Abstract
Cancer cells contain multiple genetic changes in cell signaling pathways that drive abnormal cell survival, proliferation, invasion, and metastasis. Unfortunately, patients treated with single agents inhibiting only one of these pathways—even if showing an initial response—often develop resistance with subsequent relapse or progression of their cancer, typically via the activation of an alternative uninhibited pathway. Combination therapies offer the potential for inhibiting multiple targets and pathways simultaneously to more effectively kill cancer cells and prevent or delay the emergence of drug resistance. However, there are many unique challenges to developing combination therapies, including devising and applying appropriate preclinical tests and clinical trial designs, prioritizing which combination therapies to test, avoiding overlapping toxicity of multiple agents, and overcoming legal, cultural, and regulatory barriers that impede collaboration among multiple companies, organizations, and/or institutions. More effective strategies to efficiently develop combination cancer therapies are urgently needed. Thus, the Institute of Medicine's National Cancer Policy Forum recently convened a workshop with the goal of identifying barriers that may be impeding the development of combination investigational cancer therapies, as well as potential solutions to overcome those barriers, improve collaboration, and ultimately accelerate the development of promising combinations of investigational cancer therapies.

Introduction
Despite recent advances in understanding the molecular pathways that trigger cancer and its progression, the successful development of targeted cancer therapies has been hampered by the complexity of these pathways and the existence of alternate or bypass pathways that foster drug resistance. Consequently, the duration of effectiveness for targeted therapies is finite; however, combination therapies offer the potential for improved effectiveness.

Based on preclinical *in vitro* and *in vivo* combination data, clinical trials evaluating targeted drug combinations have become a significant focus for early-phase drug therapeutics with preliminary evidence of success being reported (1–10). As an example, promising results were recently presented from a phase I/II study investigating the BRAF inhibitor dabrafenib in combination with the MEK1/2 inhibitor trametinib in patients with V600 BRAF-mutant solid tumors (3). Notably, a confirmed overall response rate of 56% was documented in 77 patients with melanoma who had not been previously treated with BRAF inhibitors. When administered in combination, a lower incidence of rashes commonly associated with MEK inhibitors as well as hyperproliferative skin lesions related to BRAF inhibition were observed than in administration of each agent alone. Another recent example shows that selection of the proper patient population for combination treatment may be critical. Whole-genome sequencing of a tumor from a patient with chemotherapy-refractory, metastatic triple-negative breast cancer showed high-level *BRAF* amplification/overexpression along with downregulation of PTEN and INPP4B. This patient was subsequently treated on a phase I study with the combination of trametinib and the AKT inhibitor GSK2141795 and, within 2 months, her breast mass had nearly completely regressed. (5, 11) The investigators hope to reproduce these data on a larger scale and show multitarget therapeutic advantages.

The combination of the novel agent everolimus with the established targeted agent exemestane is another example of a promising combination regimen. Simultaneous blockade of estrogen receptor signaling and mTOR signaling in...
patients with previously treated estrogen receptor–positive metastatic breast cancer led to improved patient outcome, as evidenced by prolongation in progression-free survival. Inhibiting a target known to be relevant in hormone resistance in breast cancer (mTOR), this combination showed therapeutic benefit with minimal overlap in drug target toxicity (12).

Combining investigational cancer therapies early in their development may produce more effective cancer treatments, especially when a combination targets multiple pathways critical for progression of cancer. However, this approach to drug development presents several unique challenges, including developing and applying appropriate preclinical and clinical experiments, identifying relevant biomarkers, prioritizing promising combination therapies, avoiding or managing the overlapping toxicities of multiple agents, and overcoming legal, cultural, and regulatory barriers that impede collaboration of pharmaceutical companies, academia, and government research institutions.

