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COMMENTARY

Opportunities and Challenges in the Development of Experimental Drug Combinations for Cancer

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Manuscript received December 29, 2010; revised May 4, 2011; accepted June 8, 2011.

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It is becoming increasingly evident that cancers are dependent on a number of altered molecular pathways and can develop diverse mechanisms of resistance to therapy with single agents. Therefore, combination regimens may provide the best hope for effective therapies with durable effects. Despite preclinical data to support this notion, there are many challenges to the development of targeted combinations including scientific, economic, legal, and regulatory barriers. A discussion of these challenges and identification of models and best practices are presented with intent of aiding the research community in addressing real and perceived barriers to the development of combination therapies for cancer.

J Natl Cancer Inst 2011;103:1222–1226

Cancers are dependent on many altered molecular pathways and use multiple mechanisms of immune resistance such that single-agent therapies alone may not provide long-lasting benefit for most patients. Even dramatic objective responses to single agents are commonly short-lived as evolving mutations in the agent's primary target or changes in a downstream effector lead to drug resistance and cancer progression. For example, the median duration of response to vemurafenib (RO5185426, RG7204, or PLX4032), a highly selective mutant BRAF inhibitor under development for BRAF mutant metastatic melanoma, is approximately 7 months despite an initial response rate of 81% (1). Although it has been reported that some patients in this first cohort are still responding more than 2 years after initial treatment (2), the majority of responses are temporary and incomplete. In addition, analyses of tissues from relapsed patients and laboratory studies with cell lines are identifying several mechanisms of resistance to highly selective BRAF inhibition (3,4,5). These studies and other reports support the hypothesis that drug combinations will be necessary to provide long-term tumor control for most patients. These considerations recapitulate infectious disease paradigms in which combination therapies for disorders such as HIV/AIDS and tuberculosis are the rule rather than the exception. Potential combinations of anticancer agents include a variety of permutations of experimental agents and/or standards of care (eg, chemotherapy, targeted agents, and immunomodulators). Evidence from animal tumor models indicates that the therapeutic effects of certain drug combinations may exceed those of monotherapies. Before phase II or phase III studies of combination therapies can be initiated, rational preclinical models should guide clinical trial design and may illuminate issues such as dosing regimens (administering two drugs concomitantly or sequentially), drug interactions affecting pharmacokinetics, and

interactive toxic effects. In addition, new approaches to phase I studies of combination therapies should be considered to improve efficiency and increase our understanding of how best to test agents in combination (6).

Despite evidence of the potential for improved benefit when two anticancer agents are combined (7–10), the majority of cancer drugs follow development pathways as single agents, resulting in substantial failure rates. Roughly, 90% of the oncology drugs that entered clinical testing between 1993 and 2002 ultimately did not receive US Food and Drug Administration (FDA) approval (11). Oncology therapeutic strategies that incorporate rationally designed drug combinations at earlier stages of development have the potential to substantially improve this disappointing track record. Numerous challenges exist in developing research approaches for combination therapy, particularly for agents developed by multiple institutions, both academic and pharmaceutical based (12–17). For example, in addition to the scientific challenges inherent in optimizing drug combinations, productive collaborations can be challenged by economic considerations, issues related to contract terms including intellectual property, and a range of logistical obstacles. Mechanisms are needed to efficiently identify the potential therapeutic advantage in the combination of select anticancer drugs, drive decision making about the prioritization of rational combination trials, and then implement the clinical development of high-priority combinations efficiently. Clinical trial design for combination therapies is complex, and there is no one-size-fits-all approach; however, new and more flexible development models described here and in previous reports may simplify the process (16). Regulatory and safety considerations, such as concerns about unexpected toxic effects, are barriers to clinical development and approval. Some of these barriers are perceived rather than real, but perception can (and has) become reality. Overcoming these

barriers will take cooperation among the regulatory bodies, the academic community, and the private sector.

