were heavily weighted toward drugs that target tumor cell growth signaling, but included conventional cytotoxic therapies as well. This research has revealed numerous additive or synergistic interactions in various combinations for specific tumor genotypes, some of which revealed novel pathway interactions. Drs. Stern and Bosenberg are currently linking these functional results to phosphoproteomic data as well as exome sequencing so researchers can use it to predict combination drug sensitivity according to genotype, such as by BRAF status, ras[8] status, and other genetic aspects of a tumor.

Dr. Barrett suggested a more personalized approach to determining which combinations of therapeutics should be tested in patients. Such an approach can be taken by assessing the genomes of patients' tumor, identifying which genetic mutations are driving the growth of those tumors, and then devising combinations that block those drivers. To do this, Dr. Barrett uses a small amount of tumor tissue that can be obtained from standard or needle biopsies. Then he uses flow cytometry to separate tumor cells based on the duplications or deletions of chromosomes or other characteristics that can be measured by examining individual cells with a laser. He then uses comparative genomic hybridization to genetically profile these subpopulations of tumor cells, noting that multiple populations of tumor cells can be present in a single biopsy. From this profiling he said it is possible to detect more than 100 chromosomal aberrations, which are then quantified and ranked according to how likely they are to be influencing the development or growth of the patient's tumor. Based on this information, statistical and bioinformatics techniques are then used to depict what he calls a "wiring diagram" of the activated pathways that are fueling the tumor. This is then used to determine the most appropriate combination therapy. "There is lots of heterogeneity, but we find all the populations and can purify them out and often find convergence on these pathways," Dr. Barrett noted. "What we need to do is identify the concurrent aberrations and mutations in each tumor cell population if genomics is really going to help advance the development of these targeted therapies, particularly combination therapies."

As Dr. LoRusso noted, there are a lot of drugs of similar class. For

[8] The ras family of genes code for proteins involved in cell signaling, cell growth, and apoptosis. Mutations in ras genes can lead to cancer.

example, there are at least a half dozen MEK inhibitors and PI3K inhibitors. She suggested that perhaps combination therapies should be limited to combining a few of the best in each class. Dr. Bachman also suggested subprioritizing which compounds within a class should be tested in combination because not all inhibitors are the same. "It's important, when we start to think about prioritizing combinations, that we subprioritize, say PI3[K]/MEK combinations depending on what the inhibitors are telling us, what their potencies are," she said.

Dr. Robert Iannone, section head of Clinical Oncology and cochair for the Pediatric Development Committee at Merck Research Laboratories, suggested developing more biomarkers that predict response to monotherapies as well as additional predictive biomarkers for when they are used in combination to indicate which combinations are most promising. "We can do the cell line work and the xenograft work, but still you get to the clinic and you find that your efficacy is not as good as you had hoped based on those preclinical tests. So we really need to go one step further to understand: What are the predictive biomarkers for these monotherapies and combination therapies?" Dr. Iannone asked. Dr. Lutzker added that both predictive markers for patient selection as well as pharmacodynamic markers that show modulation of the pathway of interest are critical for combination therapies.

Dr. Lutzker noted that Genentech's initial strategy for prioritizing combinations has been to focus on drugs that were already approved and in the clinic, so as to maximize the benefit of those drugs to patients. More recently, the company has moved this rational combination development strategy earlier in the drug development process to drugs that are still in Phase I clinical testing. These strategies include combining compounds that have different mechanisms of action on the same target, such as combining two different antibodies to HER2 (antibodies that target two different epitopes on HER2). Genentech has also tested drugs for their ability to enhance the effects of bevacizumab.[9] Such drugs are thought to sensitize tumors to the effects of bevacizumab or prevent or alleviate resistance to this drug. They have also tested a combination of erlotinib,[10] which targets EGFR, and an anti-MET antibody to prevent the development of resistance to erlotinib by activation of the MET backup pathway. "These rational combination strategies have started to bear some fruit in the clinic," Dr. Lutzker said.

[9] Bevacizumab (trade name Avastin), is a drug that blocks angiogenesis, the growth of new blood vessels. It is used to treat various cancers, including colorectal, lung, and kidney cancers.

[10] Erlotinib (trade name Tarceva) is a tyrosine kinase inhibitor drug that acts on the epidermal growth factor receptor. It is used to treat non-small cell lung cancer, pancreatic cancer, and several other types of cancer.

He added that not only should combinations have a strong scientific underpinning, but that they should also be composed of pharmacologically compatible molecules. "If one drug has a very long half-life and the other one has a very short half-life, and a toxicity develops, what can you do in terms of trying to maintain safety for patients? Do you have to stop both drugs? There are a whole number of issues that need to be thought through," he said.

BUILDING ON THE BASIC KNOWLEDGE BASE

Key Suggestions to Build on the Basic Knowledge Base by Various Workshop Participants

- Government and industry support for academic explorations in basic research
- Gathering more information on gene expression, signaling perturbations, and DNA damage in tumors
- Developing tools to examine genotype/phenotype relationships
- Better understanding of the mechanisms of action of targeted therapies

Additional basic information has to be understood at the molecular level for combination therapies to be effective, several participants pointed out. They suggested that researchers gather more information on gene expression and the feedback and network responses to signaling perturbations and DNA damage. More information is also needed on the non-genetic effects that influence treatment, including the microenvironment of the tumor, the host immune response, and the proteins made by the tumor and surrounding cells.

"The problem is that the drugs target function—phenotype—whereas the measurement tools we have mainly query genotype, and the genotype/phenotype connections have not yet entirely been solved," said Dr. Stern, and this is slowing the progress in developing molecularly targeted therapies. He added that on a detailed level, "there is a fundamental lack of knowledge on how even the most effective targeted therapies work. We know trastuzumab [Herceptin] works through a number of means, but I don't think anyone here can tell us what the balance is of down-modulation, partial activation, [or how] the immune system is involved. Much basic science remains [to be elucidated]. We need to know how the target pathways interact, patterns of drug resistance and

response, and how to interpret transcriptional phenotypes so we can link what we can measure to where we can intervene."

Dr. Munos added, "Biological modeling is not predictive because we have huge knowledge gaps. Forty percent of the human genome is still [uncharacterized]. Obviously, some of that stuff does something important, and unless we figure out what it does, it's not going to work."

Dr. Chen noted that the molecular pathways that drive some tumors are exceptionally complex, and researchers continue to discover new feedback loops and other mechanisms that tumors use to bypass blocked molecular pathways. "The real question is whether we are able to win the battle over such a highly adaptive tumor. Even if we can inhibit two or even three targets, the tumor may still find a way to escape," she said.

Dr. Doroshow pointed out, "We know almost nothing at the molecular level about the toxicology of combination molecularly targeted agents." To counter that lack of knowledge, NCI is currently developing a laboratory to study the toxicology of targeted combinations at the molecular level, he said.

Dr. Stern suggested that government and industry provide more support for academic explorations in the basic research areas that are so integral to fostering more effective cancer therapeutics.

IMPROVING CLINICAL TRIALS FOR COMBINATION THERAPIES

Suggestions from Various Workshop Participants on How to Improve Clinical Trials for Combination Therapies

- Having assays to select likely patient responders
- Using adaptive trial designs to determine the best combinations, dosing, and patient selection biomarkers as the trial progresses
- Using appropriate endpoints and setting a higher bar for effectiveness
- Establishing a single Institutional Review Board of record for multi-institutional trials
- Repeat biopsies of patient's tumors to assess therapeutic effectiveness
- Developing a precompetitive venue for testing drug combinations in a limited number of patients

Patient Selection

Several speakers stressed the need to have biomarkers for patient selection, given that most of the agents being tested in combination therapies target highly specific molecular differences. "Almost every person who has cancer has an orphan disease, because there are really thousands of different subsets of cancer. Hopefully, we won't need thousands of therapies, but until we divide these cancers, we're not going to conquer them," Dr. Cantley said.

Biomarker assays for key molecular differences that researchers can use to select patients will be crucial to such dividing and conquering, he added. Dr. LoRusso noted that genetic profiling of patients might enable researchers to determine what drug ratios to test on them in combination Phase I trials. Dr. Chen added that patient selection will be important not only to improve clinical trial efficiency, but to find those patients who can fit into a narrow window of therapeutic effectiveness because they are so sensitive to a drug's effect to a target that a low enough dose can be effective without causing toxicity. This may be more important for combination therapies, she said, when significant dose reduction is often required to avoid adverse effects.

Although patient profiling would be expensive, it could save money in the long run by directing patients to the most appropriate therapies, Dr. LoRusso said. But she noted that "for the majority of cases, we lack the appropriate interrogation tools and assays for patient profiling, and even when they are available, many times we don't take advantage of them." Dr. Christian concurred and pointed out that clinical testing of drugs often precedes the development of patient selection biomarkers or biomarkers that indicate whether a target has been adequately hit.

Dr. LoRusso regretted that in her own Phase I study of breast cancer patients given a combination therapy that targets two different aberrant genes in stem cells, she did not determine if patients had those aberrant genes prior to testing them with the combination, although she plans to assess this in posttreatment biopsies. She noted that there is a concern that patient profiling and selection could slow down patient recruitment, but countered that when such profiling is done well, "it could actually help expedite rather than slow down the big picture."

Dr. Barrett added that patient profiling can be done in real time, and does not necessarily slow down the patient recruitment process. For a trial funded by Stand Up To Cancer,[11] in which he is involved (see Appendix A), "We can get a sample in on a Monday and by Thursday we can generate a report that is a rank list of what we believe the targets of the therapy

[11] See http://www.standup2cancer.org/su2c/about_us (accessed December 14, 2011).

should be," Dr. Barrett said, adding that "even 2 weeks can be almost a lifetime for some of these patients." Dr. Perlmutter concurred, saying, "For some patients that 2-week wait is extra scary. We have to not only get better and cheaper in our testing, but we also have to get faster in our testing." To do more detailed whole-genome sequencing is more time consuming, Drs. Engelman and Barrett noted, and currently is not practical for patient selection, although whole-exome sequencing has led to the discovery of a feasible number of exons—600–800—that could be assessed within 3 weeks and be potentially clinically useful, Dr. Engelman added.

Dr. LoRusso gave a positive example of patient selection in a Phase II clinical trial of a MEK inhibitor tested in combination with a BRAF inhibitor by Jeff Infante of the Sarah Cannon Research Institute in Nashville, Tennessee. She said Dr. Infante preselected his patients based on the presence of BRAF mutations in their tumors, and preliminary results suggest a better response rate with the combined therapy than what was observed with the single agents (Infante et al., 2011). The trial is still ongoing, with the majority of enrolled patients continuing in the study. Dr. Lutzker added that he preselected patients in a trial that tested a MET monoclonal antibody plus erlotinib. Such preselection was done using an assay for high-level expression of MET by immunohistochemistry. This Phase II study showed strong efficacy in this patient group in terms of progression-free and overall survival, he said. Dr. Cantley noted his team of researchers spent a lot of time discovering and testing biomarkers for early response that were quantitative, predicted clinical outcomes, and worked well across institutions. These biomarkers included those that could be evaluated in positron emission tomography (PET) scans.

Dr. LoRusso questioned the relevance of the genetic profiling being done in metastatic tumors to determine appropriate treatment combinations to patients with non-metastatic disease, who might be more likely to benefit from combination therapy. "What are the risks that are involved if we are studying these combinations in the wrong patient population at the wrong clinical stage?" she asked, especially if negative findings in a metastatic patient population led to combinations being rejected for further testing in patients with early-stage disease.

Dr. Sharon Murphy, scholar in residence at the Institute of Medicine, suggested conducting more combination therapy trials in pediatric cancer populations. She noted that there are extensive tissue banks of pediatric tumors that are clinically well annotated and could serve as valuable resources for investigators. "When we think about combination targeted therapies or targeted treatments, we should think about childhood cancer, which arguably is a better model because genetically it's simpler than many adult forms of cancer. There are fewer signaling pathways, and children need these drugs too," she said. She added that investigators

should not have to wait to test promising combination therapies in pediatric populations until after they show promise in adult Phase I trials. Dr. Chen responded that CTEP has been doing a lot of Phase I and II testing of investigational cancer treatment combinations in the pediatric population. Dr. Samuel Blackman, Director of the Oncology Early Development Unit at GSK, agreed that pediatric populations should be engaged to achieve early proof of concept, and for some subtypes of cancers such testing is easier to do in the pediatric than the adult population because pediatric patients with these tumors tend to be grouped according to the genetic drivers of their tumors and treated in disease-specific programs offered in major pediatric cancer centers.

Adaptive Trial Designs

According to Dr. Berry, adaptive clinical trial designs are especially suited for answering the numerous questions that combination therapy raises, such as which of several possible drug combinations, patient selection biomarkers, doses, and dosing schedules are the safest and most effective. He said that an adaptive design enables researchers both to answer questions as well as to raise new questions and test new hypotheses during the course of a trial. Adaptive trials use Bayesian statistics to model and predict during a trial which option is most likely to be beneficial based on the results to date. Researchers use these predictions, while the trial progresses, to increase the number of patients being tested in the arms showing the most promise, and reduce or drop the number of patients being treated in those arms generating poor results.

For example, Dr. Berry designed an adaptive Phase I/II trial for a two-drug combination therapy for leukemia in which the admissible doses expanded or contracted during the trial depending on toxicity and effectiveness. For trials of two agents given separately or together, patients are randomized to each possibility, but "as you are learning, for example, that agent 1 is not doing as well as you might have hoped, you might give it a lower probability [and assign less patients to receive this agent]," he said, adding, "At some point we make a decision as to what is going to be the confirmatory stage [for the agent that is having the best results]" (see Figure 3-1).

Another example of an adaptive trial is I-SPY 2 TRIAL (Investigation of Serial studies to Predict Your Therapeutic Response with Imaging And moLecular analysis 2; see Figure 3-2 and Appendix A), which tests various treatments for breast cancer used singly or in combination while simultaneously assessing which patient selection biomarkers are most appropriate for each treatment. This trial has five experimental arms in which new treatments are "plugged in" to be tested once other tested

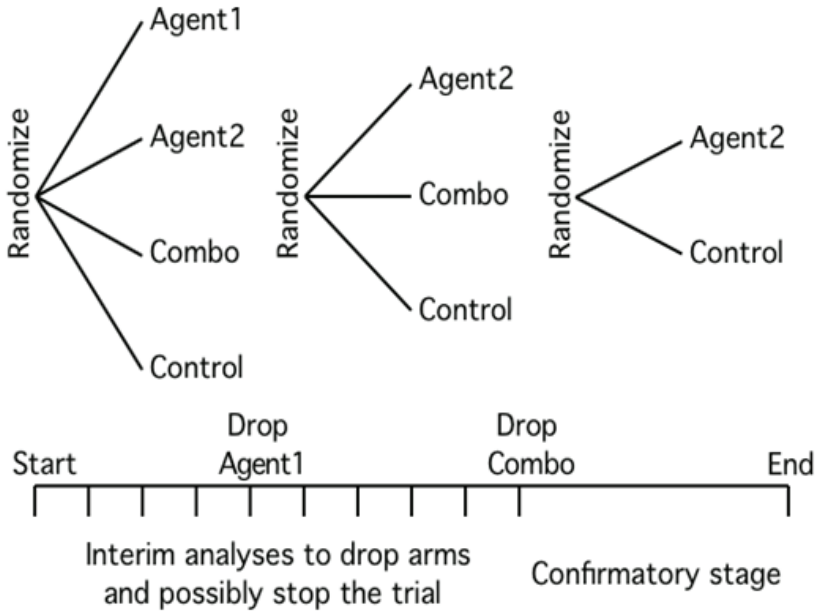

FIGURE 3-1 An example of an adaptive trial design that includes several treatment arms at the start of the trial (in this case a factorial design: agent 1, agent 2, the combination of agents 1 and 2, and a control arm). As information accrues, the arms that are not performing well can be dropped. Accrual continues with no interruption to carry out interim analyses. Interim analyses may be continued into the confirmatory stage.
SOURCE: IOM, 2010b.

agents progress to confirmatory trials or fail to show favorable results, Dr. Berry said. It has a factorial design in which single agents plus standard of care are tested against combinations of agents plus standard of care. As the trial progresses, single agents may be dropped because the results are more favorable when they are used in combination, "but meanwhile we have some experience in the single agents and some notion of synergy or additivity," Dr. Berry pointed out.