To help further the development of innovative combination cancer therapies, the National Cancer Policy Forum (NCPF) of the Institute of Medicine (IOM) held a public workshop, "Facilitating Collaborations to Develop Combination Investigational Cancer Therapies," in 2011 (13). The NCPF convenes government, industry, academic, and other representatives to consider issues in science, medicine, public health, and policy relevant to the goals of preventing, palliating, and curing cancer. The goal of the workshop was to identify barriers that may impede the development of combinations and offer potential solutions to improve collaboration and accelerate the development of effective combination treatment regimens. We present a summary of the key concerns discussed at the workshop, as well as suggestions for how to move the field forward.

### Why Combinations Are Necessary

A combinatorial approach using multiple targeted agents and/or immunotherapies could be more effective than single agents. Synergistic treatment effects may be achieved using 2 agents that target similar cellular pathways. Rational combination strategies that target different cellular pathways simultaneously may circumvent possible bypass mechanisms that contribute to drug resistance and treatment failure (14, 15). Combination therapies may also overcome the tumor-to-tumor and intratumor heterogeneity of cancer cells within individual patients, particularly in advanced disease where 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 (16–19). Tumor heterogeneity may lead to an increase in the number and diversity of potential target sites for therapy; therefore, multiple agents may allow for a broader targeting spectrum and greater impact on tumor subclones, potentially increasing the probability of therapeutic effectiveness (20). Combination therapies can also potentiate the effects of immunotherapy, in part through increased antigen presentation (21).

### Scientific Challenges in Combination Drug Development

Preclinical drug development involves assessing the effects of varying concentrations of investigational agents in in vitro or animal models to determine initial doses to test in clinical trials. There are numerous challenges to translating these data into the clinic, including cell lines or animal models that do not adequately mimic the tumor, tumor microenvironment, human immune response, or the propensity to develop resistance; and a lack of biomarkers for patient selection and prediction of efficacy. These challenges can be exacerbated in the development of combinations. For example, animal models appropriate for one therapeutic class may be inappropriate for another class with which they are being combined. Workshop speakers identified a number of suggestions to overcome these challenges (Table 1).

Although the use of combinations may confer greater antitumor efficacy, combination treatments could lead to a poorer toxicity profile over that seen with each agent alone. If this is the case, significant dose reductions for one or all involved agents may be required. The current challenge with many of these combinations is the inability to either define and/or achieve a targeted maximum tolerated dose (MTD) due to overlapping toxicities between multiple agents. As a result, novel clinical trial designs that use unique methods for dose escalation and/or different schedules of administration for novel–novel combinations should be considered to examine the possibility of identifying multiple MTDs of the components of a drug combination within a single study (22, 23). Within the context of these trials, extensive pharmacokinetics should be conducted to help define possible drug–drug interactions in terms of plasma drug levels and exposure. In addition, pharmacodynamic evaluation should also be conducted to identify possible
interactions in both tumor and normal tissue to better understand potential tissue/target effects. However, because clinical cancer drug development of novel targeted combinations is still in its infancy, we must remember that many components may affect the interpretation of tumor tissue pharmacodynamics, including handling of samples and timing of biopsies, among other factors. These variables must be taken into account in translating the laboratory data into the clinic.

The MTD of a drug combination based on initial cycles of therapy—most notably cycle one—may not reliably predict long-term tolerability. In addition, with some exceptions, full doses of each individual agent are often not tolerable in combination, and adverse effects on normal tissues may limit the spectrum and duration of combined target inhibition. Many combinations will require more intensive preclinical studies to determine the optimal sequence, schedule, and dose to minimize toxicity. Such dosing will probably be based on the pharmacodynamics or pharmacokinetics needed for synergism or additivity, acknowledging that the dose required for enhanced efficacy may not be the same as that required for single-agent activity. Drug sequence may also influence the development of drug resistance. Combinations should also be composed of pharmacologically compatible molecules whenever possible. If the half-life of the agents in a combination vary widely, dose modifications may become difficult when toxicity develops.