The economic environment for the commercial development of combination therapies is an overarching challenge. Drug development is primarily funded by the private sector; thus, business considerations play a role. Efficacy must outweigh the increased cost and development complexity of a combination product. Importantly, partnerships between companies (risk sharing and profit sharing business models) as well as between sectors (academia, industry, and government) can leverage resources and mitigate risk and have become more common for these reasons. Other solutions include improved preclinical research, innovative trial design, rational intellectual property and legal approaches, and more frequent interactions with regulatory agencies.

The need for new more effective cancer treatments has never been greater. Cancer is the second-most common cause of death in the United States; in 2010, it was estimated that more than half a million Americans died of cancer, or more than 1500 people per day (18). Given the opportunities and challenges for combination therapies for cancer, the Melanoma Research Alliance hosted the session, “Developing Experimental Drug Combinations: Opportunities and Challenges” as part of the Melanoma Research Alliance Annual Scientific Retreat held February 24–26, 2010, in Las Vegas, NV. Whereas the potential value of combinatorial therapies applies to all cancer types, the incidence of melanoma has risen faster than any other cancer during the last three decades (19), and is particularly relevant because of the recent monotherapies that statistically significantly slow disease progression and improve overall survival but infrequently produce long-term remission in patients. These monotherapies include kinase inhibitors such as vemurafenib and immunotherapies such as ipilimumab (anti-cytotoxic T-lymphocyte antigen-4). Precedent for the development of combinatorial therapies of cancer comes from the cure of most childhood leukemias with combinations of agents, which displayed only transient anticancer effects on their own. Thus, a discussion of the opportunities and challenges to developing combination therapies for melanoma in particular, and cancer in general, was held among representatives from academia, industry, and government with the goal of accelerating the delivery of new tools and treatments to patients. The discussion prepared the Melanoma Research Alliance for a continuing dialog on these issues, the summary of which is presented here.

Scientific Considerations

New treatment opportunities for melanoma fall into two broad categories as follows: immunotherapy targeting specific regulatory

molecules for the antitumor immune response and molecularly targeted pathway inhibition. Melanoma is one of the most responsive human cancers to immune modulation and has become the prototype for developing cancer immunotherapies (20), which may be applicable in a broader setting. Furthermore, mechanisms of carcinogenesis depending on aberrant intracellular signaling have been well characterized in many cancers with BRAF being the most common kinase mutation in melanoma identified to date (21). Thus, opportunities for combined therapies in cancer include combinations of molecularly targeted agents (eg, a highly selective BRAF inhibitor with a MEK inhibitor), combinations of two or more immunotherapies (eg, vaccines plus immune modulating antibodies or two immunomodulatory antibodies), combinations of signaling inhibitors with immunotherapy, or combinations of an experimental agent with standards of care (eg, radiotherapy and chemotherapy). In addition, new insights into the tumor microenvironment suggest opportunities to combine agents, which directly target the tumor cell and nontransformed cells in the tumor stroma.

A first key step in the pursuit of combination therapies is to show compelling scientific and medical rationale, that is, the potential for increased efficacy with limited toxicity. The development stage of the individual agents (what is known and not known about the drugs) will affect the approach used for the combination and is summarized in Table 1. Rigorous preclinical studies, including appropriate animal models and toxicology studies, are required to assess the potential of a combinatorial regimen and to set the stage for clinical trial design. Kwak et al. (22) proposed guidelines for the identification of potential combinations of molecularly targeted agents on the basis of biological and preclinical data. Also, prospects for melanoma combination therapies were recently summarized by Ascierto et al. (23) who described combinations of agents that could be useful for melanoma as well as scientific considerations for testing these combinations and more general considerations for combination therapy development.

In academia, basic and preclinical studies can be impeded by a lack of access to commercial and investigational agents. The US National Cancer Institute (NCI) has created several resources to facilitate research in the area of drug combinations. To address the need for commercially available agents for in vitro use, NCI developed COMBO plates for in vitro combination studies. These 96-well plates containing all commercial FDA-approved anticancer drugs are available at no cost to academic investigators. Another resource is the NCI 60, a platform incorporating 60 tumor cell lines that is being used to investigate the effects of two-drug combinations for all commercially available anticancer agents. NCI will make the results of these studies available to academic investigators for further hypotheses-driven research (24).