The I-SPY 2 TRIAL is innovative in that there is an adaptive design with regard to both treatment and the patient selection biomarker for the treatment. Dr. Berry stressed this is critical given that researchers continue to uncover new biomarkers for patient selectivity. "We have to figure out ways that we can update that information and use additional markers to understand who benefits from treatment. The only way to do it is to build it into our clinical trial structure and learn as we go," he said. Dr. Iannone highlighted that trials can be more efficient if patients in a clinical trial of

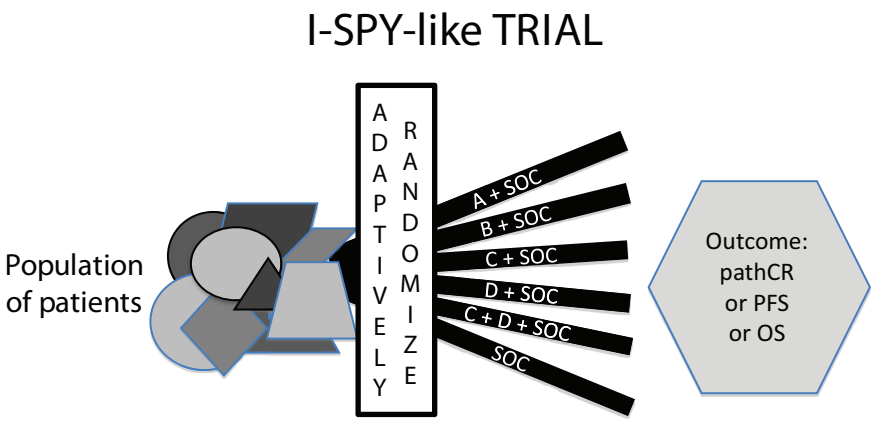

FIGURE 3-2 Design features of an I-SPY-like trial. In this design, patients are adaptively randomized within biomarker subsets to multiple therapies or combination therapies. The bottom four arms in the figure constitute a factorial design for agents C and D that are being investigated simultaneously with agents A and B. All comparisons are to standard of care. The therapies' benefits are assessed within patient subsets defined by biomarkers. The adaptive randomization aspect enables study arms that are performing well within a particular patient subset to be assigned with higher probability to patients in that subset. Arms that are performing poorly are assigned with smaller probabilities, and if they do sufficiently poorly in a subset, they will no longer be assigned to those patients. If they do sufficiently poorly in all subsets, then they are dropped from the trial. Drugs that have established a sufficiently clear biomarker signature based on their performance will be graduated from the trial.
NOTE: OS = overall survival; pathCR = pathological complete response; PFS = progression-free survival; SOC = standard of care.
SOURCE: Berry presentation (June 13, 2011).

combination therapies can easily move from one arm to another, based on some early measure of success or failure through a specific pharmacodynamic response biomarker. Efficiency is especially improved if there is a high negative predictive value and patients can be quickly assigned to another treatment arm without needing another baseline biopsy. "There is an efficiency for investigators, but there is a huge efficiency and potential upside for patients as well," he pointed out.

Dr. Larry Rubinstein, statistician at the NCI Biometric Research Branch, agreed that the adaptive trial designs Dr. Berry presented were well suited to trials of investigational drug combinations because they avoid the problem of setting the maximum tolerated dose prematurely, which often occurs with standard Phase I trial designs that have a small

number of patients. Adaptive trial designs also address the ethical imperative of aiming to benefit patients by focusing on the dose combinations that are most promising, he said. The randomization of patients to biomarker tests is also an important way to assess whether the biomarker indicates if a patient is likely to do better when given a particular treatment, versus whether a patient is likely to do better regardless of which treatment he or she receives, that is, it enables researchers to distinguish between predictive and prognostic markers.

But in addition to assessing the clinical toxicity of varying doses of experimental agents, Dr. Rubinstein suggested introducing in vivo pharmacodynamic assays for efficacy or toxicity, or even using these assays during the course of a clinical trial to assess whether the individual agents are hitting their targets and otherwise working mechanistically as expected. "This means you may end up terminating escalation for an agent, not on the basis of toxicity, but because you appear to have reached the limit of its efficacy," he said. Such pharmacodynamic assays could be a part of an adaptive clinical trials design, he noted.

Dr. Doroshow emphasized the importance of demonstrating a mechanism of action early in a clinical trial to validate one's presumptions in this regard. "We have an enormous number of presumptions going into first-in-human studies, and often those presumptions are wrong," he said. "It's critical to get this proof-of-mechanism information for the subsequent development of which combination to utilize. If you don't have an assay to demonstrate target inhibition, it's almost impossible to develop an appropriate schedule, in terms of relating systemic exposure to the targeting effect." Thus, NCI is currently developing more than 50 assays for evaluating the mechanisms of action of molecularly targeted agents, Dr. Doroshow reported (see Appendix A).

Dr. Steven Piantadosi, director of the Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai Medical Center, stressed that some sort of factorial clinical trial design must be used to investigate the interactions of agents when they are used in combination, and that there be enough sampling points in the "two-dimensional dose space" from which researchers can reap adequate information about how the response changes over that two-dimensional surface. Dr. Lutzker added that "modeling the dose–response curve is really critical in that aspect."

Repetitive Tumor Biopsies

As a means for assessing whether drug agents are hitting their targets in patients, several conference participants suggested conducting assays on repetitive biopsies of patients' tumors. Dr. Cantley also suggested examining repeat biopsies from clinical trial patients to assess not only

whether each target of a combination therapy has been hit individually, but that "you have hit something that you know should be a consequence of inhibiting both," he said.

In addition to analyzing patient tumor samples prior to a clinical trial, Dr. Engelman noted that his research group biopsies every patient who becomes resistant to a tested targeted therapy. As many as five biopsy cores are taken in one procedure, at no greater risk to patients than a single biopsy, because these cores are removed through a single transducer needle that makes only one puncture to access tissue specimens from the site. "We could be more aggressive about getting tissue for lots of studies," he said. Dr. Engelman added that patients are more than willing to have such biopsies performed.

Dr. Perlmutter agreed about the general willingness of patients to have needle biopsies performed, but noted some situations in which a biopsy may not be feasible. "I don't think you would ask a brain cancer patient to give you a biopsy, but many cancers are biopsied," she said. "Patients are often more than happy to provide multiple biopsies, but doctors often do not request them," she added, stressing that a trial should get as much data as possible and patients generally recognize that providing specimens is in their best interests. Dr. Cantley added that the combination of clinicians and patient advocates stressing the importance of the biopsies required in the clinical trials he has been involved with has led to patient willingness to have these biopsies performed and to enroll in protocols in which such biopsies are mandatory.

Dr. LoRusso stressed that serial biopsies of patients are the best way to assess "not so much what went right, but more importantly what went wrong" in a clinical trial. She said within the previous year, her research team used full-time technicians to biopsy at least 300 out of 500 patients. "I feel we are still relying too heavily on surrogates and I haven't found many surrogates that have led me down the appropriate path of taking that drug forward into the appropriate patient subset," she said. She added that imaging results are also inadequate surrogates. She uses imaging, such as PET or DCE-MRI (dynamic contrast enhanced-magnetic resonance imaging), to assess treatment effectiveness during the course of a clinical trial, but these are very expensive, she said, "for the amount of information that we are not getting because of the variability of multiple factors, including the heterogeneous patient population in a Phase I trial."

Determining Appropriate Dose and Schedule

Several participants noted that it can be challenging to determine appropriate dosing because of the variability in how patients respond to different agents. Dr. LoRusso raised the question of whether "all doses of

combinations are created equal or do we need to personalize the doses of the individual drugs relative to the mutational status and changes in the tumor," which she said no one has explored yet, but added "it's not an insignificant issue and I don't think we can forget it as we are developing these combinations." Dr. Doroshow suggested that NCI's toxicogenomics program (see Appendix A) should help researchers find correlations between pharmacokinetics and systemic exposure with the genomic profiles of various tumors according to the class of drug being tested. This information is being made public as it is gathered.

Dr. Chen suggested that if the goal of the therapeutic outcome is to achieve a sustained major response or cure, then one should consider giving short but intensive doses that are lethal to the tumors. If that goal is not achievable and continuous therapy exposure is required, she suggested that lighter, less intensive therapy may have to be given so it can be tolerated, or that combination therapy be given sequentially rather than concurrently.

Dr. Chen added that hundreds of clinical trials testing combinations of these targeted agents reveal they can be quite toxic. Often there is an increase in the severity and frequency of the known toxicity of the single agents used in combination, although sometimes new toxicities arise. In some cases there appeared to be synergistic toxicity, perhaps due to the nonspecific targets of these molecules, and significant dose reductions were required. Some combinations, such as the VEGF (vascular endothelial growth factor) inhibitor sunitinib and the mTOR inhibitor temsirolimus, had to be abandoned because of their combined toxicity.

According to Dr. Chen, combinations of agents that target parallel pathways are less likely to have overlapping toxicity and are better tolerated, as are agents with more specificity. She added that combinations appear to be less tolerable if they target the more downstream elements of signaling pathways. In all cases, the maximum tolerated dose based on cycles one and two do not appear to predict long-term tolerability. Dr. Chen stressed that what she has learned from all these clinical trials is that full doses of each individual agent are often not tolerable in combination, and that the adverse effects on normal tissues may limit the spectrum and degree of duration of combined target inhibition. This raises numerous questions about the best way to develop a combination dosing strategy to reduce toxicity. These questions are probably best addressed with more intensive preclinical studies to determine the optimal dose and schedule, she said. Such dosing will probably be based on the pharmacodynamics or pharmacokinetics required for synergism, keeping in mind that the dose required for synergism may not be the same as that required for single-agent activity, she said.

Dr. LoRusso pointed out that the maximum tolerated doses of the

drugs used in a combination are not necessarily meaningful. "There are various trial designs that could actually hurt you sometimes more than help you, depending on which is the most important drug, and how the ratios need to be defined in the clinical scenario," she said. She added that often toxicities, such as rashes, are expected to be worse in combinations of drugs if each drug has shown such a side effect in Phase I trials. Dr. Herbst noted that about half of the combination targeted cancer therapies currently being tested clinically have shown dose-limiting skin toxicity. However, sometimes the side effect is not seen in the Phase I trial of the combined drugs. Also, additional toxicities not predicted by single-agent studies can surface when the drugs are tested in combination. "What we sometimes can predict or theorize based on preliminary monotherapy data may not actually come true when we do the combination," Dr. LoRusso said.

Dr. June added that the T cells used in cell-based immunotherapies are living and often long lasting and self-replicating, so they have different pharmacologic and pharmacokinetic parameters than drugs for which simple clearances can be assessed. Because of this, a clinical trial design quite different from a standard Phase I approach is needed. For example, in a Phase I clinical trial of a cell-based immunotherapy, his research group tries to identify an optimal biologic dose rather than the more standard maximum tolerated dose.

Appropriate Endpoints and Other Study Measures

Researchers are finding that immunotherapies such as Provenge and various tumor vaccines used to treat cancer often extend survival without delaying time to progression, Dr. Schlom pointed out. These therapies often stabilize rather than diminish the size of tumors and may also extend survival without diminishing the growth rate of metastatic cancers. These findings suggest that traditional endpoints may not be appropriate for clinical trials of immunotherapies, according to Dr. Schlom, and that overall survival might be the best indicator of their effectiveness. It is not clear whether this applies only to combination immunotherapies or also to treatments that combine an immunotherapy with standard chemotherapy or targeted treatments. However, he noted that preliminary data from one study (NCI, 2011b) showed that a tumor vaccine combined with docetaxel did extend time to progression over the docetaxel treatment given singly. Dr. June added that for many immunotherapies, determining the optimal biologic dose is the most appropriate aim of Phase I studies, as opposed to determining the maximum tolerated doses. Especially for immunotherapies that apply live cells, such as modified T cells, the typical dose-escalation Phase I clinical trial design is not appropriate, he said.

A few participants suggested there should be higher standards for clinical response in trials of combination therapies. "Given the fact that we will be running out of patients and resources [to test combination treatments], we need to be setting our bars way higher than we are," Dr. LoRusso said.

Dr. Wendy Demark-Wahnefried, associate director for Cancer Prevention and Control at the University of Alabama at Birmingham Comprehensive Cancer Center, encouraged researchers to include lifestyle factors, especially measures of energy balance and obesity, when assessing the effectiveness of combination therapies because obesity has been shown to affect some of the same molecular pathways targeted by certain cancer drugs. Breast and endometrial cancers, for example, are hormonally driven cancers that are affected by obesity, she said, and collecting body mass index data at baseline and at follow-up of patients with these cancers being treated with combination therapies could provide useful information. Dr. Cantley agreed, adding that prostate, colorectal, and pancreatic cancers are also affected by obesity, presumably through its effects on IGF1, and that he has suggested to industry to modulate those effects by using the diabetes drug metformin in clinical trials. "This is something we're very much aware of," he said.

Dr. Chen stressed that though many targeted therapies show evidence of being therapeutic in the clinic when used singly, many of those treatments fail clinical trials when they are used in combination. For example, VEGF and EGFR inhibitors showed no effect when given with chemotherapy to treat several cancer types, including colon, pancreatic, kidney, and breast cancers, she pointed out. Combinations that target mTOR have also failed Phase II or III trials. "Do we have a failure of the hypothesis or a failure of the clinical trials because we did not use the right dose or choose the right patients? All these possibilities are possible for different scenarios," she said.

Speeding Up the Collaborative Clinical Trial Process

Dr. Vassiliki Papadimitrakopoulou, professor of medicine in the Department of Thoracic/Head and Neck Medical Oncology at MD Anderson Cancer Center, pointed out that multiple steps need to be satisfied to have several pharmaceutical companies and academic institutions collaborate in combination therapy trials of investigational anticancer agents, including coordinating Institutional Review Board (IRB) reviews, data sharing and analysis, intellectual property agreements, Investigational New Drug (IND) applications, etc. It can take years to accomplish all those steps so that a collaborative, multisite clinical trial of combination therapy can begin. There is concern that during that lengthy start-up

time, scientific advances will occur that might indicate that the combinations in the trial are no longer the most promising ones to test, she pointed out. "We need to speed things up," she said.

Dr. Cantley added that a major time impediment is acquiring the IRB approvals from multiple institutions. He suggested that presenting a strong trial concept initially to the IRBs can help speed things up, as can having regular face-to-face meetings and teleconferences, and having investigators with clinical trial experience on a research team, in addition to the Principal Investigators, to provide valuable advice and help others to benefit from their experience. Dr. Papadimitrakopoulou suggested that patient advocates can help speed up the process by putting more pressure on academia to make their IRBs more expedient. Dr. Perlmutter suggested that every multicenter trial have a single IRB[12] and noted that for the I-SPY 2 TRIAL there are 15 different versions of informed consent. "It certainly adds expense and confusion that is totally unnecessary," she said. Dr. John Hohneker, senior vice president and global head of development of the Integrated Hospital Care Franchise at Novartis Pharma AG, added that many institutions are afraid to commit to and execute an agreement without having their own IRBs approve it.

Dr. Flaherty suggested that time and resources could be saved in the long run if there were a precompetitive venue for testing drug combinations in a limited number of patients—less than 20—to more rapidly sift out combinations likely to be effective in the clinic. Sponsors would have an incentive to contribute their drugs to such a system because it would be an efficient way of triaging combinations that they do not have the resources and the time to test, according to Dr. Flaherty. "We need to create some kind of mechanism for cranking through these combinations in relatively small patient numbers in a much more rapid fashion than we currently have the capacity to do," he said.

Drs. Christian and Flaherty also called for strong patient advocacy to support a list of vetted important targets and combinations that should have priority status for clinical tests. "Figuring out a way of having a rolling, ongoing dialogue about prioritization is absolutely critical for the early combinations," Dr. Flaherty said. Dr. Christian added, "There are all these patient advocacy groups and we just need to figure out how to make them talk to each other about this most important topic."

[12] On July 26, 2011, the U.S. Department of Health and Human Services announced that the federal government is contemplating various ways of enhancing the regulations overseeing research on human subjects, as described in an Advance Notice of Proposed Rulemaking (HHS, 2011).

4

Overcoming Cultural Challenges to Collaborations

Many participants addressed a number of cultural challenges to collaborations, including

- Competitiveness and unwillingness to share data and resources;
- Tendency to focus more on developing blockbuster drugs than achieving breakthroughs;
- Resistance to innovation; and
- Lack of experience and resource investment by some pharmaceutical companies in immunotherapies used in combination therapies.

Suggestions from Various Workshop Participants on Overcoming Cultural Challenges to Collaborations

- More communication and transparency among collaborating partners
- Greater involvement of patients in determining how tissue resources are shared and used
- A safe harbor for industry to facilitate greater availability of failed investigational compounds for research
- Financial incentives to encourage more collaboration
- Restoring the research and development focus of pharmaceutical companies

COMPETITIVENESS

Although companies are by nature competitive and that can impede collaboration, several participants mentioned the willingness of drug companies to collaborate in the development of combination cancer therapies, especially if they suspect their investigational agent would work better with another company's drug and they did not have something comparable in their portfolio. "They would rather do it with two of their own drugs, because it makes life easy, but if it's a really good idea, there is a lot of willingness to collaborate," Dr. Engelman said, based on his experience working with several drug companies. Dr. Cantley concurred, adding, "The barriers are not that high if the data are really convincing. Where there's compelling science, people will want to collaborate. Companies are very forward thinking about it."