The molecular pathways that drive many tumors are exceptionally complex, and research must continue to understand feedback loops and other mechanisms that may allow tumors to bypass blocked molecular pathways. If a pathway is known to be the driver of tumor growth, it may be necessary to maximally dose the agent that targets that pathway while escalating the dose of the agent that targets a bypass pathway. Moreover, the pharmacokinetics requirements for drug efficacy could be quite different for tumors driven by a mutated oncogene versus a wild-type gene. More information is needed on gene expression and the feedback and network responses to signaling perturbations and DNA damage in cancer cells. Better understanding of the nongenetic effects that influence treatment efficacy, including the microenvironment of the tumor, the host immune response, and the proteins made by the tumor and surrounding cells is pivotal in advancing these drug combinations forward.

### Clinical Trials of Combinations

The growing number of targeted therapies proposed for testing in combination, as well as the limited resources from government, foundations, and industry for such testing and the finite number of patients in whom combinations can be tested, suggests the need to prioritize which combinations are tested in clinical trials. Prioritization can be challenging; engaging patient advocates, federal agencies, and pharmaceutical companies in the process is important. Even with restricting combinations to a particular type of targeted agent or immunotherapy, the possibilities are too large to test in a combinatorial approach without some way of prioritization—more possible combinations exist than patients and resources needed to test them in clinical trials. Several ways to address the challenge of combination prioritization are listed in Table 2.

### Table 1. Suggestions for improving preclinical development of combinations

- Develop animal models that better reflect human cancer.
- Use noncancer animal models as surrogate efficacy models for anticancer immunotherapies.
- Develop strategies and tools to ensure target engagement and inhibition, better distinction of on- and off-target toxicities, maximization of dose and schedule, and identification of resistance mechanisms.
- Incorporate greater use of modeling and simulation.

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### Table 2. Suggestions for prioritizing which combinations to test in the clinic

- Use strict preclinical benchmarks for effectiveness, such as tumor shrinkage, and demonstration of consistent effects in multiple animal models, including xenografts.
- Conduct high-throughput *in vitro* screening of drug combinations to detect synergy.
- Prioritize agents within a drug class and combine the best, pharmacologically compatible agents in each class.
- Use human tumor tissues to investigate pathway activation.
- Test combinations that
  - optimize the benefit of drugs already approved;
  - have a known biologic mechanism for which there is an assay;
  - show adequate pharmacokinetics and some evidence of activity or target engagement at clinically relevant doses and exposures; and
  - have validated biomarkers for patient selection and pharmacodynamics.

NOTE: Adapted with permission from IOM (Institute of Medicine; ref. 13).
Patient selection is critically important for improving clinical trial effectiveness and efficiency. Improper patient selection may result in agents being shelved prematurely because of poor performance in initial clinical trials. Most of the agents being tested in combination therapies target highly specific molecular changes, so biomarker assays to identify these targets will be crucial to matching the right patient to the right treatment. Genetic profiling of patients might enable researchers to tailor drug dosing for each patient in early-phase combination trials. Patient selection might also identify patients who are extremely sensitive to a drug's effect and thus may benefit from a very low dose that does not cause toxicity. This may be especially important for combination therapies because significant dose reductions may be required to avoid adverse effects due to pharmacokinetic interactions.

Novel clinical trial designs could speed the development of combination therapies (24). For example, adaptive trial designs enable researchers to answer the initial questions posed and test new hypotheses during the course of a trial. Adaptive trials use Bayesian statistical methods to model and predict, during a trial, which option is most likely to be beneficial based on the results to date (Fig. 1A). 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 the number of patients being treated in those arms generating poor results. Adaptive clinical trial designs are well suited to address a number of issues in combination therapy development, such as which of several possible drug combinations, patient selection biomarkers, doses, and administration schedules are the safest and most effective.