Table 1. Development considerations for combination therapies

Drug development		Drug B	
		Early	Late
Drug A	Early	Combination opportunity is theoretical	Dose, efficacy, and toxicity of at least one compound is well defined
	Late	Dose, efficacy, and toxicity of at least one compound is well defined	Combination opportunity on the basis of a solid understanding of the dose, efficacy, and toxicity of each agent as a monotherapy

A third NCI resource is the Chemical Biology Consortium, an initiative created to facilitate drug discovery and development of new investigational agents for cancer. A limitation of these in vitro screens is the increased biologic complexity of in vivo tumors that depend on nontransformed components of the tumor microenvironment. Nevertheless, the in vitro combinatorial screens provide a rapid means of empirically identifying candidate drug pairs that can be further tested using in vivo cancer models.

Organ site cancers are not a single disease and identifying subpopulations of patients most likely to benefit and/or are least likely to incur serious toxic effects from a particular drug or combination increases the probability of success. In melanoma, for example, several different subtypes have been identified on the basis of common genetic mutations, in molecules such as BRAF, NRAS, PTEN, cKIT, and GNAQ (25). The development of companion diagnostics to identify patients who will benefit from agents targeting aberrant molecular pathways, although sometimes costly, may be an important component in developing both monotherapies and combination therapies for cancer.

Clinical Trial Design

Clinical trial design for combination therapies is complex, and there is no uniform approach (6). Trial design for a combination must be driven by preclinical studies, the characteristics of the individual compounds, and the patient population of interest. Three typical combination scenarios and clinical trial design recommendations are summarized in Table 2. When the combination of two drugs demonstrates potential antitumor activity but neither drug has single-agent activity (Scenario 1), there are three variables that should be optimized: 1) the ratio of the drugs, 2) the dose of each drug in the combination, and 3) the administration regimen (A with B, A before B, or B before A). The variables of drug ratio and overall dose require a phase I trial using a factorial design followed by either a single-arm phase II design with a fixed ratio and dose and concomitant administration. Alternatively, one could adaptively vary the ratio and/or dose of each drug on the basis of interim analyses to improve the efficiency of the trial. When one drug is active (A), but potentially modulated by the administration of a second drug which by itself is inactive (B) (Scenario 2), one should consider a phase I design in which the dose of A is fixed and the dose of B is modulated, and vice versa, to explore the influence

of the inactive drug on the safety, efficacy, and pharmacodynamics of the active compound. A randomized phase II design (A vs AB) should follow, as recently recommended by the NCI's Investigational Drug Steering Committee (26).

The most common scenario is that both drugs are active independently, but the combination is expected to be more effective than either agent alone (Scenario 3). A phase I dose-seeking trial should ideally be designed around a testable hypothesis. For example, 1) both drugs can be given at full dose, 2) one drug modulates the pharmacokinetics of the other, 3) one drug modulates the pharmacodynamics of the other, or 4) one drug increases the toxicity of the other. If there is a possible pharmacokinetic interaction (eg, one may decrease the clearance of the other), consider starting at 25%–50% of the standard dose of one drug and the full dose of the other. The pharmacokinetics of one drug should therefore be evaluated with and without the second and rapidly escalate it if there is no evidence for interaction. If there is a possible pharmacodynamic interaction (eg, one may increase the toxicity of the other), consider designing the trial such that patients receive one drug alone in the first treatment cycle, followed by the combination.

A phase I trial might not be necessary under certain circumstances. Preclinical data may suggest that a pharmacokinetic interaction is unlikely, as indicated by in vitro studies and knowledge of metabolism and transport of both drugs. In addition, a drug combination may go straight into a phase II study if in vivo animal studies showed that both drugs can safely be given together at the full dose without increased toxicity compared with monotherapy. If there is no formal phase I trial, the safety of the full dose of the combination should be tested as an initial cohort in the phase II study.