Dr. Lutzker said that even when a company already has a similar compound in development, if another company's compound is performing better and would increase the likelihood of a successful combination, "we would go after that company to do a codevelopment plan. It just has to do with where you are in your own portfolio." Dr. Canetta added that when he is asked by the press how his company's competition is going with Roche, in regard to developing new melanoma drugs, he responds, "We are competing against melanoma, not Roche, and if there are modalities that make sense to put together, that's what we will do."

Dr. Blackman stressed the need for communication, collaboration, and transparency among companies developing cancer therapies. "We have to realize that we are all pretty much working on the same things, and the only way we will succeed is to list indications we would be willing to go to with our own internal combinations and maybe with the partner combination. At least in these early phases, we need to talk to each other, and make sure that we agree that we are either going to all go into the same space because we think there is some compelling biological reason and fundamental differences between the agents, or we are going to go in different directions to cover more ground and learn more as a field about where this combination may be active." Dr. Lutzker noted that he has had a lot of discussions with companies in which they've made each other aware of what is in their drug development pipelines for combinations.

Dr. Blackman suggested that there be more collaborations between academia and industry in which academic institutions conduct the retrospective analyses of samples and data from previous trials and other studies to find biomarkers for patient selection so that the next clinical trials can be more successful and compounds are not shelved prematurely because a lack of patient selection made them perform poorly in clinical trials.

SHARING RESOURCES

The discovery of such biomarkers often depends on the availability of annotated patient specimens from previous trials and other studies. Dr. Cantley stressed that more effort should be made to collect patient specimens during clinical trials, and to store and make these tissues available for future research on biomarkers. Dr. Perlmutter suggested that NCI's Cooperative Groups, which conduct many of the government-funded clinical trials for cancer, be required to do more tissue banking and to share patient specimens collected. "Patients are getting quite impatient that they sometimes are asked to sign a consent that says 'Let my tissue be used elsewhere,' and the initial institution refuses to send it. Patients are now forming together to add text into their informed consents that says 'you can only use my tissue if you will publish the analysis you do and openly share the tissue,'" she said.

Dr. Hohneker added that there is substantial variability in how IRBs interpret patient consent to grant the use of their specimens and data collected during the course of a study for the purposes of another research project. "We need very vocal patient representatives on IRBs that can bring in the fact that patients want the option [to share their specimens with other researchers] and that would help enable that data be available in the future," he said. Once patient response biomarkers are discovered and validated, the next challenge is to have physicians routinely use them for their cancer patients and make them part of their standard of care, Dr. Engelman pointed out.

Several participants mentioned that it can be challenging to acquire failed compounds, biologics, and other investigational drugs for academic studies. "There are a number of drugs that pharma works with that are on target, but don't survive the preclinical testing. These compounds would be very valuable to investigators working at the cell biology level. I would hope that they could be made available," Dr. Stern said.

Dr. Michael Caligiuri, director of the Ohio State University Comprehensive Cancer Center and chief executive officer of the James Center Hospital & Solve Research Institute, agreed and said, "It is still exceedingly difficult for academia to get ahold of two or three investigational agents that come from two or three different companies, and lots of investigators are spending lots of money synthesizing compounds that already exist on company shelves." His own institution has invested several hundred thousand dollars a year to synthesize these compounds, he said, and sponsored, along with other partners, a roundtable that resulted in a white paper on how to overcome the obstacles to sharing drugs for preclinical studies (OSU, 2011). Dr. Schlom showed a long list of potential immune stimulants housed by industry that other researchers have not

been able to access, and said that lack of access has held up the field (see Table 4-1).

Dr. Flaherty agreed, saying that access to drugs should be the number one priority. "Until we figure out a way to improve that, then the other things, such as the need for surrogate endpoints, aren't really as critical," he said.

Recently, NCI has procured or synthesized several hundred molecules with anticancer potential (see Appendix A). Dr. Doroshow said NCI can supply these compounds to NCI intramural scientists and to its contrac-

TABLE 4-1 Rankings of Immunotherapy Agents with High Potential for Use in Treating Cancer

Rank	Agent	Agent Category
1	IL-15	T cell growth factor
2	Anti-PD1 and/or anti-B7-H1 (PD-1L)	T cell checkpoint blockade inhibitor
3	IL-12	Vaccine adjuvant
4	Anti-CD40 and/or CD40L	Antigen presenting cell stimulator
5	IL-7	T cell growth factor
6	CpG	Vaccine adjuvant
7	1MT: 1-methyl tryptophan	Enzyme inhibitor
8	Anti-CD137 (anti-4-1BB)	T cell stimulator
9	Anti-TGF-β	Signaling inhibitor
10	Anti-IL-10 receptor or Anti-IL-10	Suppression inhibitor
11	Flt3L	Dendritic cell growth factor/vaccine adjuvant
12	Anti-glucocorticoid-induced TNF receptor (GITR)	T cell stimulator
13	CCL21 adenovirus	T cell attracting chemokine
14	MPL	Vaccine adjuvant
15	PolyI:C and/or PolyICLC	Vaccine adjuvant
16	Anti-OX40	T cell stimulator
17	Anti-B7-H4	T cell checkpoint blockade inhibitor
18	Resiquimod and/or 852A	Vaccine adjuvant
19	LIGHT and/or LIGHT vector	T cell stimulator
20	Antilymphocyte activation gene-3 (LAG-3)	T cell checkpoint blockade inhibitor

SOURCES: Schlom presentation (June 14, 2011) and Cheever, 2008.

tors, but not to extramural investigators. A program is being established to allow investigators to submit requests for in vitro studies of the effects of specific combinations of these investigational agents (Mayfield, 2011).

Industry representatives expressed a varied response to the request to share investigational drugs. Dr. Lonberg responded that the supply of study drugs is not limitless, and that the scarce supplies of these drugs forces even large companies to prioritize the studies in which they are used. Dr. Bachman pointed out that GSK puts their failed compounds in places such as Sigma Chemical Company, where others can easily access them. "We try to freely give those out. It's just a request that is sent." He added that GSK is also making available to all academics the epigenetic toolbox it has created to study epigenetic effects in studies of cancer drugs. GSK also publishes in the public domain[1] its genomic and other data on cell lines or compounds that are not relevant to the intellectual property (IP) of one of its molecules, including test results for a number of inhibitors on nearly 300 cell lines.

Dr. Caligiuri suggested the development of a safe harbor for industry where risk is mitigated and the compounds are distributed in a responsible fashion with meaningful collection and sharing of the data. Dr. Bachman noted that he is willing to share his industry's compounds with researchers in academic institutions, but the intellectual property (IP) language of those institutions contradicts that of the industry's, and the lawyers are often unable to work out an agreement authorizing the sharing of the compounds. "Everyone is risk averse," Dr. Caligiuri explained. "Unfortunately, attorneys are hired to protect universities and they miss the big picture."

Dr. Cantley noted that his organization uses financial incentives to foster collaborations. "If you just pay a bunch of people's salaries and ask them to work together, you'll get them to work together, but if you actually hold above them a million and a half dollars and say, 'if you do that, we'll give you the money,' there's a reward for actually getting them to do what we need them to do," he said, and noted the investigators are only paid for patients as they enroll them, "so there's some money up front to get people playing [together]."

RESISTANCE TO INNOVATION

Participants cited another major impediment to progress in combination therapies: the drug industry's reluctance to embrace innovation and its tendency to want to run business as usual. For example, Drs. Schlom and Flaherty said this attitude is especially impeding progress in cancer

[1] See https://cabig.nci.nih.gov/caArray_GSKdata/ (accessed December 14, 2011).

immunotherapeutics, which do not fit the typical drug development paradigm, as they often involve cells rather than compounds, and show different functionalities depending on their dose and how they are combined. Many potential immune stimulants have failed standard preclinical tests run by pharmaceutical companies because singly they are not effective at the maximum tolerated dose, but there is abundant evidence that when these "failed" compounds are used with tumor vaccines at lower doses, they enhance the vaccine's efficacy, Dr. Schlom pointed out. "But it's alien to them—immunotherapy is still something that most pharmaceutical companies don't want to deal with right now," he said.

Dr. Flaherty added that "what has held back progress in this area is that individual sponsors wanted to see that they are in sight of the finish line, in terms of having an approvable drug, either as a single agent or in combination with an archival therapy—something that's stable and static and not a moving target. But we can't wait for each of those agents to find their home as single agents. All of these immunologics were stalled because they didn't have single agent activity and therefore a finish line in sight." He stressed that this thinking goes contrary to the notion of what he called "codependent targets"—targets that will only demonstrate real benefits in combination with other therapies.

Dr. Hohneker pointed out that the manufacturing and development of the biologics used in immunotherapy is not a core competency of every pharmaceutical company. Immunotherapies require a major investment of resources that some companies have not yet made, and are not willing to make until there is more proof of concept demonstrated in this area. Dr. Munos noted that the "play it safe" attitude of most pharmaceutical companies has taken industry away from making breakthroughs. "We've encoded so-called 'best practices' into standard operating procedures, hoping that this would replicate past successes, instead of finding new breakthroughs," he said. Dr. Munos noted that the drug industry has shifted its resources away from early discovery research into late clinical trials, and suggested "bringing back the passion for R&D [research and development]. There's hardly been a breakthrough in history that was not underpinned by a lot of passion. We need to bring that back and focus on breakthroughs, not blockbusters." He suggested such research could be financially supported using the resources currently being spent to test compounds that are of limited clinical relevance and likely to give an incremental benefit at most.

5

Legal Issues in Collaborations

Legal issues can act as impediments to collaborations to develop investigational combination therapies for cancer. These issues include sharing risk and indemnification, allocating intellectual property rights, and forging agreements between industry and government.

Suggestions from Various Workshop Participants to Address Legal Issues in Collaborations

- Giving patients more autonomy in deciding how much risk they are willing to take with experimental therapies
- Beginning conversations about collaboration and IP at an earlier stage of development
- Reserving IP protections for direct drug candidates, and embrace precompetitive collaborations for work upstream of specific candidates
- Developing standardized material transfer agreements, perhaps modeled on those used by the National Cancer Institute's Pediatric Preclinical Testing Program
- Specifying upfront those aspects of an agreement that are negotiable and those that cannot be changed
- Restricting collaborations to research and development to avoid antitrust violations

INDEMNIFICATION

Dr. Hohneker said that a major stumbling block for developing combination therapies with multiple sponsors and investigators is determining patient safety and attribution of and reparations for serious adverse effects that patients may incur during the course of a clinical trial. This can be particularly nettlesome for combination therapies of investigational agents for which the toxicities are not fully known. Determining indemnification and having institutions share risk in clinical trials is a major issue for combination immunotherapy clinical trials, Dr. June noted.

Dr. John Mendelsohn, president of the MD Anderson Cancer Center, suggested that if patients and FDA are willing to accept the risk of unexpected toxicities, clinical tests could go forward with such combination therapies. If a new toxicity develops, the clinical trial could then be suspended for 3 months or so until animal models reveal more appropriate dose combinations to test, he said. Dr. Saber indicated that FDA would not be averse to such a scenario, but thought the drug industry would be more cautious and unwilling to pursue this testing tactic. Dr. Mendelsohn added that "the biggest risk aversion occurs in our own IRBs—they are the ones slowing things down more than anything. We must work with them to teach them that if the patient wants to accept the risk, it's okay."

INTELLECTUAL PROPERTY

Several speakers pointed out that solutions are needed for some of the thorny intellectual property issues that arise with combination therapies, especially those with more than one industry sponsor. Dr. Schlom pointed out that a major impediment to companies sharing their cell lines and drug candidates preclinically is intellectual property issues, while others stressed that intellectual property rights impede clinical trials of combination cancer therapies.

As Ms. Anishiya Abrol, associate at Hogan Lovells, pointed out, intellectual property agreements can be complex because a number of variables have to be decided, including who owns the compound and the process for manufacturing it, as well as who owns the data and new indications that might stem from the collaborative research. All parties also have to agree on how patents will be enforced and whether patents will be worldwide or only focused on certain key countries. Trade secrets may still have to be protected even if no patentable inventions result from the research.

"These are difficult questions to ask and answer at a very early stage," when there is so much uncertainty about what will result from the collaboration, Ms. Abrol said. But she added that "there's been discussion

about having these conversations earlier and earlier." She noted that early in drug development research, companies and academic institutions use material transfer agreements that include intellectual property protections for preliminary collaborative research.

"Ideally, we'd all like to say that we freely exchange knowledge and allow people to go forth and use that knowledge to develop new products. But ultimately, the real value comes from the patent and the ability to exclude others from making, using, offering, and selling that product. That ability to exclude others is what really garners the economic value of a patent, and which is why IP usually is a stumbling block in many instances because there are a lot of costs that go into developing these products that have to be recovered," Ms. Abrol said.

Dr. Munos took a more negative view of intellectual property and called it the "IP fortress" that causes companies to attempt to maximize the value from all their IP and impedes sharing. "It's the legal equivalent of being pennywise and pound foolish because overall it is very counterproductive," he said. "A good rule for sharing is let's not get hung up in IP. Knowledge is not competitive, it's precompetitive. Everything upstream for a drug candidate is basically knowledge, and it shouldn't be encumbered by any IP. IP clearly starts when you have a direct candidate, but the industry should join hands and forces upstream of drug candidates, in order to bridge the knowledge gap and improve our understanding of basic cell biology and pathology," Dr. Munos said.

One positive example of such collaboration that Dr. Munos gave was that of the Structural Genomics Consortium (Wellcome Trust, 2011), whose aim is to determine the three-dimensional structure of medically important proteins using a high-throughput approach. A consortium was created for this project because "just hammering out all the confidentiality agreements and so forth in order to do the job would take more effort and more resources than to do the work in itself," Dr. Munos said. "When it comes to IP, there is some indication that we're clearly beyond decreasing return and into negative return," he added. Other encouraging examples in which IP issues were successfully dealt with so that collaborative research could proceed are the I-SPY 2 TRIAL, the Biomarker-based Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial and work of the Biomarkers Consortium (see Appendix A).

Dr. Chen pointed out that CTEP has modified the IP language in the Cooperative Research and Development Agreement (CRADA) for individual agents to "provide a platform to allow for combination studies." Dr. Jason Cristofaro, intellectual property advisor at the NCI Division of Cancer Treatment and Diagnosis, expanded on CTEP's efforts to foster collaborative, multisite cancer research. CTEP currently has more than 80 collaborative agreements with pharmaceutical companies that use its net-

work of Cooperative Groups, which includes more than 3,100 academic institutions and cancer centers that conduct clinical cancer research. The advantage of working through CTEP is that it offers a single framework by which drugs are entered into the drug development pipeline and are tested at a multitude of different locations, without the need to negotiate separate agreements at each of these sites.

The CTEP agreement includes stipulations about how intellectual property rights will be granted to a drug sponsor. This IP option was modified in September 2003 to provide non-exclusive royalty-free (NERF) commercialization licenses for inventions arising from combinations studies. Dr. Cristofaro noted that there are 150 combination clinical studies currently being pursued in cancer. Two-thirds of these—100 studies—are CTEP-sponsored studies because the NERFs removed the risk from the partners to combine agents in studies, he said.

Dr. Cristofaro explained that if studies show that a combination of therapies is more effective than the single agents used separately, that result is a patentable invention. The new IP option gives both parties who provided the single agents in a combination therapy trial the right to exploit that invention. They still have to negotiate with each other if they want to move their combination forward, but they do not have to negotiate with a third party who otherwise might have ownership of the combination in the invention. "This has been enormously successful at providing the framework that encourages folks to do combination studies," he said.

CTEP modified the IP provision of the CRADA again in 2009 because it lacked provisions for certain rights related to the disposition of inventions, such as biomarker assays, that are generated from the patient samples and data collected in the study. The latest IP provision divides inventions into those that stem from the drugs tested, and those that were developed during the course of a study that did not use or incorporate the pharmaceutical agents. The latter group of inventions would cover the data that could lead to the development of biomarker assays, and the new IP provision grants collaborators the license to use this intellectual property for their own research purposes.

The IP provision also grants a label license that enables the companies to use the data and information they receive on the invention in their label for the drug or drug combination. This limited commercial label license does not grant the right to make and sell the assay or invention that has been created, so the academic testing sites can still partner with small diagnostic companies to develop diagnostics using the biomarker data collected in a clinical trial, and the diagnostic companies can still sell, make, and profit from the diagnostics, with the understanding that the original collaborator will still have the right to put the information

on their label. Many drug industries view this arrangement favorably because they do not want to get involved in creating diagnostics for their drugs, according to Dr. Cristofaro.

