Commentary: Tackling the Challenges of Developing Targeted Therapies for Cancer

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Now is a time of unprecedented opportunity and progress in cancer drug development. Fueled by an explosion of information about the biological underpinnings of cancer, new drugs, directed at critical molecular targets, are being introduced into cancer treatment at a rapid rate. Witness the transformation of treatment for advanced kidney cancer, a disease for which five new drugs have received FDA approval in just the last 5 years. During this same interval, targeted therapies have been introduced for treatment of other tumors that have historically been resistant to treatment with cytotoxic chemotherapy such as hepatocellular cancer, gastrointestinal stromal tumors, and glioblastoma. For many other cancers, however, the promise of effective targeted therapies remains unfulfilled. Cancer drug development remains an expensive, inefficient, and risky business with limited participation by oncologists and cancer patients in clinical trials. This has contributed to a limited impact on mortality for many cancers and for millions prolongs the daily challenges encountered with diagnosis and treatment of their disease.

More than 800 drugs are now in clinical development for cancer indications yet success rates in bringing drugs to market remain in the range of only 5%–8%. Many factors may contribute to these low success rates: little scientific insight into the determinants of drug sensitivity and resistance; poorly conceived and executed clinical development plans; heterogeneous patient populations and lack of biomarkers to identify patients most likely to benefit from specific treatments; unclear, conflicting, or burdensome regulatory requirements; and lack of agreement among clinicians, investigators, and regulators as to what constitutes clinical benefit in some circumstances. Moreover, the same biological insights that have enabled development of targeted treatments now challenge product developers to focus on molecularly defined tumor subtypes, to develop analytically and clinically validated biomarker tests to guide therapy, and to introduce clinical trial endpoints, other than survival, that objectively demonstrate meaningful clinical benefit. With the introduction of molecular pathology, patients and their oncologists now deal with a greater variety of malignant diseases than ever before, each of which is less common than cancers diagnosed by histology alone, and each of which likely benefits from a unique approach to treatment. Finally, with many new drugs slowing tumor progression rather than causing tumor shrinkage, cancer drug trials may require more patients and the more frequent use of placebo controls, thus presenting greater recruitment challenges. Contemporary trials may require a long period of time to reach major clinical endpoints.
more expensive clinical documentation to record progression events, and additional regulatory scrutiny, especially when studies seek approval of both drugs and diagnostic tests that are used to select patients for treatment.

In an effort to address some of these issues, the Engelberg Center for Health Care Reform at Brookings Institution and Friends of Cancer Research convened conferences in 2008 and 2009, with support from the American Society of Clinical Oncology, the American Association for Cancer Research, the Lance Armstrong Foundation, and Susan G. Komen for the Cure. The conferences aimed to frame key issues and develop new approaches that would improve the efficiency and reduce the cost of cancer drug development while ensuring that scientific rigor and regulatory standards are preserved. The conference format facilitates multisector collaboration on specific issues in clinical research by convening expert panels comprised of representatives from academia, government, industry, and the patient community that work during the months leading up to the conference to identify areas of consensus and to propose solutions to specific challenges in oncology drug development. Past topics have included the following: issues relating to optimized data collection for supplemental new drug applications; the utility and validity of blinded independent review of progression events in clinical trials; the regulatory approach to drug and biomarker co-development; and the scientific, clinical, and regulatory challenges of combining targeted new molecular entities that may have limited antitumor activity as single agents. Each of these areas presents unique challenges and requires thoughtful solutions that remain focused on the overall goal to deliver safe and effective new therapies to cancer patients as quickly as possible.