The primary objective of the therapeutic outcome should also be considered when designing the trial. If a sustained major response or cure is the goal, 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 thought to be necessary, lighter, less intensive dosing may be needed for long-term tolerability or combination therapy may need to be administered sequentially rather than concurrently. In either case, trials ideally should be designed and sized to assess long-term effects on safety and efficacy, including both progression-free and overall survival.

Determining appropriate dosing in combination trials can be challenging due to the variability of tumor response to different agents. Hundreds of clinical trials testing combinations of targeted agents indicate that they can be quite...
toxic, often more than observed in preclinical models. Sometimes drug combinations will be abandoned if the combined toxicity requires such extensive dose reductions that the actual administered doses may be ineffective (e.g., sunitinib and temsirolimus; ref. 25). When combinations of drugs must be administered at a substantially lower dose than planned because of toxicity, it is often unclear whether the lower dose would truly be too low to show efficacy, as such dose reductions typically result in the abandonment of further efficacy analyses. When drugs are combined, the impact on the therapeutic window often remains unknown, especially if toxicity truly serves as a biomarker of target effect (26). Therefore, prematurely abandoning combinations due to substantial dose alterations may be the wrong approach. It may still be informative to test the clinical efficacy of these low-dose combinations, using schedule alterations when appropriate and relying on preclinical efficacy data to assist in toxicity management and maximum target effect.

For phase I trials of mechanism-based, relatively nontoxic, novel targeted therapies, and particularly for immunotherapies, determining the optimal biologic dose, defined as a dose that reliably alters and/or modulates a drug target or achieves a target plasma concentration, may be more desirable than aiming to reach the MTD (27, 28). However, extensive variations in steady-state drug levels among humans and the lack of strong evidence showing modulation of validated drug target biomarkers in tumors often prevent the widespread use of this technique (28).

Determining the most relevant endpoints to assess combinations is critically important. Researchers are finding that immunotherapies, such as sipuleucel-T and other tumor vaccines, often extend survival without delaying time to progression (29, 30). Such findings suggest that these commonly used endpoints may not be appropriate for clinical trials of immunotherapies, and overall survival might be the best indicator of their effectiveness (31). It is unclear whether this applies only to combination immunotherapies or also to treatments that combine an immunotherapy with standard chemotherapy or targeted treatments. Several suggestions to address the challenges for improving the design and conduct of such studies are provided in Table 3.

### Challenges to Collaboration

In addition to the scientific challenges involved in drug combination development, several cultural, legal, and regulatory issues must be addressed to advance collaboration. Table 4 highlights a number of suggestions for overcoming these challenges to collaboration.

### Culture

The differing institutional cultures that collaborating scientists work in—the pharmaceutical industry, academia, regulatory, and other government agencies—can be a major roadblock in the development of combination therapies. All of these stakeholders have different interests, perspectives, and talents that can drive teamwork to ensure that we continue to advance innovative research—or impede collaboration and lead to distrust and wasted development resources. Different or misaligned stakeholder perspectives may derail potential solutions to challenges about intellectual property, conflict of interest, antitrust, appropriate rewards, or publication policy, or may create a climate of mistrust that ultimately leads to the failure of a project. The traditional incentive structures of academia can greatly impede progress toward better collaboration (13, 32). Concern about protecting intellectual property causes duplication of efforts by drug developers. Even worse, an insular system among stakeholders—restricting the flow of information and ideas—increases the overall development time of effective combinations.