Dr. Sherry Ansher, associate branch chief of the Agreement Coordination Group at NCI, stressed the importance of that biomarker language in the new IP option by pointing out that of all the new clinical trials entailing treatment studies done under INDs, 80–85 percent of them for 2010 included embedded correlative biomarker studies. She added that since the inception of this IP option into material transfer agreements, "there has been a huge increase in the number of material transfer agreements that we've been able to execute, and about 10 percent of those are for combinations." Dr. Ansher also pointed out that there are specific material transfer agreements that have been developed for NCI's Pediatric Preclinical Testing Program (PPTP). The eight institutions currently involved in the PPTP agree to do a subset of testing on pediatric tumors to determine agents that should be prioritized into clinical trials. "This program has been successful and may be something to build on as a model for adult clinical trials as well," Dr. Ansher said.

But Ms. Deborah Banker, vice president of research at the Leukemia & Lymphoma Society, pointed out that CRADAs often are not sufficient for a combination trial to proceed. Dr. Ansher speculated that might be because of outstanding scientific issues or issues on the part of the drug company, such as the study not being a priority. "Companies have to expend resources by providing the drugs to us for their studies and oftentimes, they don't fit with their development plans," she said. "We do think that's changing as companies realize that they actually can get more out of their agents by putting them into combination earlier, because for some of those agents that have minimal or no activity on their own, this may be a real area where they can benefit in combination with other therapeutics."

Mr. Wes Blakeslee, executive director of Johns Hopkins Technology Transfer, discussed the IP challenges involved in industry–academia collaborations. He pointed out that a major IP impediment is that universities cannot grant companies in advance licensing to subsequent technologies that result from studies done collaboratively. "We don't know who the inventors are going to be on the subsequent inventions so I can't prenegotiate a deal for inventors that I don't know," he said. "This is one of the areas that people think is difficult to deal with, but we don't have any trouble figuring out how to do this," he added. Such negotiations are easier if the lawyers from all parties understand this issue, Mr. Blakeslee said.

Mr. Blakeslee also stressed that when pharmaceutical companies sponsor research at universities, the universities are reimbursed for their costs and services; the indirect cost provided for in contracts with indus-

try (in addition to what researchers are paid) is not for profit. He pointed out that although leadership at his academic institution believes the university should own the IP resulting from a study that uses the expertise of its investigators, it is flexible in giving industry sponsors the opportunity to acquire a license to use that IP. "Usually the option you get for that license is a very fair and reasonable one. I don't know of one sponsored study at Hopkins that's generated IP and the company who sponsored the research didn't get it on terms that were very favorable to them," Mr. Blakeslee said. He added that because Johns Hopkins University is a tax-free entity, it is restricted from doing any commercial work. This restriction prohibits the university from entitling sponsors to any of the IP that results from studies in advance of the study being done. Johns Hopkins also has a charter that stipulates that researchers have to be able to publish their research results.

Dr. Schlom raised the issue of the excessive amount of time needed to finalize collaborative agreements. "I know these are referred to as products. But they're also potential therapies and people are dying while these things take a year and a half to 2 years for no good reasons," he said. Dr. Cristofaro agreed that the CRADA process involves several layers of review that can have multiple iterations and be time consuming. He added, "Standard agreements don't work because lawyers want to tinker with them so they best represent the interests of their clients—that's what good lawyers do."

Dr. Ansher noted that she did an agreement in as little as 4 months because of the motivation of both the company and NCI to move things forward. She said one way of speeding up the contracts process is to specify what aspects of an agreement are negotiable and what aspects, such as data sharing and publication rights, cannot be changed. Dr. Cristofaro called for developing core principles that must be followed in any agreement. Dr. Martin Murphy, CEO of the CEO Roundtable on Cancer, elaborated on the standard clauses the CEO Roundtable developed for agreements between industry and academia (see Appendix A). Ms. Lydia McNally, vice president, and head of Oncology Patents at Novartis Pharmaceuticals Corporation, agreed that "it is the core principles that matter, as opposed to model agreements, because we have to look at every drug or compound differently. But having core principles really makes the process much quicker because everyone is starting at the same place, and just minor tweaking is needed for the specific situation."

Mr. Blakeslee added that it can be expedient to identify the appropriate person to contact in the company about a material transfer or other intellectual property agreement, and that often time is wasted waiting for the right person to respond. "Our experience has been that delays haven't occurred when we've had a lawyer to talk to and get the deal negotiated,

but rather when there's nobody to talk to and we spend the year working our way up the line to get somebody with decision-making authority who's willing to talk to us about exactly what the agreement should look like," Mr. Blakeslee said. Ms. Abrol added, "Once you get somebody on the phone who is knowledgeable about these issues, you can cut through them pretty quickly. It's simply a matter of getting the decision maker on the phone, because often times the initial three or four rounds are people who can't make decisions."

Ms. McNally noted that Novartis saves time in its contract negotiations by not involving lawyers most of the time, but rather just using an agreed-on material transfer agreement that can be reused with the same institution for different applications. "So anytime you request a compound, we don't have to have a contract discussion, we only have to have a scientific discussion on whether or not we're going to agree for this study. The lawyers don't have to be involved at all, and that's been very effective," she said. Mr. Blakeslee said his institution has such standard agreements with most of the big pharmaceutical companies it deals with on a regular basis. "Once in a while, you go to a different division and they don't accept the company's standards and we need to start all over again. But for the most part, they work very well," he said.

ANTITRUST LEGISLATION

Although some drug companies have expressed reluctance to conduct collaborative R&D on investigational drugs with other companies because of concerns about violating antitrust laws, Mr. Robert Leibenluft, partner at Hogan Lovells, explained that these laws should not restrict such collaborations. He pointed out that antitrust laws were established to promote competition to drive innovation, lower prices, and improve the quality of products on the market. The Federal Trade Commission (FTC), which oversees pharmaceutical mergers, is most concerned with the merging of pharmaceutical companies that have research efforts in a narrow area, for which there are no comparable research efforts being done by other companies, Mr. Leibenluft said. But it is hard to predict if R&D collaborations will lead to companies having monopolies on the products that might result from them. Mr. Leibenluft noted that "the agency is a little bit reluctant to go after R&D collaborations, because they realize that many of those efforts may not end up in a product being sold."

The joint antitrust guidelines for collaborations among competitors from FTC and the Department of Justice (DOJ) can be accessed online,[1]

[1] See http://www.ftc.gov/opa/2000/04/collguidelines.shtm (accessed December 14, 2011).

he noted. The guidelines have a section on joint ventures in R&D which recognizes that if companies have complementary assets, technology, and knowledge, R&D collaborations may enable these companies to more quickly and efficiently develop new or improved goods, services, or production processes. "There's a recognition that R&D joint ventures really can be procompetitive," Mr. Leibenluft said. He added that embedded in the FTC/DOJ guidelines, there is a safety zone for R&D competition analyzed in terms of innovation markets (see Box 5-1).

To encourage collaborations, Congress passed the National Cooperative Research Act of 1984 and the National Cooperative Research and Production Act of 1993. These acts ensure that entities that register with the DOJ or the FTC before they venture into research collaborations will have limited liability and more lenient treatment. But Mr. Leibenluft noted that "antitrust counseling can get you in pretty safe territory, without having to go through the requirements of these Acts."

Mr. Leibenluft stressed that antitrust rules prohibit companies from collaborating to fix their prices and restrain trade such that together they have a larger market share and market power. "If you had collaborators that together were the only entities doing research in a certain area, that would raise antitrust issues. On the other hand, if there are lots of companies who are doing research, there is probably little concern because there are going to be lots of those products out there," he said, and the burden of proof is with the FTC. "If you're working on a collaboration for which

BOX 5-1
Department of Justice/Federal Trade Commission *Collaboration Guidelines*: Safety Zone for R&D Competition Analyzed in Terms of Innovation Markets

- Applies where there are three or more independently controlled research efforts in addition to those of the collaboration that possess the required specialized assets and incentives to engage in research and development (R&D) that would be a close substitute of activity in the collaboration; and
- In defining close substitutes, consider:
  - o Nature, scope, and magnitude of R&D efforts
  - o Access to financial support
  - o Access to intellectual property, skilled personnel, or other specialized assets
  - o Timing
  - o Ability, either alone or with others, to commercialize innovations

SOURCES: Leibenluft presentation (June 14, 2011) and FTC and DOJ, 2000.

it's very speculative whether it would result in a breakthrough, you're more likely to pass antitrust muster because you're further away from really getting to competing products, and that would mean the likelihood of competitive harm is less."

In its review of a collaboration, the FTC or the DOJ also considers the potential pro-competitive benefits and whether there are less restrictive alternatives than the collaboration. "If you don't need the collaboration [to achieve the same result], the antitrust enforcers would prefer that the competition continue," Mr. Leibenluft said. "But if there's a strong argument to be made that, on their own, companies or entities can't get to where they need to be, then that strongly supports a collaboration," he added.

Because of its concern that no one company dominate the market with its products, the FTC is also less likely to be concerned about violations of antitrust laws if there are several similar collaborations, according to Mr. Leibenluft. "A collaboration involving everybody in the pharma industry would raise more serious antitrust concerns obviously than if it's a few players, and there's others out there who have their own collaboration in competition," he said.

Another consideration is whether the collaborators will compete with each other over the product that is produced from a collaboration, or whether that collaboration also encompasses commercializing the products. "You can have an R&D joint venture, where certain efforts are made to discover something, and then both parties in the collaboration might compete with each other on marketing, pricing, and producing that product. If that happens, then the antitrust issues are much reduced because there's competition in the final product that's being sold to the market," Mr. Leibenluft said.

Companies also shouldn't be extending their collaborations to encompass areas outside the research and development area of the collaboration, he said. "The general thrust of the antitrust laws is that competition is good. If you need to collaborate, that may be fine, but you shouldn't have that spill over into things that you don't really need to be talking about or coordinating," Mr. Leibenluft said.

He summed up his presentation by stating that there are fewer antitrust concerns with research and development ventures when:

- Several comparable R&D efforts are ongoing;
- The collaborators do not already have entrenched products;
- The collaboration is limited to core research efforts, with the collaborators free to independently commercialize the resulting products; and

- It is possible to demonstrate convincing benefits that the collaboration will achieve that could not as easily be achieved independently.

Mr. Leibenluft noted that it is possible to obtain prior guidance with the FTC or the DOJ, both of which oversee antitrust laws. Antitrust lawyers are also used to advising research and development efforts. "I don't think it should be an insurmountable barrier if it's done right," Mr. Leibenluft concluded.

6

Financial Challenges

Several participants noted financial challenges linked to cancer drug development, including the expense of developing knockout[1] and other animal models, RNA sequence libraries, and creating enough study drug to test, which is especially problematic for biologics. Most of these challenges pertain to combination therapy development as well as drug development in general. Dr. Stern noted that investigators rely on RNA libraries to do screening, but those libraries are often prohibitively expensive and suggested the federal government could become involved in supporting those libraries.

Dr. Doroshow pointed out that standard grants from the National Institutes of Health (NIH) do not provide funding for validating assays, despite the growing importance of patient selection assays in clinical trials.

Dr. June noted that clinical trials for many immunotherapies are expensive because the cells need to be manufactured, "so we are paying for both the cost of the drug, which is a biologic or a cell, and the standard clinical trial costs. Raising funds is a very large challenge and the NCI grants don't cover these kinds of trials. It requires multiple kinds of support from grants, foundations, and philanthropy." He pointed out that cell therapies are not necessarily more expensive than antibody therapies

[1] A knockout mouse is a laboratory mouse in which researchers have inactivated, or "knocked out," an existing gene by replacing it or disrupting it with an artificial piece of DNA, in order to better understand how a similar gene may cause or contribute to disease in humans.

because they do not have to be given for as long a period of time. "The cost of goods for us to manufacture one of these cell therapy infusions is $15,000, which is less than 3 months of antibody therapy. Right now, patients are often getting antibodies for their lifespan. If you have a self-replicating cell that can continue to make antibodies, the cells may actually in the end be more cost-effective," Dr. June said.

7

Regulatory Issues

Several participants expressed concern that there was a lack of clarity about FDA regulations regarding combination therapies and clinical trials of investigational agents used in combination that makes industry less willing to participate in collaborations. "The regulations or their interpretations are confusing and creates all sorts of hurdles," summed up Dr. Perlmutter.

One area of confusion is the difference between a combination product versus using drugs in combination, which Dr. Richard Pazdur, director of FDA's Office of Oncology Drug Products, clarified. An example of a combination product is Excedrin®, which has aspirin, acetaminophen, and caffeine, all in the same product, he said. This is different from drugs used in combination. Although some participants expressed concern that there was a regulatory requirement that necessitatated showing the contribution of individual agents in drug combinations, Dr. Pazdur said that requirement is only for drug combination products (Woodcock et al., 2011). "Our guidance clearly states that we are not going to demand independent isolation of the effect of each of the components when you are using two unapproved drugs together," he said. Dr. Robert Temple, deputy center director for clinical science at FDA's CDER, added that "the whole idea of how you demonstrate the contribution of a combination has historically been more flexible than people imagine," and said that the agency is currently working on clarifying its rule for combination products so it can be interpreted more flexibly. "If two drugs have no

pharmacologic effect that's relevant, but do have such an effect when you put them together, that might be enough," Dr. Temple said.

Suggestions from Various Workshop Participants to Address Regulatory Challenges

- Focusing on combinations with a compelling biological rationale and strong preclinical data
- Seeking dialogue with FDA early in the development process, and frequently as development progresses
- Establishing more dialogue between FDA and the European Medicines Agency, to enhance harmonization of regulations
- Obtaining more clarification from FDA regarding the types and levels of evidence needed for combination therapies
- Getting better guidance from FDA on how sponsors should best interact with multiple FDA offices involved in combination product development

FDA DRAFT GUIDANCE

FDA recently released a draft guidance for industry on the codevelopment of two or more unmarketed investigational drugs for use in combination.[1] At the conference, Drs. Sherman and Temple discussed the major premises on which this guidance is based. These premises include the need for combination therapy, the agency's flexibility in ascertaining the contributions of individual agents in a combination, the need to demonstrate the biological rationale for the combination, and the case-specific nature of IND submissions and labeling issues for which FDA encourages sponsors to consult with the agency as early as possible and frequently throughout the development process (Woodcock et al., 2011).

Drs. Saber, Temple, and Sherman all stressed that FDA recognizes the need for combination therapy and has experience with regulating combination therapy with investigational agents, not just for cancer, but for many other diseases, including infectious diseases and hypertension. Dr. Sherman added that there are times when it is even unethical or impossible to study agents as single therapies because the agents are much more likely to be effective in combination due to the rapid development of resistance to single therapy or other factors. "With hepatitis C, resistance develops within days, so it's only possible to expose patients with

[1] See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf (accessed December 14, 2011).

the disease for literally under 3 days. One can gain a little bit of information about each compound, but not much," Dr. Sherman said. Dr. Temple added, "If two drugs together do something wonderful, who wants to be randomized to the trial to see which component contributed?" He also noted that often a new drug has to be added to another therapy that could not be omitted in a trial because it is the standard treatment with some documented efficacy, which makes it difficult to assess the contribution of the two therapies used in combination. In those cases, the agency has the label for the new drug state that it should be used in combination with the older drug. "We don't know whether the older drug is still necessary, but we live with it because what else can you possibly do?"

Dr. Sherman stressed that there should be a compelling biological rationale for the combination for FDA to consider approving it. "That doesn't necessarily mean there needs to be a greater than additive effect," she said. However, she cautioned that "perpetuating products that definitely are toxic and don't do much more than hinder the disease progression a tiny bit is not very interesting and not very patient friendly. Patients are not interested in hope and promises, but in things that work," Dr. Sherman said. She concluded her presentation by stating that "a clear regulatory pathway [for combination therapy] exists."

SHOWING THE CONTRIBUTION OF EACH DRUG IN A COMBINATION

Dr. Dagher raised the issue that even though the new FDA draft guidance is not for fixed-dose combination products, for which one would have to show the contribution of each compound used in the combination, it still seemed to suggest that sponsors would have to show the contribution of each drug used in combination to some degree, although perhaps not in a clinical trial. Dr. Pazdur responded by saying that a clinical trial with four separate arms was not going to be needed to show the rationale for combining drugs, but rather compelling preclinical information or results from Phase II trials or related information, such as relevant information about other members of the drug class that are already approved. Dr. Temple added that "there are going to be cancer therapies where most of the action comes from hitting one receptor and you are putting another compound in there to deal with the resistant tumors that grow later. Those are very hard to prove in a clinical trial, but you will have laboratory evidence that shows the resistant cells are now killed off by the added drug."