Although the FDA has issued guidance on data collection requirements for new drug applications, uncertainty remains regarding the type and extent of data collection required. Sponsors therefore continue to collect comprehensive information on adverse events and use of concomitant medications for essentially all registration-directed trials, even those seeking supplemental indications. Doing so drives up cost, adds complexity, and more importantly, may distract investigators from focusing on medically important new safety information and diminish their enthusiasm for participation in clinical trials that collect large amounts of data that are never used to inform regulatory decisions or change labeling. Many medically important new drugs have initial and multiple supplemental indications. The extent and nature of data collection for the supplemental studies should be guided by what is already known about the safety profile and pharmacology of the drug, the similarity of the intended new patient population to that for the approved use, the potential for previously unrecognized drug interactions, and the risk/benefit assessment for the intended new use. At the same time, there are risks to reducing data collection requirements for supplemental applications, particularly the possibility of missing new safety signals. The expert panel tackling these issues proposed adhering to certain core principles to mitigate these risks, such as reducing data collection only if the existing drug safety database was sufficient to support full regulatory approval of the initial indication, collecting serious adverse events, deaths, and adverse events requiring dose modification or discontinuation in all patients, and if medically appropriate, collecting targeted adverse events in all patients that are based on the known safety profile and pharmacology of the drug. To address the question of “What might be missed?” by otherwise reducing data collection, a simulation exercise led by the American Society of Clinical Oncology was undertaken to re-analyze data already collected from eight completed randomized trials in both the metastatic and adjuvant settings. This analysis suggests that few clinically important events would be likely to be missed and that as long as the core principles are followed, comprehensive adverse event data collection could be limited to only a subset of patients enrolled in trials that seek supplemental new indications.

Progression-free survival (PFS) is an endpoint being used with greater frequency in pivotal randomized trials of targeted therapies. PFS includes all patients in the study analysis and has the advantage compared with overall survival of being reached sooner and of not being confounded by the impact of subsequent lines of therapy. However, PFS is fraught with problems of defining what constitutes progression and when progression occurs and of minimizing bias in assessment of progression events by the treating physician, particularly in open label studies. To deal with these issues, special care must be taken in the design of studies that use PFS as a primary endpoint including blinded treatment assignment whenever feasible, comprehensive assessment of all lesions at baseline, prospective designation of target lesions in each patient, clear specification of the frequency and modality of imaging assessments, and others. PFS is, in many ways, the most complex and expensive clinical endpoint used in oncology drug trials. There is, of course, also the issue of the magnitude of improvement in PFS that constitutes benefit to a patient if there is no improvement in overall survival or symptom control. Given the complexity of the PFS endpoint, FDA has frequently required blinded independent assessment and central review of progression events in registration-directed trials. Such reviews add considerable time and expense to the conduct of clinical trials and legitimate questions have been raised as to their ultimate utility in de-
testing and mitigating bias. The expert panel dealing with this issue carefully considered not only the utility of these reviews but also the evidence that blinded independent review can introduce other biases into evaluation of the study results that may create new problems. On the basis of their analysis, the panel concluded that a strategy of independently reviewing approximately 20% of the total study population would generally be sufficient to detect a statistically significant hazard ratio of 88% of the time in a study with a large treatment effect [1]. A larger audit may be required for studies with a moderate treatment effect, but for studies with a small treatment effect, the blinded review may itself introduce sufficient random variation as to no longer be useful to validate the investigator assessment.