Increasing development complexity and costs are necessitating collaborative approaches to drug development; it is likely that companies will no longer successfully develop groundbreaking therapies in isolation. A single pharmaceutical company rarely has adequate resources to effectively and expediently address the complex mechanisms by which cancer cells become resistant to treatment. Precompetitive collaboration, or collaboration among companies, to achieve goals that can be more effectively accomplished by a group effort and have the potential to benefit the oncology community as a whole has been proposed as a critical driver for reinvigorating the biomedical enterprise by creating and unlocking value (32, 33). Realizing that major cancer discoveries are not typically best pursued in isolation, funding agencies such as Stand Up To Cancer are actively trying to

### Table 3. Suggestions on how to improve clinical trials for combination therapies

- Develop a precompetitive venue for testing drug combinations.
- Develop assays to identify patients more or less likely to respond to the drugs.
- Use adaptive trial designs.
- Use appropriate endpoints.
- Set a higher bar for effectiveness.
- Establish a single Institutional Review Board of record for multi-institutional trials.
- Deploy informed consent forms that allow for broader use of patient specimens and patient information for future studies.
- Obtain repeat biopsies of patients’ tumors to assess therapeutic effectiveness.

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promote collaboration by only distributing resources to teams from multiple organizations and disciplines.

It can take years to accomplish the many steps required to complete preclinical work, resolve intellectual property issues, and initiate a collaborative, multisite clinical trial of combination therapy. During that lengthy start-up time, new scientific advances may arise, showing that drug combinations currently under clinical evaluation are no longer the most promising ones to test. The process could be streamlined through acceptance of broader, forward-looking consent forms, coordination of Institutional Review Board (IRB) reviews, data sharing and analysis, intellectual property agreements, and investigational new drug applications. A major time constraint is acquiring the IRB approvals from multiple institutions. Presenting a solid trial concept initially to IRBs can help expedite the process, as well as frequent communication and involving multiple investigators (in addition to the principal investigators) with clinical trial experience on a research team. Patient advocates can press academia to make their IRBs more efficient and can also push for a list of vetted important clinical trials that should have priority status for evaluation.

There is a great need for increased communication, collaboration, and transparency among the various stakeholders developing cancer therapies. Although companies are by nature competitive, recently drug companies have expressed a willingness 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 have nothing comparable in their own portfolio. Even when a company has a similar agent in development, if another company’s agent is likely to conduct better in combination, there should be a strong incentive to collaborate.

More collaborations between academia and industry would also be beneficial. It can be very challenging for academic researchers to acquire investigational agents that are currently in development, especially if they come from different companies, and it is often difficult to obtain agents that have dropped out of development. However, if academic institutions can obtain these agents, they may be able to conduct research that informs future clinical trials and drug development. For example, institutions may study combination effects on targets or conduct retrospective analyses of samples and data from previous preclinical and clinical studies to find biomarkers for patient selection.

The routine collection of patient specimens during clinical trials will be critical for identifying and validating such biomarkers and warrants financial support, along with efforts to store and make these tissues available for future research. There is substantial variability in how IRBs interpret patient consent about the future use of their specimens and data collected during the course of a study. Inclusion of strong patient advocates on IRBs can help to ensure that patients who want to share their specimens and/or relevant data with other researchers for future studies have the ability to do so.

### Legal issues

Legal issues, such as sharing risk and indemnification, allocating intellectual property rights, and forging agreements among industry, academia, and government can
impede collaborations to develop investigational combination therapies for cancer.

A major stumbling block is assessing the safety of the combination and attribution of, and reparations for, serious adverse effects that patients may incur during a clinical trial. This can be particularly problematic for combinations of investigational agents for which the toxicities are not fully known. Determining indemnification and sharing risk among institutions for clinical trials is also a major issue for combinations with immunotherapies.

Intellectual property issues can be a major impediment to collaboration among pharmaceutical companies and can extend drug development timelines. Intellectual property agreements can be complex, with numerous variables, including who owns the agent and the process for manufacturing it, who owns the data and new inventions that might stem from the collaborative research, and how and where patents will be enforced. In addition, trade secrets may still have to be protected even when no patentable inventions result from the research. Lessons can be drawn from examining the positive and negative experiences of past industry collaborations, such as the Inter-Company Collaboration for AIDS Drug Development, a group of 15 pharmaceutical organizations that interacted in the development of combination antiretroviral drugs (34, 35).