When one participant asked if sponsors can show the contribution of the agents in separate trials and not within the same trial, Dr. Sherman responded that it depended on the totality of the evidence. "It could be separate trials, separate populations, some pharmacokinetic results in

healthy volunteers, or just preclinical evidence," she said. Dr. Pazdur added that a lot of the FDA's decision making in this regard is going to be results driven. "We are looking for big results here. If you have a single-arm trial of drug A that has a 5 percent response rate, a single-arm trial of B that has a 10 percent rate, and you add these drugs together and, with reasonable numbers of patients, you have a 60 percent response rate, we'll take that," he said. Dr. Temple concurred that FDA would not require a long-term study of the single agents if they worked so well together.

But building onto Dr. Pazdur's example, Dr. Temple added that if there is a 10 percent response rate for each of the agents and only a 15 percent response rate for the combination, there is little evidence that the combination is significantly better than the single agents and a factorial study that can separate the effects of each agent in the combination may be required by FDA. "Unless you [dramatically] save people's lives, we still want to know what the contribution of each is, because there is a downside—there is toxicity from each of them so you are paying something of a price [to combine them]," he said, adding that the new draft guidance discusses the flexibility allowed in the sources of information that show the contributory effects. "We are planning to use our heads, the lab, animal data—a wide variety of sources to determine whether there is really a significant contribution," he said. When Dr. Ellen Sigal, chair and founder of Friends of Cancer Research, pressed him to define what a "significant" effect is—whether it's more than 50 percent, for example—Dr. Pazdur responded, "That's difficult to answer because it depends on the safety of the drug as well as what available therapies are around to treat that condition, and what endpoints they have been approved on or have shown in clinical practice."

EFFECT OF COMBINED TOXICITY ON SINGLE-AGENT APPROVAL

Dr. Schlom said that a major industry concern is that if two drugs that show minimal toxicity in Phase II or III trials are combined and then elicit major toxicity, neither drug will be approved by FDA as single agents. "There is no guidance about this and if FDA says it will decide this case by case we go back to the same old story—we don't know what the FDA is going to do," Dr. Schlom said. Dr. Temple added that for this scenario to happen, it would be due to something that was surprising and unexpected, and that sponsors might be required to assess which of the drugs might be linked to the toxicity. He gave an example of two drugs used in combination that caused hepatotoxicity that only surfaced after 2,000 people were tested. For such a situation, the sponsor would be asked to examine the transaminase levels in response to each of the drugs and

assess whether one of them causes abnormal levels. "It wouldn't be that hard to figure out which was the troublesome drug. If something really weird and terrible were to emerge only when you use the combination, you would have to sort out what did it. You would be worried about each of them having that side effect unless you had a cogent explanation," Dr. Temple said. But he added that wouldn't necessarily mean that approval would be denied for the single agents.

Dr. Saber said that "combinations are no different than single agents in terms of proof-of-concept and toxicology studies." She noted that FDA is flexible when it comes to life-threatening conditions and is willing to accept some toxicity preclinically. "We do allow compounds to go forward in a clinical trial knowing they are toxic. We balance the toxicity against benefit," she said. Dr. Sherman added, "With serious and life-threatening conditions, patients and their physicians are willing to take greater risk. This is a basic tenet of how the agency functions, and it applies here." Dr. Pazdur stressed that for cancer treatments, efficacy is the major hurdle to cross, not toxicity, because FDA accepts a high degree of toxicity for cancer treatments and thus excessive concern about this issue is unwarranted.

MULTIPLE INDS?

There was some discussion about how many INDs are needed for combination therapies. "Probably more than one. We're working on that," Dr. Temple said. He added that if the drugs used in the combination are in different divisions of FDA, each division will probably want to review its own IND, but if they are only being studied together and not singly, one IND may suffice. Dr. Pazdur pointed out that frequently the drugs may be initially studied together, but later might be studied individually, and Dr. Temple said that in those cases another IND will be required for the single-use study. Dr. June pointed out that few cell-based immune therapies for cancer are FDA approved, which means multiple INDs are required to test them in combination, and coordinating those multiple INDs is challenging, especially with regard to ascertaining who holds the IND and how indemnification will be conducted because there are different criteria for this at state institutions, universities, and government. "We have had to develop best practices for each of these to try to get trials approved," Dr. June said, and added that researchers often seek feedback from FDA in pre-IND meetings.

LABELING COMBINATION THERAPIES

Dr. Temple pointed out that the guidance recognizes that there will not be much dose–response information for each drug used in an inves-

tigational combination therapy, but suggests sponsors acquire as much of this information as early as possible. As for labeling requirements, he noted that sponsors can copackage their product if they want, but he assumed most would rather package their own product and have their own label. The label should specify the drugs with which the compound has been tested in combination and what those results were, and probably will say the drug should be used in combination, according to Dr. Temple. He added, however, that although Herceptin (trastuzumab) was designed for use with certain drugs with which it was tested in combination, "that didn't mean [a physician] couldn't add it to something else and it doesn't mean they actually had to use the other drug."

However, Dr. Pazdur urged sponsors to be cautious about what treatments they test in combination because the drug will be usually be labeled with that combination indicated, even if the new drug was tested in combination with a standard therapy that was not very effective. He gave the example of the new drugs for melanoma being tested with dacarbazine (an alkylating agent), which he labeled "a toxic placebo" because it is a relatively ineffective drug for melanoma. "I really couldn't understand why people wanted to marry their new drug that had very impressive response rates or potentially a survival advantage with a relatively ineffective drug," he said.

COORDINATION OF DIAGNOSTIC AND THERAPEUTIC REGULATION

Another regulatory challenge for combination therapy is the coordination between the different divisions in the FDA when diagnostic devices and drugs are used in the same clinical trial. Dr. Papadimitrakopoulou noted that regulation was a major issue for the innovative clinical trial BATTLE 2 because it involved investigational diagnostic biomarker assays in addition to investigational new drug agents. This required oversight from CDER as well as the Center for Devices and Radiological Health (CDRH), and together they required a much larger amount of data than normally would be needed for a proof-of-concept trial, which BATTLE 2 exemplified (see Appendix A). "There's a lot of novelty in these trials that creates fears about how we can do them," she said.

Dr. Temple stressed that such trials are becoming increasingly more common in oncology because it is desirable to develop a companion diagnostic that identifies patient responders, thereby preventing patients from being exposed to a drug to which they cannot respond. Dr. Pazdur agreed that companion diagnostics should be an integral part of drug development and should be explored preclinically when developing a new drug. "It's new ground for pharmaceutical companies because they must have

the interactions with either the in vitro diagnostic companies or develop that in-house expertise in itself," he said. It has been challenging for FDA as well, he added, noting that FDA staff in its oncology drug division meet with FDA staff in its in vitro diagnostic division for "every application to have a pathway for the in vitro diagnostic either to be approved or an alternative pathway to have the marker tested at the time of approval." Several pathways could be considered for this, he said, including 510(k) clearance for the diagnostic.

But Dr. Sigal noted that the time frames for developing a drug and companion diagnostic are not always parallel, to which Dr. Pazdur responded that for a life-threatening illness such as cancer, "if there is not a companion diagnostic for the drug, they will find a way around it to approve that drug. It may be using a university-based test while an in vitro diagnostic is being developed." He added, "This is an issue we have to really work on and develop with the pharmaceutical industry. This is new ground that requires attention because it is an integral part of the drug development program."

FDA VERSUS EUROPEAN REGULATION

Dr. Canetta pointed out that copackaging is not legal in Europe and in certain other countries. "For people who do global development, that is a big obstacle," he said. Dr. Dagher added that "whether it's combinations or not, drug development is a global activity." He said that the only guidance available from the European Medicines Agency (EMA) is focused on fixed-dose combinations, and he requested that "as you further develop thinking and finalizing this guidance and/or your thoughts on other rules that may be rewritten or written, any discussion with the EMA on the thinking would be helpful. We know that you can't always get entirely unanimous thinking. But from a global perspective it would be useful."

Dr. Canetta noted that the regulatory philosophy in Europe differs substantially from that in the United States. With regard to companion diagnostics, for example, Dr. Canetta said that Europe requires diagnostic tests that are reproducible, stable, and valued in itself, and "what the physician does with the test in Europe is not considered an EMA issue. It's something that the physician can utilize as a tool." However, in the United States, the diagnostic test has to be proven by validating it in a clinical setting in a particular trial in order for it to appear on the label with a companion drug. Dr. Hohneker added, "In Europe, the industry is not viewed by the investigator community as the evil empire," and instead there is more interdependence of the investigator community and industry. Because of European regulations, the pharmaceutical industry provides a lot of support to do clinical trials, whereas in the United States,

"Pharma is not wanted—they just want our money or our drugs, but they don't want us at the table because they claim it taints the collaboration or the investigation and we have to get around that. Pharma does have something to offer, both intellectually and also scientifically to the discussion and collaborations. If we really want to level the playing field between the U.S. and Europe, we have to think about the cultural barriers that exist in the U.S. that don't in Europe."

The FDA draft guidance is mainly for small molecules and not for vaccines and other products. But Dr. Dagher pointed out that there are a lot of good principles in the guidance that could apply to other kinds of products such as antibodies combined with drugs or vaccines. Dr. Sherman responded that the guidance was directed toward small molecules used in combination because that was what industry asked FDA to address, but the same principles could be applied to other types of treatments used in combination.

8

Codevelopment of Therapies for HIV as a Model

Two speakers gave presentations on how combination therapies for human immunodeficiency virus (HIV) were developed, and how the lessons learned from that experience are applicable to developing investigational combination cancer therapies. Dr. Carl Dieffenbach, director of the Division of Acquired Immunodeficiency Syndrome (AIDS) at the National Institute of Allergy and Infectious Diseases (NIAID) pointed out that HIV, like cancer, is extremely heterogeneous and because of the numerous different strains and the ability of the virus to rapidly mutate to elude the immune system, combination therapies have been key to keeping the virus in check in infected patients. "The problem with HIV is we literally have almost an infinite number of viruses," said Dr. Gary Nabel, director of the Vaccine Research Center at NIAID. "Within a single individual shortly after infection, there are essentially millions of variants, so like for cancer therapy, where the cancer cells are constantly mutating, combinations for us are very important."

In 1996, three agents were successfully combined to treat HIV after they were shown to induce rapid reduction of viral loads and led to sustainable undetectable levels of virus in the blood. Since then, the entire field of therapeutics has focused on optimizing these combinations for safety, tolerability, and dosing. Currently, more than 30 compounds are approved for treating HIV and six fixed-dose combinations are available.

Dr. Dieffenbach pointed out that since 1998, NIH's main role in HIV drug development has been to focus on strategy trials—that is, once a single agent is approved, showing how to combine it in appropriate ways

with other agents. For these studies "the industry has been really good to us, in terms of donating drugs for trials," Dr. Dieffenbach noted. His NIH division just completed a series of prevention trials using antivirals, and all of those drugs were donated, with the total cost of the drugs being approximately $50 or $60 million. "It's been a very productive partnership because we built an industry, in terms of training a series of clinicians, putting together the infrastructure to run these kinds of drug trials. That has then largely become industry supported," Dr. Dieffenbach said.

One lesson learned from this experience is the need to target two steps in the life cycle of the virus, according to Dr. Dieffenbach. Combinations that target a single step tend to have overlapping toxicities and run the risk of pharmacological and potentially virological interference, he said. He added that potency matters in terms of the dosing and the impact. "Unlike cancer chemotherapy, these are drugs that are designed to be taken every day for the rest of the patients' lives so what we want is a safe drug," Dr. Dieffenbach stressed.

THE IMPORTANCE OF SURROGATE MARKERS

HIV drug development benefited immensely from the ability to use viral load as a validated surrogate for response to therapy, Dr. Dieffenbach stressed. Dr. Nabel added that "the fundamental difference scientifically between HIV and cancer is that we really have a crystal clear biomarker—viral load—that makes it so much easier for everybody, because you really can rally to one thing. That's how we ended up getting six targets of different classes because you were all aligned to that one thing," he said. Dr. Nabel suggested that it would help the combination cancer therapy field if advocacy groups and scientists joined together to formulate a plan for showing the utility of biomarkers. "There has to be some kind of coalescence, and what may be hurting your efforts in advocacy and the scientific efforts is the lack of focus and the ambiguity and the biomarkers," he said. He added that the use of HIV neutralizing antibody as a biomarker for vaccine effectiveness has also helped the development of HIV vaccines.

It is also helpful to have a system for measuring the comparative effectiveness of various combinations, Dr. Dieffenbach pointed out. He showed a recent effort to do this in HIV by Shen and colleagues (2008, 2009). These researchers, through simple mathematical manipulations, were able to rate combination therapies on their ability to inhibit virus replication and graphically represent which ones were the best treatments (see Figure 8-1). He raised the question of whether a similar approach could be used to compare the effectiveness of combination cancer chemotherapies.

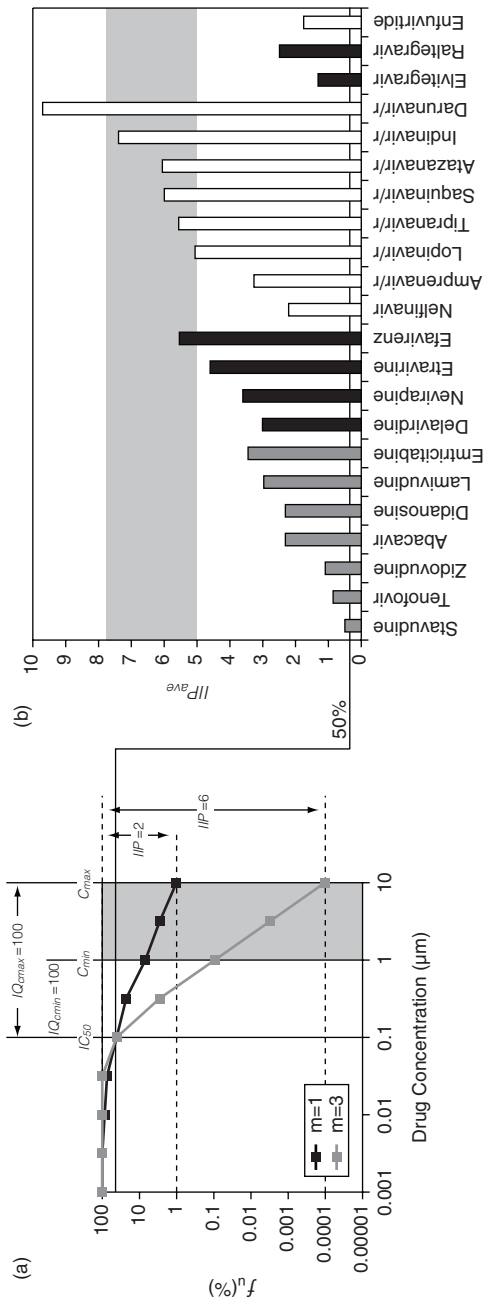

FIGURE 8-1 Instantaneous inhibitory potential (IIP) of antiretroviral drugs. The IIP of hypothetical and current antiretroviral drugs can provide insights on which drugs would work well in combination. (a) The dose–response curves for hypothetical drugs show that there is a 10,000 fold-difference in antiviral activity depending on the slope. (b) Estimates of average IIP for current antiretroviral drugs are given. The grey shaded area is the estimated range of average IIP values needed to stop viral replication in a patient with a viral load of 30,000 copies/milliliter. Only one drug, darunavir, may likely halt viral replication without a combination.
SOURCE: Dieffenbach presentation (June 14, 2011). Reprinted from Shen, L., S. Rabi, and R. Siliciano. 2009. A novel method for determining the inhibitory potential of anti-HIV drugs. *Trends in Pharmacological Science* 30(12):610–616, with permission from Elsevier.

VACCINES IN COMBINATION THERAPIES

Current areas of exploration and codevelopment in the HIV arena include vaccine-drug combinations and combination vaccines that might ultimately liberate patients from the need to continue on anti-HIV drug therapy for the rest of their lives. One approach is to use standard antiviral therapy to reduce viral levels and then use vaccines to provide a new level of immunity that gives patients the ability to control the virus once the drugs are stopped. In the United States there are 7 to 10 therapeutic HIV vaccines currently in trial, according to Dr. Dieffenbach.

Dr. Nabel noted that combination vaccines have a long history beginning with the polio vaccine. This vaccine was successful because it prompted immunity to all three strains of polio. "There's a historic precedent for a combination therapy that essentially wiped out a devastating human disease and wouldn't have happened in any other way," he said.

Three types of combinations for vaccines are being explored for HIV. One is combinations of different vectors or delivery platforms for the vaccines that stimulate qualitatively different immune responses. Another type combines different inserts in the vaccines. This approach increases the breadth of response that improves protection against diverse viral strains. The third type of combination joins drug and antibody treatments with immune stimulants. Such combinations show efficacy not seen with either one alone, according to Dr. Nabel.