Legal Issues

Legal issues are often cited as barriers to the development of combination therapies. This is particularly true when the therapeutic agents come from different sources, such as separate biopharmaceutical companies or academic centers. Yet, there are very few true legal barriers. In reality, other tensions such as patent, regulatory, and transactional dynamics are sometimes expressed in legal terms. Agreements between partners can nevertheless be delayed by these perceived barriers.

A frequent source of contention is the struggle to define which party will own the rights to any invention developed during the

Table 2. Clinical trial design considerations for three typical scenarios for two drug combinations (drug A and drug B)

Scenario	Phase I	Phase II
Scenario 1: A plus B is active, but neither A nor B is active as a single agent	Optimize the ratio of A : B and the dose of the combination	A single-arm design at a single ratio and dose using the response rate as the clinical endpoint. A randomized adaptive design that varies the ratio and/or dose can also be used.
Scenario 2: B is inactive, but modulates the activity of A	Effect of dose of B on toxicity and efficacy of A or effect of dose on a biomarker	Randomized design testing A vs A plus B using a fixed dose of A and one or multiple doses of B
Scenario 3: Both A and B are active but the combination works better than either one alone	Consider no phase I, but if a phase I study is needed, design around a testable hypothesis such as: 1) A and B can be given at full dose; 2) A modulates the pharmacokinetics of B; 3) A modulates a biomarker of B; or 4) A increases the toxicity of B	Randomized design

course of research to develop a combinatorial strategy. In fact, such inventions are rare, and it is highly unlikely that they will measurably affect the exclusivity or economic value of the combination therapy being developed. Freedom to operate, in fact, protects both patent holders of each component, and thus, the definition of rights is straightforward to resolve by contract if the parties are reasonable.

In addition to intellectual property, sources of possible contention include the division of expenses and profit, proposals for exclusive arrangements, disagreements about commercial strategy, and the complexity of combination product pricing. Uncertainty about the commercial potential of combination regimens and the potential impact of combination therapy development on single agents can also negatively influence negotiations. In general, the greatest barrier to agreement on combination therapy is the desire of one party to extract more value from the partnership than is warranted by its contribution to the collaboration. This potential barrier results when the negotiation is viewed as a zero-sum exercise, with an economic winner and a loser. However, collaborations can create added value for each partner, particularly when there is strong preclinical data supporting enhanced efficacy for the combination therapy. First, the probabilities of ultimate success in FDA approval (and therefore the market) increase, thereby mitigating the risk of financial losses associated with development paths that ultimately fail. Second, a more effective regimen has a longer market life cycle because it is not as easily displaced by other agents competing for the same market.

Resources provided by the NCI Cancer Therapy Evaluation Program (CTEP) may facilitate research on combination therapies involving sponsors from different sectors. NCI/CTEP holds collaborative development agreements with more than 80 industry partners for more than 100 investigational agents, as well as clinical trial agreements with academic institutions, consortia, and cooperative groups. NCI/CTEP developed a template agreement language for these multisector collaborations that addresses data sharing and intellectual property. Provisions were included to ensure access to data by all parties who provided agents and the use of the data for scientific and regulatory purposes that is consistent with the development of a single agent. In addition, there is an option for each collaborator to receive fully paid, co-exclusive or nonexclusive royalty-free licenses to any inventions from the combination studies (27). Best practices specific to academic-industrial partnerships have also been produced by the Government-University-Industry Research Roundtable of the National Academies (28), the Association of University Technology Managers (29), and other groups. Despite the perception to the contrary, it is extremely rare to have antitrust concerns in the development of combination therapies between two companies unless there is an exclusive arrangement that would prohibit one partner from developing combinations with the products of third companies. A final perceived barrier is the fear of product liability. Liability is rarely a major factor in oncology clinical trials designed for patients with advanced treatment-refractory disease, because these patients are more likely to accept some risk of toxicity for a potential clinical benefit (30). Liability issues become more important in trials designed for otherwise healthy at-risk individuals or those with early-stage cancer. The development of enhanced biomarkers

predictive of recurrence in patients with stage I–III cancers would allow for identification of high-risk individuals, thereby diminishing liability risks for the development of combinatorial adjuvant therapies. Detailed and properly explained clinical trial consent documents would also minimize the liability risk in trials designed for otherwise healthy at-risk individuals or patients with early-stage cancer.