Some drug companies may also be reluctant to conduct collaborative research and development on investigational drugs because of antitrust concerns. However, antitrust laws 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 the benefits of the collaboration likely exceeded those achievable on an independent basis. Guidance from the U.S. Federal Trade Commission and the Department of Justice about antitrust issues is available and includes recommendations for joint ventures in research and development (36).

Regulatory issues

There is concern over the lack of clarity about U.S. Food and Drug Administration (FDA) regulations on the development of investigational agents in combinations, resulting in drug companies being less willing to participate in collaborations. In an attempt to address this issue, the FDA recently released a draft guidance for industry on the codevelopment of 2 or more unmarketed investigational drugs for use in combination (37). The premise for this guidance is the clinical need for combination therapies, the FDA’s flexibility in ascertaining the contributions of individual agents in a combination, the need to show the biologic rationale for the combination, and the case-specific nature of investigational new drug (IND) submissions and labeling issues for which FDA encourages sponsors to consult with the agency early and often in the development process (38). The European Medicines Agency has also recently released a draft guidance on regulatory issues surrounding combination therapies (Fig. 1B; ref. 39).

For combination regimens, sponsors are often required to show the contribution of each drug component. However, there are times when it is unethical to study single agents because they may be much less likely to be effective as monotherapy than in combination. In these cases, a multiarm clinical trial is not required to determine the need for combining agents; rather, compelling preclinical data, results from phase II trials, or related information can be used. The FDA encourages pre-IND consultations, especially for innovative study designs, to discuss potential issues about combination testing.

Moving Forward

Given the complexity of cancer and the mounting evidence that combination therapy is likely to result in more effective cancer treatments, it is imperative to build greater collaborations among industry, academia, and government for developing combination investigational cancer therapies. Several suggestions for how to facilitate such collaboration have been presented in this article.

It is important for the entire drug development community to embrace and integrate collaboration models to advance combination investigational cancer therapy development. There is an urgency to identify solutions for the identified barriers because patients are waiting and their lives are at stake. New and better therapies, many of which will require novel drug combinations, are desperately needed if we are to make an impact on outcomes for patients with cancer.

Disclosure of Potential Conflicts of Interest

R. Canetta is employed by Bristol-Myers Squibb and has ownership interest (including patents) in BMY, MIN, and ZMH. J.A. Wagner is employed by Merck Research Laboratories as Vice President, PLM, and has ownership interest (including patents) in Merck. J. Hohneker is employed by Novartis Pharma AG as Global Head of Development for Integrated Hospital Care and has ownership interest (including patents) in Novartis AG. He also served as chair for the workshop that contributed to the content of this article and was intimately involved with workshop development. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The responsibility for the content of this article rests with the authors and does not necessarily represent the views of the Institute of Medicine (IOM), its committees, or its convening activities.

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Acknowledgments

The activities of the IOM’s NCPF are supported by its sponsoring members, which currently include the National Cancer Institute, the Centers for Disease Control and Prevention, the American Association for Cancer Research, American Cancer Society, the American Society of Clinical Oncology, the Association of American Cancer Institutes, Bristol-Myers Squibb, C-
Change, the CEO Roundtable on Cancer, GlaxoSmithKline Oncology, Novartis Oncology, the Oncology Nursing Society, and Sanofi Oncology. The authors thank the workshop planning committee, speakers, and participants. Planning committee members included J. Hohneker (chair), R. Canetta, Michael Chamberlain, Roy S. Herbst, P.M. LoRusso, Frank McCormick, Richard Pazdur, Philip D. Porter, Ellen Sigal, I.A. Wagner, and A. James Zwiebel.

Received July 26, 2012; revised September 19, 2012; accepted September 21, 2012; published OnlineFirst October 12, 2012.

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Accelerating Cancer Therapy Development: The Importance of Combination Strategies and Collaboration. Summary of an Institute of Medicine Workshop

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Clin Cancer Res  Published OnlineFirst October 12, 2012.