One cancer-related example Dr. Nabel gave for that third type of combination treatment is standard chemotherapy combined with a vaccine aimed at boosting immunity to tumor-promoting proteins generated by human papillomavirus (HPV). He said this combination completely suppresses the growth of cervical tumors in a mouse model, whereas neither treatment alone is effective. He emphasized that "if you were to require that each agent in the combination be tested alone and approved based on a marginal degree of efficacy, you would not have approved this drug or vaccine, and you would never have gotten to test the combination. Going forward, it's really important to recognize that this criteria of having even marginal—10 percent—effects is one that's going to limit the opportunities for finding new and effective drug and immunotherapies," he stressed.

THE KEY ROLE OF PATIENT ADVOCATES

Another lesson learned from HIV combination therapy development that may be applicable to the development of cancer combination therapies is the key role patient advocates played in fostering collaborations, Drs. Dieffenbach and Nabel pointed out. "A highly educated patient population has pushed NIH and industry to do these combinations. This

productive working relationship with the activist community really has driven this type of integrated drug development," said Dr. Dieffenbach. Dr. Nabel added that there were specific granting mechanisms that promoted development in certain areas, including the NCDDG Program (National Cooperative Drug Discovery Groups),[1] which were cooperative grants between scientists and industry. "It really put together the best of basic scientists exploring specific targets with industry in a way that allowed both to focus on drug development and on scientific discovery of new targets. That really helped to spread the effort onto particular targets and made progress quick in those areas," Dr. Nabel said. Dr. Dieffenbach agreed, noting that "these grants turned out to be quite catalytic, because what happened over time is the industry got to know the leaders scientifically, and these natural bonds have continued over time."

Several participants were struck by the success of combination therapy development for HIV. "We need to, having the HIV experience as the lead, think about how to get from AZT to 32 drugs on the market, and how to use them in combination wisely," said Dr. Flaherty. Dr. Perlmutter added, "Thirty years ago, AIDS was not even really acknowledged and went from being the most lethal and scary disease to one that is relatively manageable with a cocktail. There are lots of cancer patients that are out there ready to take their cocktail."

Dr. Sharon Murphy stressed the powerful role of advocacy groups that put pressure on NIH and pharmaceutical companies. Such a loud voice given to combination therapy by advocates joining together and focusing on the same specific goals has not happened within the cancer arena, she pointed out. "We need to learn from this," she said. Dr. Perlmutter agreed, noting that the AIDS community "had crystal clear goals." She suggested researchers invite advocates to put pressure on the appropriate drug companies to have them collaborate more. "You know where it might be profitable to work early and you can invite advocates to [put pressure on] them," she said. But she added that there will not be millions of patient advocates coming together without any clear strategy, which researchers can help provide. Dr. Nabel added that mutual education between advocates and scientists was helpful in the AIDS arena. "The scientists were somewhat disconnected from what the real people with the disease were feeling and vice versa—the advocates didn't understand some of the scientific problems. When people could bridge that [educational] divide and make those connections, that's when things started to happen," he said.

[1] See http://dtp.nci.nih.gov/branches/gcob/gcob_web3.html (accessed December 14, 2011).

9

Examples of Collaborations Relevant to Cancer

During the course of the workshop, participants cited several examples of successful collaborations in the development of investigational combination cancer therapies, including preclinical and clinical collaborations between two drug companies, as well as clinical trial collaborations involving academic institutions and multiple companies, such as I-SPY 2 TRIAL and BATTLE 1 and 2, and some research funded by Stand Up To Cancer, the latter of which encompasses both preclinical and clinical drug development.

A few preclinical collaborations between two drug companies were cited. Dr. Bachman noted that GSK and Novartis are collaborating in the development of a cancer therapy that combines GSK's MEK inhibitor with Novartis's PI3K inhibitor. Although GSK had its own PI3K inhibitor in the pipeline, the GSK inhibitor had different properties from the Novartis P13K inhibitor that made the collaboration worth pursuing, Dr. Bachman noted. "Rather than just us focusing on our own inhibitor, we talked to Novartis. Similarly Genentech and Roche are collaborating on the preclinical development of a combination treatment that targets both P13K and MEK, and AstraZeneca is collaborating with Merck in the preclinical development of a combination that targets PI3K and ATK," Dr. Engelman pointed out. "It's very exciting that these companies, when they see an idea that they think is good, are willing to go through the painful process of teaming up to codevelop molecules. What's very telling here is that these companies are codeveloping molecules that aren't approved—they

are both being developed when neither one is really even that close to an FDA approval," he said.

Dr. Canetta noted additional clinical collaborations between two pharmaceutical companies, each contributing their own investigational drug. These collaborations included Bristol-Myers Squibb and Roche in the clinical testing of a combination for melanoma, and Bristol-Myers Squibb and Genentech in the clinical testing of a combination for colorectal cancer, done under the auspices of CTEP. These trials show that it is possible to do combination trials with experimental agents and address concerns about intellectual property and regulatory issues. "All that it takes is recognition of the unmet medical need and willingness to cooperate," he said.

Even more complex, multi-industry collaborations have been forged, as exemplified by the I-SPY 2 TRIAL and BATTLE 1 and 2 trials (see Appendix A). Mr. David Wholley, director of the Biomarkers Consortium, said that having the Foundation for the National Institutes of Health (FNIH) act as a trusted third party was key to forging the 19 agreements involved with the I-SPY 2 TRIAL. FNIH acts as the holder of the IND and as the manager of the IP rights that stem from the trials. Mr. Wholley said an outside legal counsel who has worked with the I-SPY 2 TRIAL and is skilled in the area of IP licensing said she was amazed that FNIH was able to garner these agreements, and noted it would not have been possible if FNIH was not a trusted third party and a nonprofit organization.

Dr. Herbst noted that the four companies sponsoring the BATTLE 2 trial have been flexible in the choice of agents the investigators have used, even as this choice evolved when more knowledge on targeted therapies emerged. "The company allowed us to work with drugs from other companies and bring other collaborators in. We have a good example where academia and industry really worked well together," Dr. Herbst said.

The PI3K team funded by Stand Up To Cancer has invested $500,000 to purchase 50–100 gram quantities of 10 investigational drugs that recently entered Phase II clinical trials and that were of interest to them for combination therapies. The team's strategy is to test these drugs as single agents and in combinations, and to immediately inform the companies that make these drugs if they observe efficacy in any of our mouse models as indicated by tumor shrinkage. They then work with the companies that make the drugs to facilitate their biomarker-driven combination trials (sometimes involving two companies).

Agents used for testing are obtained from both industry and CTEP, and accrual is facilitated by interactions with the Translational Breast Cancer Research Consortium, the Gynecologic Oncology Group, and other individual centers, Dr. Cantley noted. The PI3K team also lever-

ages complementary trials that were already in the works when the PI3K team formed.

"Collaborations with industry have offset many of our costs," Dr. Cantley pointed out. But he added that in general, it takes about a year to acquire a material transfer agreement with a company in order to use their investigational agent to test in their animal models, and most agreements stipulate the agent cannot be combined with any other drug. That has not deterred researchers on the P13K team from combining agents in their tests, however, Dr. Cantley said. "We always tell the company we're doing it. They may or may not tell their lawyers we're doing it. But we do it, and if we get a result that looks exciting, we come back and tell them and I've yet to have anyone complain," Dr. Cantley said. Instead, companies have been open to discussions on how to collaborate with each other to further test combinations where the agents come from different companies, according to Dr. Cantley. In two such cases those discussions have led to collaborative combination trials. "The barriers are not that high if the data are really convincing," Dr. Cantley said.

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Wrapping Up

Given the complexity of cancer and the mounting evidence that targeted cancer treatments and cancer immunotherapies are likely to have stronger and more long-lasting effects when combined makes it imperative to develop greater collaborations among industry, academia, and government in the development of combination investigational cancer therapies. During the course of the workshop, participants offered numerous suggestions for how to facilitate such collaboration.

In the preclinical arena, participants suggested more effort and funding to develop animal models in which to test investigational drug combinations and their mechanisms of action and pharmacokinetics, as well as resistance mechanisms. These animal models could entail tumor explants or be genetically engineered to develop tumors with the molecular defects commonly seen in human tumors. Surrogate efficacy models can be used to assess the effects of combinations of immunotherapies, which cannot be tested in standard explant models. Alternatively, researchers could create animal versions of the immunotherapies that have been developed, and test them in animals with intact immune systems. Tumor cell lines could also be grown in different microenvironments to see how they affect agents and their targets, and more effort should be made to grow tumor cell lines in three-dimensional culture situations. "There are multiple models, and we still don't know what is the best model to use to determine which combinations to go forward with," summarized Dr. Hohneker.

There could be more interplay between the bench and the bedside,

participants suggested. Researchers could use animal models to suggest which combinations of agents would be most effective at countering the specific molecular defects in patients' tumors. If clinical testing of such combinations cause toxicity or resistance, the same combinations could be retested in animal models to assess better dosing, scheduling, or the molecular resistance mechanisms and what other agents might counter them. Studies of biopsies collected from patients with tumor progression could also point toward more effective combinations of agents.

Several participants pointed out the need for higher standards for both preclinical and clinical effectiveness. Tumor shrinkage is likely to be a better endpoint in laboratory studies than blocking tumors from forming or from growing, whereas overall survival is likely to be a better endpoint than time to progression in clinical studies, they argued.

Given the numerous possible combinations and limited number of patients and other resources, there has to be some prioritization of what combinations should be tested clinically. Suggestions for prioritizing included testing only those combinations that:

- Perform well and consistently in several xenograft models;
- Have a biological mechanism for which there is an assay;
- Have demonstrated adequate pharmacokinetics and some evidence of activity or target engagement at clinically relevant doses and exposures;
- Are composed of the best in each class of agents that are pharmacologically compatible; and
- Have validated biomarkers for patient selection and pharmacodynamics.

Some participants cautioned that effective combinations should not be judged on the basis of the single-agent activity of their components, as many combinations have been found to be effective even though studies of the single agents did not show significant effects. There also was concern about the additive, synergistic, or unexpected toxicities that can result from combinations, particularly those that target the same pathways. Researchers need to explore more creative innovations in the approach to dosing and scheduling to avoid toxicity and improve efficacy, several participants suggested. Agents could be used intermittently or sequenced in a manner that makes sense from a biological, mechanistic perspective.

To aid both preclinical and clinical investigations, more basic information could be gathered on genetic expression, and feedback and network responses to signaling perturbations and DNA damage. Some participants stressed that information is also needed on the non-genetic effects that influence treatment, including the microenvironment of the tumor, the

host immune response, and proteins made by the tumor and surrounding cells.

In the clinical arena, there was enthusiasm for using adaptive trial designs to determine the best combinations and dosing strategies, and to assess patient selection biomarkers as the trial progresses. "Adaptive trial designs may really facilitate the ability to screen for drugs," Dr. Hohneker summed up. Several participants suggested repeat biopsies of patient tumors to assess effectiveness and confirm mechanism of action of investigational agents. Assessing the maximum tolerated doses of all the drugs used in combination may not be meaningful or appropriate, especially for combinations that employ immunotherapies. But researchers should have enough sampling points so they can model the dose–response curve.

Several participants suggested that different cancer patient advocate groups join together to encourage the same specific goals, particularly because such advocacy proved highly valuable in fostering rapid development of effective treatments for HIV infection. Patient advocates could be helpful in putting pressure on companies and institutions to work more collaboratively, have quicker IRB reviews, and share patient specimens. Advocates can also work with investigators to assess and promote the clinical testing of priority combinations. Mutual education between advocates and scientists can be helpful in furthering progress.

Companies could communicate more about their compounds in preclinical development and join forces when they do not individually have all the agents needed for an effective combination in their portfolios, and other companies can supply the missing agents. Compelling those collaborations will be the "good science" underlying them, Dr. Hohneker said. "If the data are there, people will work together. I don't think you'll find much resistance to good science."

More efforts should be made to collect patient specimens during clinical trials, and store and make these tissues available for future research on biomarkers, several participants noted. The development, validation, and use of biomarkers for patient selection and treatment effectiveness will be key to the success of cancer combination therapies. Easier access to study drugs would also be helpful. Safe harbors for companies and institutions, such as FNIH and the CEO Roundtable on Cancer Life Sciences Consortium, have proven helpful in negotiating collaborations and managing the patents and other intellectual property rights that result from such collaborations. A safe harbor to distribute study drugs to investigators, or to do preliminary clinical testing of combinations, might substantially further development of combination cancer therapies, many participants stressed.

Within the regulatory arena, FDA recognizes the importance of combination therapies for cancers and is currently revising its guidelines on the combination of investigational therapies and codevelopment of

a diagnostic with a therapeutic. The agency has indicated that it wants to be flexible in what is required of sponsors, and will sometimes accept preclinical data instead of extensive clinical testing of drug combinations. FDA welcomes pre-IND consultations, especially for innovative study designs. "We still will have to show the contribution of the agents, but the encouraging part is that how we do that is something that can be discussed," as Dr. Hohneker pointed out. More effort should be made to make FDA regulations compatible with EMA regulations so as to foster global drug development, some participants suggested.

To help tackle some of the other complex legal issues linked to developing combination therapies, such as IP and indemnification, there could be more reliance on NERFs and the development of standard clauses and core principles to make legal negotiations more expedient. Identifying key decision makers, who are knowledgeable about the legal issues, can also be helpful in legal negotiations. Antitrust issues are not likely to pose barriers to collaborations among companies, particularly if they will not limit competition; if the collaborators do not already have entrenched products; if the collaboration is limited to core research efforts; and if it is possible to show benefits that the collaboration will achieve that could not be achieved as easily on an independent basis. It is possible to obtain prior guidance with the FTC or the DOJ about antitrust issues. Antitrust lawyers can also advise research and development efforts.

There are several examples of collaborations in the early development as well as the clinical testing of combination cancer therapies. These collaborations show that barriers are not insurmountable and provide examples for others to follow. Particularly notable innovative clinical testing examples are the I-SPY 2 TRIAL and the BATTLE 2 trial. Several scientific tools to aid cancer combination therapy development are available in the public domain, including GSK's epigenetic toolbox and preclinical data, NCI's mechanism-of-action assays and preclinical models for combinations, as well as the investigational agents that NCI makes available for preclinical testing.

Several participants stressed the importance of doing whatever it takes to facilitate collaboration in the development of combination investigational cancer therapies. "There is really an urgency to identify solutions for the barriers because we have patients at stake," said Dr. Hohneker. Dr. Mendelsohn agreed with the urgency to speed up combination drug development, given that "one-third of our patients will not live 5 years—that's a half-million people a year." Dr. Hohneker concluded the conference by stating, "The takeaway is that for success and learning, it takes a team of people who are very committed and passionate, and willing to work together to come up with the solutions, as well as strong collaborations, persistence, good science, and the willingness to learn."

Appendix A

Examples of Collaborations

SCIENTIFIC TOOLS TO AID CANCER COMBINATION THERAPY DEVELOPMENT

NCI recently developed scientific tools that can aid cancer combination therapy development, including proof-of-concept assays for experimental agents, microarrays for testing drug combinations, an epigenetic toolbox to learn more about the biology of cancer, and an NCI drug repository that provides drugs for testing of combinations.

Mechanism-of-Action Assays

NCI is currently developing more than 50 assays for evaluating the mechanisms of action of molecularly targeted agents. Once validated, these assays will be made available to the research community at no charge. These tools include assays for many of the molecular mechanisms related to cancer, such as activation of various tyrosine kinases and oncogenes, DNA damage, and apoptosis. Some of these assays detect more than one molecular mechanism simultaneously, including an assay that has antibodies that detect all the different phosphorylation sites on MET. NCI is also funding researchers to develop multiplex assays appropriate for use in the clinic with a single biopsy. These multiplex assays could be used, for example, to assess two or more molecular pathways for drug resistance.

In addition, NCI has developed "combo plates" specially formatted for researchers to use in testing new compounds in combination with

commercially available anticancer drugs (Mayfield, 2011). A plated set of about 100 FDA-approved oncology drugs is now available without charge to the research community. Information about this resource and how to obtain it can be found on the Division of Cancer Treatment and Diagnosis Developmental Therapeutics Program website.[1]

Preclinical Models for Combinations

To assess the effects of combining anticancer agents on tumor growth inhibition, NCI's toxicogenomics program is testing 5,000 unique combinations for the 100 commercially available anticancer drugs across many clinically relevant concentrations on the NCI-60 panel, which includes 60 human tumor cell lines.

For about 10 percent of the combinations, some synergistic effects appear to be greater than the additive effects alone. The researchers are trying to confirm synergistic activity in a variety of different xenograft animal models. Some of the antagonistic or additive effects that have been observed were unpredicted, Dr. Doroshow noted. For example, some cell lines that are insensitive to the individual agents used in the combination, such as dasatinib and 6-MP, are sensitive when the agents are used in combination. "This shows us that there are many things about the drugs, old and new, that we think we know and, in fact, we don't," Dr. Doroshow said. "Such systematic screening will provide, we hope, novel information for the investigative community to help us understand how to put some of these agents together."