Biomarker-driven clinical trials introduce regulatory challenges when the goal is biomarker assay and drug co-development in that the test and the drug must meet both regulatory standards for marketing approval and clinical use. Within the FDA, reviewers of in vitro diagnostic tests and drugs reside in different centers of the agency (i.e., Center for Devices and Radiological Health and Center for Drug Evaluation and Research) that apply separate review processes to satisfy their respective statutes and regulations. The requirement that both the drug and the test demonstrate clinical benefit and the different evidentiary standards applied by the two FDA oversight divisions creates many challenges. For example, although it may be sufficient to demonstrate that a drug has clinical benefit in a biomarker-defined population to obtain drug approval, regulatory approval of the biomarker test may also require demonstration that the drug is ineffective in the biomarker-negative patient population. Thus, investigators and sponsors may find it challenging to design clinical trials that are acceptable to both divisions and provide conclusive evidence of the safety and effectiveness of both the test and the drug. Analytical validation of the test is a necessity but clinical validation is increasingly required by FDA and may require large prospective trials to generate data sets that support such claims. The expert panel tackling this issue set out as a goal to develop a regulatory pathway that would facilitate the accelerated development and approval of a cancer therapy used in a population defined by a specific biomarker test. The proposed criteria for this “targeted approval” are that the drug must be indicated for use in cancer treatment, the assay must be analytically validated, and the drug must demonstrate, in a population defined by the test, a prespecified statistically significant change in a clinical endpoint that is reasonably likely to predict clinical benefit. Under such circumstances, it is proposed that the FDA would approve the drug for use in the population identified by the biomarker test and approve the test for use in identifying the patient population for treatment with the drug with the caveat that the test has not been proven useful to identify patients with expected lack of benefit from the drug. Post-marketing studies would be required and would establish the utility of the test and the drug in the biomarker-negative population. It is tempting to speculate that such a strategy could be pursued in the regulatory review of drugs that have recently shown high response rates in molecularly defined patient populations such as patients with melanoma that harbors a BRAF V600E mutation [2]. The panel proposed that, in these circumstances, reimbursement by insurers for off-label use of the drug would not occur until completion of the postmarketing studies. This novel regulatory pathway builds on the accelerated approval pathway for drugs in place at the FDA for nearly 2 decades and offers an approach to more efficient and less costly drug-biomarker co-development.

Despite the many important advances in understanding tumor biology and using biomarkers to identify and select patients likely to benefit from or be resistant to treatment, there are too few examples of clinically useful biomarkers that can identify drug sensitivity and predict clinical benefit. Why is it so difficult to identify positive predictive biomarkers? The challenge lies primarily in understanding the heterogeneity of cancer and the plasticity of the cancer genome. Tumors with drug-sensitizing mutations can simultaneously harbor or develop drug-resistance mutations, as in the case of the EGFR T790M mutation [3]; there may be downstream pathway activating mutations as in the case of KRAS [4]; activation of a parallel pathway that circumvents a pharmacological block is also known to occur as in the case of mesenchymal-epithelial transition factor gene (MET) amplification causing resistance to small-molecule EGFR inhibitors [5]; or pathway blockade can result in feedback upregulation of the pathway to overcome the block [6]. Overcoming the multiple redundancies and crosstalk of critical signaling pathways will require that targeted therapies be used in combination to achieve optimal effect. Such combinations might include drugs that have little or no activity as a single agent but that produce substantial antitumor effects when used in biologically rational combinations. Existing regulations require that, for fixed combination drug products, the sponsor demonstrate the contribution of each drug in the combination to the beneficial effect of the combination product. Even when individual drugs are combined in a novel regimen, the FDA has generally recommended that factorial trials be employed to demonstrate the effects of the drugs individually as well as together. But in the era of targeted therapy for cancer, such an approach might be scientifically illogical, medically unfeasible, and ethically inappropriate. The expert panel deal-
ing with this complex subject has provided examples and specific criteria for the development and regulatory approval of two new molecular entities given in combination, particularly when one or both agents have little antitumor activity as single agents. Such an approach must be driven by a strong biological rationale and some preclinical evidence of greater than additive antitumor activity for the proposed combination. The toxicity profile of each individual agent must be carefully studied and documented and potential pharmacological interactions between the agents must be understood. With this information in hand, a clinical development plan can be developed that efficiently evaluates the combination against a standard of care to prove its clinical utility. Modification of existing regulatory guidance to enable such approaches will be critical to enable and incentivize the rapid development of new targeted drug combinations that will likely be essential to make more rapid progress against cancer.

The thoughtful and creative approaches to solving vexing problems in contemporary cancer drug development described in this issue of *The Oncologist* are the result of an inclusive, collaborative effort between clinical investigators, statisticians, regulatory scientists, laboratory researchers, patients, and drug and device manufacturers who were convened around a common goal: to translate insights in cancer biology into clinically useful, safer, and more effective products for patients and into policies that accelerate their availability. The output of these expert panels illustrates the power of this collaboration to improve the scientific, clinical, and regulatory approaches to drug development and—hopefully—to accelerate the development of safe and effective treatments for patients with cancer.

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