Regulatory Concerns

Regulatory considerations are of paramount importance in the development of combination therapies for cancer. The expense, complexity, and time needed to prove that a combination product is both superior to the standard care and to monotherapy with each agent are substantial barriers to development (15). A major issue that the FDA should address stems from the fact that companies considering development of combinations of agents are often in the process of developing one or more of the components as single agents. Under these circumstances, there is a concern that unexpected toxic effects associated with the combination will either slow the concurrent development of the single agent or create new liability (14). The FDA does not currently have a mechanism for single-agent indemnification, that is, attributing an adverse event (toxicity) to one component of a combinatorial treatment regimen but not the other. Furthermore, the FDA has not clearly articulated policies of toxicity review and drug labeling that would allow single-agent development to proceed unfettered by toxic effects, which only arise when the agent is used in a novel combination. Although there have been varying interpretations of the FDA combination rule, it is intended for drugs combined in one physical form. The agency is creating a guidance document on regulatory policies specific to combination regimens composed of experimental drugs and has recently solicited relevant commentary from the public on draft guidance (31).

Because combinatorial strategies will always be easier to develop when one of the components is already approved as a single agent, accelerated approval of single agents would dramatically enhance the development of combinatorial approaches to treat cancer, an important aspect distinct from the conventional consideration of making promising agents more available to cancer patients. Enhancements in the accelerated review process that allow for market approval contingent on a postmarketing phase III study would, therefore, have important benefits for the approval process for combinatorial therapies.

To address the regulatory issues that may cause unnecessary delay in the drug development process, sponsors should have discussions with regulatory agencies about novel development approaches and the level of preclinical evidence needed before a clinical trial is initiated and frequently throughout the course of the trial. Improved FDA guidance, including the draft guidance recently announced, will enhance development efforts for combination therapies for cancer.

Conclusions

Recent scientific advances have led to the development of promising individual therapeutic agents, but it is becoming increasingly

clear that tumor cells have redundant prosurvival pathways that will need to be overcome through combination treatments. In addition to scientific and clinical issues, numerous operational challenges including economic, legal, and regulatory hurdles exist in developing combination therapies, particularly when different sponsors are involved. Although some barriers are only perceived, these difficulties can be addressed through the use of smart practices and creative approaches. Combination therapy development can be facilitated through improved preclinical research to predict the best therapeutic strategies, thereby reducing the complexity and cost of clinical trials; innovative clinical trial design, including modeling and simulation studies; early and frequent discussions with regulatory agencies to discuss novel developmental approaches; increased collaborations between industry, government, and academia; and risk sharing and profit sharing business models. New molecularly targeted agents and immunotherapies provide many promising options for combination strategies which, in addition to refined FDA guidance, will help speed the development of more effective treatments to end suffering and death from cancer.

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Funding

This work was supported by the Melanoma Research Alliance.

Notes

The authors are solely responsible for the writing of this commentary and the decision to submit the commentary for publication. R. W. Humphrey and D. L. Bonk are employees of Bristol-Myers Squibb Co, the makers of ipilimumab (Yervoy), and hold stock in this company.

Affiliations of authors: Global Development (RWH) and Law Department (DTB), Bristol-Myers Squibb Company, Princeton, NJ (RWH); Melanoma Research Alliance, Washington, DC (LB-L, SLT); Oncology Translational Medicine, Novartis Institutes for Biomedical Research, Inc, Cambridge, MA (KMD); Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD (JHD); Pfizer Oncology, Pfizer, Inc, New London, CT (SJM); Cancer Research Center and Department of Medicine, University of Chicago (MJR); Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine (SLJ, DMP).