Dr. Doroshow estimated that all 5,000 combinations will be evaluated by the end of 2011, at which time the data will be made publicly available on the NCI website. NCI scientists are also modeling the effectiveness of combining investigational agents with approved agents. Furthermore, they are exploring combinations of 300 investigational agents in a variety of concentrations (Mayfield, 2011). Dr. Blackman suggested researchers correlate the findings from NCI's combination screening program to clinical data on such combinations to assess how predictive the assays are. Dr. Doroshow responded that it certainly can be done across the NCI database of Phase II trials. Dr. Amy Abernethy, director of the Duke Cancer Care Research Program, suggested testing combinations of oncology and non-oncology commercially available drugs for their antitumor effects, and Dr. Doroshow responded, "Repurposing non-oncologic drugs is not something we are doing, but is something of significant interest to Dr.

[1] See http://dtp.nci.nih.gov/branches/dscb/oncology_drugset_explanation.html (accessed December 14, 2011).

[Francis] Collins and to the NIH, and activities are under way to do this." Dr. Bachman said that GSK is also exploring such drug combinations.

Investigational Agents Available for Preclinical Testing

Until recently, Dr. Doroshow said, the Department of Health and Human Services' Office of General Counsel prohibited NCI from purchasing or synthesizing patented agents for research purposes. But that policy changed in 2009, and NCI has acquired more than 300 investigational agents anticancer potential for in vitro testing, including multiple representatives of each class. A program is being established to allow investigators to submit requests for in vitro studies of the effects of specific combinations of these investigational agents (Mayfield, 2011). Dr. Doroshow said NCI can supply these compounds to NCI intramural scientists and to its contractors. But at the present time, the Office of General Counsel at the NIH prohibits them from sending these agents to extramural investigators. He noted, however, that NCI does have the repository space and other resources, expertise, and willingness to provide these compounds to extramural investigators if the legal issues prohibiting this can be overcome.

I-SPY 2 TRIAL[2]

The I-SPY 2 TRIAL is a Phase II multisite clinical trial testing multiple experimental drugs while simultaneously assessing the effectiveness of various biomarkers to predict response to the investigational agents. The trial was launched on March 17, 2010. The I-SPY 2 TRIAL builds on I-SPY 1 TRIAL,[3] which was designed to evaluate neoadjuvant chemotherapy in patients with locally advanced breast cancer, and brought together data from multiple molecular biomarker studies and biomedical imaging (Barker et al., 2009).

In the I-SPY 2 TRIAL, 800 patients with locally advanced breast cancer will have their tumor biopsies characterized by a panel of biomarkers, some of which are established and approved and some of which are exploratory or need to be qualified. The results from these biopsies will be used to divide the patients into different groups that will receive 1 or combinations of 12 experimental drugs and/or standard drug therapy

[2] Information on the I-SPY 2 TRIAL is from *Extending the Spectrum of Precompetitive Collaboration in Oncology Research: Workshop Summary* (IOM, 2010a) and Dr. Wholley's presentation on June 14, 2011.

[3] The I-SPY 1 TRIAL was a collaboration involving NCI's Specialized Programs of Research Excellence, the American College of Radiology Imaging Network, Cancer and Leukemia Group B, and NCI's Center for Biomedical Informatics and Information Technology.

prior to surgery. Using biomedical imaging, the effect on the tumor will be measured at four points during the 6 months that patients receive treatment, and when the tumor is removed. The patients will then be followed for 5 years.

This innovative study uses an adaptive trial design to enable researchers to use early data from one set of patients to guide decisions about which treatments might be more useful for patients later in the trial. The study design also enables drugs to be dropped quickly from the trial if they are ineffective or harmful (FNIH, 2010). Tumor response is also assessed by biomarker category. If the data indicate drugs are not improving the tumor response in patients with particular biomarkers, patients with those biomarkers will be assigned other drugs.

In addition, the study design allows drugs to be graduated to Phase III trials sooner if they are shown to be beneficial. Once drugs graduate to Phase III testing or are dropped, new drugs will seamlessly be entered into the trial to take their place.

Promising data on biomarkers in I-SPY 2 TRIAL can be used to support an application for Premarket Approval at FDA or to request to use a biomarker to stratify patients in a Phase III validation study.

The trial is testing the most promising drugs by class across many companies, each of which is contributing the experimental agents. The unique structure of the trial and the multiple companies involved in it, however, create numerous challenges, especially in the regulatory arena. Usually multiple drugs and biomarkers require multiple trials, each with its own IND. Even when a drug is successful in the first phase of testing, the trial has to be stopped and a new one created to continue testing in the next phase. This is extremely time consuming and inefficient. To speed up the process, the Biomarkers Consortium, trial organizers, and FDA worked together to develop a plan in which the master IND being used by the trial is held by FNIH, who manages the Biomarkers Consortium along with several other large biomedical partnerships. FNIH was chosen because it was seen as a trusted, neutral third party that can sponsor and manage the trial fairly and effectively.

In addition, the initial five experimental agents that will be used in the trial were approved for testing purposes by FDA and the relevant IRBs before the trial started. Other agents that will be evaluated in the I-SPY 2 TRIAL (there will be as many as 12, contributed by more than 6 different companies) will be submitted to FDA and IRBs for approval for testing purposes as the trial progresses so that by the time investigators are ready to add new agents to the trial, they will be ready to enter. Each time a new agent is added to the trial, an appendix is added rather than changing the protocol. An effort was made to involve all the stakeholders from all the sites as early as possible. For example, in preparation for IRB

approval, 45 key stakeholders were brought together for education and feedback. This changed a traditionally long linear process, with consecutive approvals by various participants and inefficient reapproval loops, to a more streamlined team effort.

No single company stands to be the sole beneficiary of the I-SPY 2 TRIAL. The intellectual property resulting from the trial will be handled according to the Biomarkers Consortium policies:

- Preexisting IP related to agents contributed by companies will remain with the company owning that IP;
- Preexisting IP related to biomarkers and platforms will remain with the inventing companies, and be licensed for use in the project. In some cases the tests have been published and are available commercially;
- New IP will be managed by FNIH, acting as a trusted third party to hold and license the new inventions. FNIH will return a fair share of royalties (less expenses) to inventing organizations;
- FNIH prosecutes and manages resulting patents; and
- Data are expected to be broadly applicable and available as quickly as possible.

Institutions participating in the I-SPY 2 TRIAL use common data elements and a shared information technology infrastructure, which employs tools provided by caBIG.[4] Within the caGRID, the underlying architecture of caBIG, the I-SPY 2 TRIAL is leveraging several bioinformatics platforms, including caTISSUE, caARRAY, and caIntegrator. Access to the data is democratized and credit is shared.

The I-SPY 2 TRIAL is expected to cost approximately $26 million over 5 years (FNIH, 2010). Some funding secured for the trial includes contributions from Eli Lilly, Genentech, Johnson & Johnson, and Safeway, Inc. FNIH is working to raise the remaining funding from pharmaceutical and other companies, nonprofit cancer organizations, and philanthropic foundations and individuals. Only some pharmaceutical companies that have funded the I-SPY 2 TRIAL are participating in the trial. As Mr. Wholley noted, "there is no pay for play around the selection of the agents. Fundraising is separated from the contribution of the agents." An independent agent selection committee consisting of oncologists without conflict of interests chooses which agents are tested in the trial, based on rigorous scientific criteria.

[4] caBIG stands for the cancer Biomedical Informatics Grid, an information network that enables members of the cancer community to share data and knowledge. See https://cabig.nci.nih.gov (accessed December 14, 2011).

BATTLE TRIAL[5]

The objective of the BATTLE trial is to use biopsy tissue from lung cancer patients in real time to suggest the best treatments they should receive for their tumors. Similar to the I-SPY 2 TRIAL, BATTLE aims to treat patients more effectively with a personalized medicine approach while simultaneously discovering and validating biomarkers. As Dr. Herbst explained, BATTLE, which is funded by the Department of Defense, is a platform for translational research for testing three hypotheses:

- Real-time biopsies can more accurately reflect the aberrant signaling pathways of lung cancer;
- Matching targeted agents with abnormal pathways will improve disease control in lung cancer patients; and
- Eight-week disease control is an acceptable surrogate for efficacy in patients with pretreated lung cancer.

BATTLE 1 began in 2007 at MD Anderson Cancer Center. It consisted of four adaptive trial designs, and was available to all lung cancer patients; the only prerequisite was a core biopsy of their tumor. Following biomarker analysis of their tumor sample under an umbrella protocol, patients were adaptively randomized to one of four treatments with targeted cancer therapies, including one treatment which was a combination of two agents, and one treatment that was a multitargeted inhibitor. Because of the involvement of different research groups and pharmaceutical companies, each treatment had its own separate Phase II clinical trial. Initial published results of BATTLE 1 (Kim et al., 2010, 2011) suggest that lung cancer patients "are going to do differently, not only based on having a mutation, but the specific type of mutation and the correlate for that is it's probably affecting different signaling pathways," Dr. Herbst said. He and his colleagues continue to mine the frozen tumor tissue they collected to discover new biomarkers.

BATTLE 2, which became active in 2011, uses a similar protocol to BATTLE 1, but has some improvements, including the use of fine needle aspirations prior to core biopsies to ensure adequate tumor cells are accessed (see Figure A-1). This trial is being conducted at MD Anderson and Yale Cancer Centers in collaboration with Merck, AstraZeneca, and Bayer/Onyx, who are providing the five agents that will be tested in four treatments, two of which are two-agent combinations.

Dr. Herbst estimated that BATTLE 2 costs $20,000 per patient, not

[5] Information on the BATTLE trial is from Dr. Herbst's presentation (June 14, 2011) and Dr. Papadimitrakopoulou's presentation (June 14, 2011).

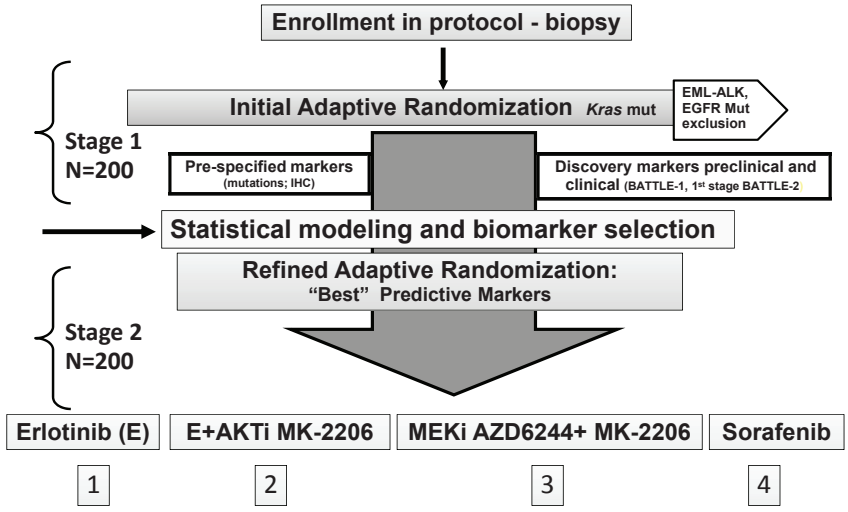

FIGURE A-1 The BATTLE 2 trial protocol. The protocol includes a mandatory biopsy, initial adaptive randomization, statistical modeling and biomarker selection, and a refined randomization phase where the best predictive markers are selected. Two of the four treatment arms include combination therapies.
NOTE: EGFR = epidermal growth factor receptor, EML-ALK = echinoderm microtubule-associated protein-like/anaplastic lymphoma kinase fusion gene, IHC = immunohistochemistry, mut = mutation.
SOURCE: Papadimitrakopoulou presentation (June 14, 2011).

including the $7–$8 million infrastructure costs that support it. Dr. Papadimitrakopoulou stressed the complexity of BATTLE 2 and the numerous steps it took to develop the study, which can be seen in Figure A-2.

For this trial, researchers had to forge three three-way IP agreements and four contracts between MD Anderson Cancer Center and pharmaceutical sponsors, as well as submit four NCI grant applications (initial PO1 and resubmission, initial RO1 and resubmission). Protocol development and the first IRB approval were achieved in July 2009, followed by 10 protocol revisions and approved amendments, based on recent clinical trial results and the evolution of scientific knowledge. The trial was activated in June 2011.

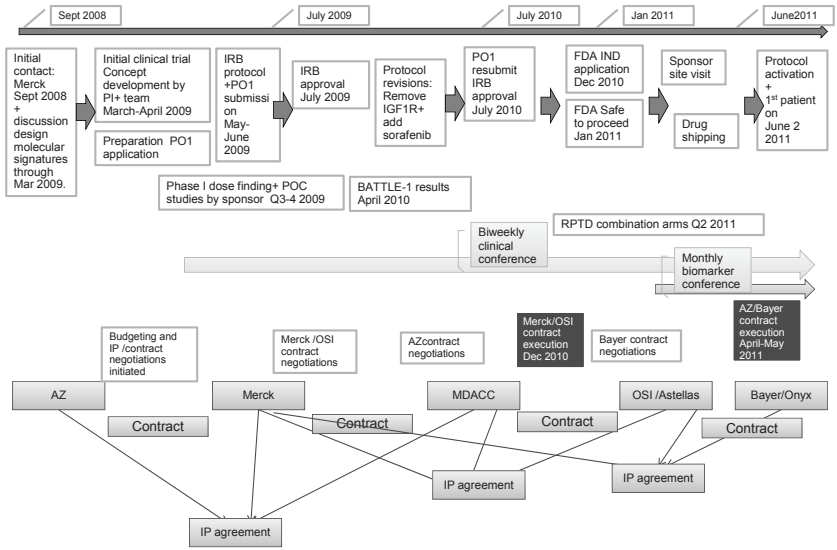

FIGURE A-2 The BATTLE 2 clinical trial preparation steps. Preparations took nearly 3 years before protocol activation in June 2011. The time line reflects contract negotiations and intellectual property agreements, concept development, grant applications, Institutional Review Board approval, protocol revisions, the Food and Drug Administration Investigational New Drug application, site visits, and drug shipping.
NOTE: AZ = AstraZeneca, FDA = Food and Drug Administration, IGFR1 = insulin-like growth factor receptor 1, IND = investigational new drug, IRB = institutional review board, IP = intellectual property, MDACC = MD Anderson Cancer Center, OSI = OSI Pharmaceuticals, PI = principal investigator, POC = proof of concept, RPTD = recommended phase treatment dose.
SOURCE: Papadimitrakopoulou presentation (June 14, 2011).

STAND UP TO CANCER PI3K TEAM[6]

Stand Up To Cancer funds an innovative platform of preclinical and clinical development of agents that target PI3K in women's cancers. The team responsible for this platform come from eight academic institutions and cancer centers and includes pathologists, biomarker experts, clinicians, mathematical modelers, biostatisticians, and cell-based assay experts, as well as patient advocates. The treatments they are developing

[6] Information on the Stand Up To Cancer PI3K Team is from Dr. Cantley's presentation (June 14, 2011).

all target PI3K because it is mutated frequently in breast, endometrial, and ovarian cancers, on which they are focused.

The PI3K research team is exploring combinations of targeted agents in animal models and using those results combined with biomarker analyses of tumor biopsies to guide selection of patients into clinical trials that are supported by the same Stand Up To Cancer program. For example, Dr. Cantley pointed out that single-agent therapy with a PI3K inhibitor or another type of drug he called "Z" has not been effective in his animal models of breast cancer, but the combination has produced cures in a mouse model. "When the two are used together you get a dramatic effect—we can actually take the drug away and these tumors don't come back—but if you looked at either one of these [alone], you wouldn't get excited at all." He added that the combination is well tolerated and he hasn't had to reduce the dose of either drug to have the combination work.

"Our animal models are really what are driving our hypotheses," said Dr. Cantley. These animal models involve mice genetically engineered to have mutations that are seen frequently in human cancers in combinations that mimic what occurs in the clinic. Although all the mice are genetically engineered to have an initial mutation or set of mutations, researchers assess subsequent secondary mutations that develop and these are quite heterogeneous, Dr. Cantley noted. "We're seeing the same kind of heterogeneity that we probably see in human disease," he said.

The genetically engineered mice are treated with the same agents being tested in the trials the investigators are designing for human patients. Such testing and genetic analysis of the animal tumors identifies resistance mechanisms, leading to hypotheses for innate or acquired resistance to PI3K inhibitors in the human trials, and suggests combination therapies to test in patients.

Patients enrolled in PI3K clinical trials are asked to provide a tumor biopsy sample at entry as well as a subsequent biopsy if the cancer progresses. These biopsies are analyzed for the same resistance mutations seen in the mouse models, and are used to guide which experimental therapy patients receive. The trials incorporate novel imaging approaches, such as functional quantitative imaging before and a few weeks after initiation of the drugs, to more quickly ascertain likely responders.

SAFE HARBORS FOR COLLABORATION

Several safe harbors have been established with the aim of fostering collaborations in the development of cancer biomarkers or drugs, including combination therapies. Organizations discussed at the workshop include the CEO Roundtable on Cancer's Life Sciences Consortium,

the Cancer Immunotherapy Trials Network, FNIH and its Biomarkers Consortium, and the Reagan–Udall Foundation.

Life Sciences Consortium of the CEO Roundtable on Cancer[7]

The CEO Roundtable on Cancer was established in 2001 and consists of 17 representatives from 11 pharmaceutical companies and 26 representatives from NCI-Designated Comprehensive Cancer Centers. The Life Sciences Consortium is a task force of the Roundtable and brings together Roundtable members to further its goals, which are to:

- Develop standards across the life sciences industry to expedite the R&D process;
- Develop a pool of precompetitive intellectual property for biomarkers; and
- Diminish the regulatory burden of new cancer drug approval.

To help achieve its first goal of expediting the R&D process, the Life Sciences Consortium acted on findings that the most rate-limiting steps in the development of clinical trials were contracting and budgeting (Dilts and Sandler, 2006). To expedite the contract and budget negotiations required between industry and publicly funded investigators before the launch of a collaborative trial, the Consortium and NCI reviewed copies of 78 redacted clinical trial agreements and identified 45 key concepts related to intellectual property, study data, subject injury, indemnification, confidentiality, and publication rights. From these agreements, they then gleaned the exact language that embodied the key concepts and used it to create standardized and harmonized clauses for clinical trial agreements that are designed to serve as a starting point for contract negotiations (CEO Life Sciences Consortium and NCI, 2008). The analysis found that several key concepts showed greater than 67 percent similarity across the agreements, suggesting that negotiations frequently reach common results for these concepts. The U.S. Department of Justice gave the proposed clauses a favorable review and indicated that it had no intention to challenge the initiative (DOJ, 2008).

Nine out of eleven of the Life Sciences Consortium companies have adopted the START (Standard Terms of Agreement for Research Trial) clauses for their oncology programs, with one making it a standard operating procedure, and another using the clauses for all therapeutic areas. The Consortium plans to use the same process to develop standardized

[7] Information on The Life Sciences Consortium is from IOM (2010a) and comments from Dr. Martin Murphy.

material transfer agreements for academic collaborations in the laboratory to expedite the process of preclinical development.

The Life Sciences Consortium recently began addressing its second goal of developing a pool of precompetitive intellectual property for biomarkers. It plans to work with NCI as a safe harbor for this effort because NCI currently has a robust biomarker program, according to Dr. Gregory Curt, chair of the Life Sciences Consortium and the U.S. medical science lead of emerging products at AstraZeneca-Oncology. Consortium companies will present their biomarker programs under confidentiality to NCI, which will select the most promising markers for coinvestment and collaboration. This will reduce the duplicative and expensive research that individual companies and NCI are spending on biomarker development and should, along with the START clauses, significantly reduce the amount of time needed to validate biomarkers (IOM, 2010b).

"At the CEO Roundtable, we've tried to create an independent safe harbor where companies can do together what otherwise it's impossible to do, so real progress can be made," said Dr. Martin Murphy. He added that a new initiative of the Roundtable is to give an award to the pharmaceutical company that lowers barriers to collaboration better than any other pharmaceutical company on the Roundtable. He added that often resistance to changing the culture of companies comes not from the upper echelon of the company, but rather from middle levels. "The intent is simple: To try to [emphasize] throughout the entire organization, if not now, when, and if not us, who?" Dr. Murphy said.

The Foundation for the National Institutes of Health[8]

FNIH was created by Congress in 1990 and incorporated in 1996 to support NIH in its mission to improve health by forming and facilitating public–private partnerships for biomedical research and training. According to the Foundation's website, FNIH "unites experts, funding, patients and resources around common biomedical research goals identified by NIH—all in an effort to respond to the most urgent priorities in human health, both domestically and around the world. Unique in its mandate, the Foundation builds partnerships that enable ambitious, multipronged, sweeping attacks on problems that would be impossible to mount otherwise. Individuals and interests large and small can all make important contributions toward solving even the most complex health challenges" (FNIH, 2011a).

The Foundation is a non-profit, 501(c)(3) charitable organization that

[8] Information about the FNIH and Biomarkers Consortium is from IOM (2010a) and Mr. Wholley's presentation on June 14, 2011.

has raised more than $560 million in private-sector funds for more than 100 projects, including partnerships between the private sector and federal agencies such as the Biomarkers Consortium and the I-SPY 2 TRIAL. "We're really skilled at pulling together the types of governance mechanisms that make these things work," Mr. Wholley said.

The Biomarkers Consortium

Mr. Wholley elaborated on the Biomarkers Consortium, a project of FNIH. This consortium's founding partners included FDA, NIH, the Centers for Medicare & Medicaid Services (CMS), the Biotechnology Industry Organization, and the Pharmaceutical Research and Manufacturers of America. The Biomarkers Consortium was prompted by the growing awareness of the importance of validated biomarkers in the success of targeted therapies. But biomarker development and validation lag far behind the development and clinical testing of the innovative treatments that depend on the biomarkers for their success. Such validation requires multiple studies with large amounts of data to ensure the integrity and reproducibility of results, and is quite expensive and time consuming. This validation is difficult to accomplish in a single institutional setting, Dr. Wholley pointed out, and thus requires partnerships and a strategic approach. In addition, there is clear direction from FDA, according to Dr. Wholley, to develop consensus across sectors with regard to validated biomarkers, and recent draft guidance from FDA (2010) cites the value of consortia in developing and validating biomarkers.

The Biomarkers Consortium was launched in 2007 to facilitate the development and validation of biomarkers using new and existing technologies in a precompetitive context. The Consortium aims to qualify biomarkers and validate the underlying analytical technologies for specific applications in diagnosing disease, predicting therapeutic response, or improving clinical practice. In the spirit of precompetitiveness, however, the Consortium will not qualify or validate biomarkers in areas that directly intersect with certain compounds being developed by a specific company.

The Consortium is expected to generate information that can inform regulatory decision making, and its results are broadly available to the entire scientific community, not just its participants. "The whole goal of the Consortium is to drive significant public health benefit," said Mr. Wholley.

The Consortium has nearly 50 contributing members, including pharmaceutical companies, academic researchers, and numerous nonprofit organizations. The Executive Committee of the Consortium has senior

representatives from NIH, FDA, the pharmaceutical industry, FNIH, CMS, and patient advocacy groups. Steering committees for four major disease areas (cancer, immunity and inflammation, metabolic disorders, neuroscience), composed of 20 to 30 individuals each, also have equal representation from NIH, FDA, industry, and academia. These committees, along with the Executive Committee, decide what biomarker projects to pursue, and direct smaller project teams of 8 to 10 people, who also have balanced representation across all the sectors and carry out the project. Projects are approved based on their scientific merit, precompetitive quality, and feasibility.

The project plan, which is developed by both the steering committee and project team, includes governing policies for intellectual property and data sharing, confidentiality, conflict of interest, selection and award of grants and contracts, and antitrust issues, which are posted on the Internet (FNIH, 2011b). The Biomarkers Consortium has launched 12 projects aimed at validating biomarkers for cancer and metabolic disorders, as well as neuroscience biomarkers, and those linked to inflammation or immunity. "All of our projects and our governing structure is fully representative of all the stakeholders from top to bottom, including FDA, industry, NIH, academia and it's been a pretty successful mechanism for generating these projects," Dr. Wholley said.

Cancer Immunotherapy Trials Network (CITN)

Started in 2010, CITN is funded by NCI and the Fred Hutchinson Cancer Research Center and employs the collective expertise of academic immunologists to conduct multicenter research on agents that boost patients' own immune systems to fight their cancer (FHCRC, 2011). By collaborating with member institutions, industry sponsors, and philanthropic foundations, CITN aims to spearhead regulatory approval of promising agents and advance the knowledge of antitumor immunity and its application in immunotherapy.

The mission of the CITN is to select, design, and conduct early-phase trials that would not otherwise be possible, using novel regimens and providing high-quality immunogenicity and biomarker data that elucidate mechanisms of immune responses to inform subsequent development pathways. CITN supplies both clinical trial facilities and increased access to agents that are on prioritized lists for testing. There are 27 member sites involved in CITN, including all the large cancer centers, and the first clinical trials are expected to be launched by the end of 2011, according to Dr. June.

Reagan–Udall Foundation

The Reagan–Udall Foundation is a potential source of support for collaborations in development and regulatory science. Created in 2007 by the FDA Amendments Act of 2007, the Foundation was designed and given statutory authority to collaborate closely with FDA on scientific priorities to advance the agency's mission to modernize medical, veterinary, food, and cosmetic product development, thereby accelerating innovation and enhancing the safety of medical products. The Foundation collaborates or contracts with stakeholders, such as FDA, university consortia, public–private partnerships, academia, nonprofits, and industry, to efficiently and effectively advance its goals and priorities. The Foundation is currently working on regulatory issues related to developing multiple drug regimens for tuberculosis as well as identifying common mechanisms of cardiotoxicity for oncology drugs.[9]

[9] See http://www.focr.org/component/option,com_eventlist/Itemid,41/id,27/view,details/ (accessed December 14, 2001) and http://www.gatesfoundation.org/Grants-2011/Pages/Reagan-Udall-Foundation-OPP1027026.aspx (accessed December 14, 2001).

Appendix B

Workshop Agenda

June 13 and 14, 2011
The Keck Center of the National Academies, Room 100
500 Fifth Street, NW
Washington, DC 20001

June 13, 2011

7:30 am **Breakfast and Registration**

8:00 am **Welcome from the IOM National Cancer Policy Forum**
John Mendelsohn, MD Anderson Cancer Center, and Chair, National Cancer Policy Forum

8:05 am **Session 1: Workshop Introduction**
Moderator: John Hohneker, Novartis Pharmaceuticals, Workshop Planning Chair

Rationale for Developing Combination Targeted Cancer Therapies
- Jeffrey Engelman, Massachusetts General Hospital

Application of Genomic Tools to Assist in Combination Therapy Development
- Michael Barrett, TGen

Patient Advocate Perspective
- Jane Perlmutter, Gemini Group

Panel Discussion (30 minutes)

9:35 am **Session 2: Scientific Challenges and Opportunities: Preclinical Issues in Codevelopment**
Moderator: James Zwiebel, National Cancer Institute

Perspectives from the National Cancer Institute
- James Doroshow, National Cancer Institute

Perspectives from Academia
- David Stern, Yale University
- Carl June, University of Pennsylvania

Perspectives from Industry
- Kurt Bachman, GlaxoSmithKline

Panel Discussion (60 minutes)
Includes speakers and
- Haleh Saber, Food and Drug Administration
- Robert Iannone, Merck
- Michael Caligiuri, OSU Comprehensive Cancer Center

12:00 pm **Lunch**

1:00 pm **Session 3: Scientific Challenges and Opportunities: Clinical Issues in Codevelopment**
Moderator: Roy Herbst, Yale Cancer Center

Perspectives from the National Cancer Institute
- Helen Chen, National Cancer Institute

Perspectives from Academia
- Patricia LoRusso, Barbara Ann Karmanos Cancer Institute

Perspectives from Industry
- Stuart Lutzker, Genentech

Perspectives on Trial Design and Statistical Issues
- Donald Berry, MD Anderson Cancer Center
- Larry Rubinstein, National Cancer Institute

Panel Discussion (45 minutes)
Includes speakers and
- Samuel Blackman, GlaxoSmithKline

3:20 pm **Break**

3:30 pm **Session 4: The Regulatory Environment for Codevelopment**
Moderator: Richard Pazdur, Food and Drug Administration

FDA Presentation on Draft Guidance
- Rachel Sherman, CDER, Food and Drug Administration

Brookings/Friends of Cancer Research Perspective on FDA Submission
- Jeff Allen, Friends of Cancer Research

Industry Perspective
- Ramzi Dagher, Pfizer

Panel Discussion (40 minutes)
Includes speakers and
- Robert Temple, CDER, Food and Drug Administration
- Ellen Sigal, Friends of Cancer Research

5:30 pm **Adjourn, Day 1**

June 14, 2011

7:30 am **Breakfast and Registration**

8:00 am **Welcoming Remarks**
John Hohneker, Novartis Pharmaceuticals, Workshop Planning Chair

8:10 am **Session 5: Codevelopment in Vaccines, Biologics, and Other Therapeutic Areas**
Moderator: Renzo Canetta, Bristol-Myers Squibb

Experiences from HIV Drug and Vaccine Development
- Carl Dieffenbach, National Institute of Allergy and Infectious Diseases
- Gary Nabel, National Institute of Allergy and Infectious Diseases

Preclinical Issues
- Nils Lonberg, Bristol-Myers Squibb

Clinical Issues
- Jeffrey Schlom, National Cancer Institute

Multimodality Combination Therapies
- Keith Flaherty, Massachusetts General Hospital

Panel Discussion (45 minutes)

10:10 am **Session 6: Pharmaceutical and Biotechnology Industry Collaboration to Codevelop Therapies**
Moderator: Michaele Christian

Organizational Culture in Pharmaceutical and Biotechnology Companies
- Bernard Munos, InnoThink

Legal Issues
Overview of Antitrust Issues
- Robert Leibenluft, Hogan Lovells

Overview of Intellectual Property Issues
- Anishiya Abrol, Hogan Lovells

Overview of NCI's CRADA Intellectual Property Language
- Jason Cristofaro, National Cancer Institute

Panel Discussion: Perspectives on Intellectual Property Issues in Collaboration (30 minutes)
Industry perspective
- Lydia McNally, Novartis

Research institution/technology transfer perspective
- Wesley Blakeslee, Johns Hopkins

National Cancer Institute perspective
- Jason Cristofaro, National Cancer Institute
- Sherry Ansher, National Cancer Institute

11:55 am **Break: Please pick up boxed lunch and return to workshop**

12:15 pm **Session 6 (Continued)**

Practical Examples and Possible Models of Collaboration
Collaborations to Develop Drugs Targeting PI3K
- Lewis Cantley, Beth Israel Hospital/Harvard

BATTLE 1 and 2 Trials
- Roy Herbst, Yale Cancer Center

I-SPY 2 TRIAL
- David Wholley, Biomarkers Consortium

Panel Discussion (45 minutes)
Includes speakers and
- Vassiliki Papadimitrakopoulou, MD Anderson Cancer Center

1:50 pm **Closing Comments/Wrap-Up**
John Hohneker, Novartis Pharmaceuticals

2:00 pm **Adjourn**

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Acronyms

AIDS	acquired immunodeficiency syndrome
BATTLE	Biomarker-based Approaches of Targeted Therapy for Lung Cancer Elimination
BRAF	Rapidly Accelerated Fibrosarcoma (B family)
CaBIG	cancer Biomedical Informatics Grid
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CEO	chief executive officer
CGL	chronic granulocytic leukemia
CITN	Cancer Immunotherapy Trials Network
CMS	Center for Medicare & Medicaid Services
CRADA	Cooperative Research and Development Agreement
CTEP	Cancer Therapy Evaluation Program
CTLA-4	Cytotoxic T-Lymphocyte Antigen 4
DCE-MRI	dynamic contrast enhanced-magnetic resonance imaging
DOJ	Department of Justice
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
ER	estrogen-receptor

FDA	Food and Drug Administration
FNIH	Foundation for the National Institutes of Health
FTC	Federal Trade Commission
GSK	GlaxoSmithKline
HER2	human epidermal growth factor receptor 2
HIV	Human Immunodeficiency Virus
HPV	human papillomavirus
IGF	insulin-like growth factor
IIP	instantaneous inhibitory potential
IND	Investigational New Drug
IP	intellectual property
IRB	Institutional Review Board
I-SPY TRIAL	Investigation of Serial studies to Predict Your Therapeutic Response with Imaging And moLecular analysis
LCMV	lymphocytic choriomeningitis virus
MAPK	mitogen-activated protein kinase
MEK	mitogen-activated protein kinase kinase
MET	Methylnitronitrosoguanidine-HOS (Human osteosarcoma) Transforming gene
MTA	Material Transfer Agreement
mTORC1	mammalian target of rapamycin complex-1
NCDDG	National Cooperative Drug Discovery Groups
NCI	National Cancer Institute
NERF	non-exclusive royalty-free
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NOD	non-obese diabetic
OS	overall survival
PathCR	pathological complete response
PET	positron emission tomography
PFS	progression-free survival
PI3K	phosphatidylinositol 3-kinase
PPTP	Pediatric Preclinical Testing Program
R&D	research and development

SOC	standard of care
START	Standard Terms of Agreement for Research Trial
VEGF	vascular endothelial growth factor