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CONTENTS

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Cancer Treatment Reports

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,

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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-

tecting 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 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 codevelopment 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. Postmarketing 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 codevelopment.

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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References

1 Amit O, Bushnell W, Dodd L et al. Blinded independent central review of the progression-free survival endpoint. ***The Oncologist*** 2010;15:492–495.

2 Chapman P, Puzanov I, Sosman J et al. Early efficacy signal demonstrated in advanced melanoma in a phase I trial of the oncogenic BRAF-selective inhibitor PLX4032 (abstract 6LB). Eur J Cancer Suppl 2009;7(3):5.

3 Kobayashi S, Boggon TJ, Dayaram T et al. EGFR mutation and resistance of non small cell lung cancer to gefitinib. New Engl J Med 2005;352:786–792.

4 Engelman JA, Janne PA. Mechanisms of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non small cell lung cancer. Clin Cancer Res 2008;14:2895–2899.

5 Engelman JA, Zejnullahu K, Mitsudomi T et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 2007;316:1039–1043.

6 O'Reilly KE, Rojo F, She QB et al. mTOR inhibition induces upstream receptor tyrosine kinase signaling and activates Akt. Cancer Res 2006;66:1500–1508.

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Data Submission Standards and Evidence Requirements

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IMPORTANCE OF STREAMLINING DATA COLLECTION

The goal of the U.S. Food and Drug Administration (FDA) guidance documents is to provide insight into the data necessary for FDA reviewers to reliably assess the risk–benefit ratio of an investigational agent for a particular clinical indication. The current FDA registration guidance for cancer therapy trials does not completely describe the level of detail necessary for informative data capture to support claims of safety and efficacy for supplemental indications of new cancer treatments [1]. The guidance, as currently set out, does not distinguish drugs with substantive safety information and a definite benefit to patients from drugs with limited safety data that may carry safety risks that have not yet been recognized. Data collection requirements thus become essentially the same whether for a primary indication or a supplemental application. This can result in collection of excessive and sometimes unnecessary data by investigators, particularly for trials designed to explore additional indications where substantial toxicity data about an agent already exist. Further, because there is no established standard for collection of data in support of supplemental applications, sponsors interpret the requirements variably, resulting in inconsistent quality and quantity of data. Frequently, the data collected do not result in modifications to FDA labeling or inform medical practice, yet the data collection requirements add complexity and cost to conducting the study. Therefore, optimized standards for data collection should be developed for well-studied cancer therapies to improve the efficiency of safety evaluations without sacrificing the scientific integrity and validity of study results.

Streamlining data collection will help ensure better patient safety by improving the overall quality of data submitted in supplemental applications. Collecting essential data that will help inform patient safety, such as toxicities leading to death or dose discontinuations, is more important than collecting large amounts of data, such as cataloging all mild adverse events, that ultimately add little information to the existing safety profile of the drug. Collection of unused data may actually distract from gleaning crucial information. When faced with large amounts of safety data, it becomes difficult to prioritize safety events, distracting sites from focusing on the collection of important information, such as understanding what makes physicians or patients modify or stop treatment. Thus, large amounts of data can sometimes obfuscate knowledge of new and relevant safety data. Furthermore, streamlining data collection will greatly reduce the administrative burden on the clinical trial system and will focus finite resources on collecting key data elements. Reducing burdensome and unnecessary data collection will improve physician participation in clinical trials. Surveys to understand why patients do not participate in clinical trials reveal that doctors often do not recommend clinical trials to their patients. Among various other rea-

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sons, doctors cite that they are weary of the high administrative workload and liability associated with conducting clinical trials. In an effort to understand the burden of excessive data collection on trial administrators, a working group, resulting as an outgrowth of the 2008 Conference on Clinical Cancer Research and formed under the aegis of the American Society of Clinical Oncology (ASCO), solicited input from several cooperative group and industry sites. Of 110 responses received to the poll, >85% expressed the view that data optimization (as recommended below) would moderately or significantly impact site resources, allowing collection of higher quality targeted data and greater participation in the clinical trials process [2].

Potential Tradeoffs of Data Optimization

In order to further explore the tradeoffs between complete and optimal data collection, the Data Optimization Working Group assessed the extent of safety data collection necessary and sufficient to inform clinical and regulatory decisions in a supplemental application with the basic assumptions that:

- Streamlined toxicity data collection will not be used for initial indications (or the first supplemental application following accelerated approval).
- Streamlined toxicity data collection will be used only if the prior approval process included a safety database that was acceptable for a full regulatory approval.
- The statistical analysis plan will be structured to minimize the risk of missing important safety signals.
- Data on serious adverse events (SAEs), deaths, and dose modifications and/or discontinuations (with reasons) will be collected for all patients on all study arms.
- Data on targeted adverse events (AEs) would be collected based on the known safety profile and pharmacology of the drug and the study patient population.

Streamlining data collection will ensure that the data collected will be used and that unnecessary data will not be collected. Data collection requirements will vary as necessary depending on whether a sufficiently large safety and drug interaction profile already exists, the similarity of the study population to the population for approved use, the similarity of the supplemental regimen to the regimen already approved and, finally, whether the supplemental application follows initial full or accelerated approval. By collecting data on SAEs, deaths, dose modifications and/or discontinuations, and targeted AEs of interest in all patients on all study arms, sponsors are reasonably as likely to detect important safety signals as with the current data collection process.

Study Organization and Participants

At the Conference on Clinical Cancer Research held in September 2008, a panel on Data Submission Standards and Evidence Requirements proposed a framework for data collection necessary to support claims of safety and efficacy for supplemental new drug applications (NDAs) and biologic license applications (BLAs) [3]. In order to further explore elements of that framework, ASCO formed the Data Optimization Working Group. The Working Group provided a forum for all interested stakeholders (the FDA, the National Cancer Institute [NCI], academia, industry, and advocacy) to retrospectively review data sets from completed phase III trials, many that were used for FDA supplemental approvals, and discuss potential revisions to data collection standards.

Four companies and one cooperative group collaborated on this project. A statistical analysis plan was developed, reviewed by the FDA, and used by all participating sponsors. The project involved a reanalysis of eight trials, in both the metastatic and adjuvant settings, studying cytotoxic chemotherapy, targeted biological therapy, and hormonal therapy, as shown in Tables 1 and 2 [4].

Study Findings and Recommendations

The purpose of this study was to determine whether important safety information would be lost by only gathering toxicity data on a subsample of patients enrolled in a supplemental NDA trial with a drug for which a substantial toxicity profile already exists. In candidate trials where subsampling is appropriate, it is assumed that SAE information, including all deaths, dose discontinuations, and dose modifications along with the associated reasons, would continue to be collected on all patients. The reanalysis demonstrated that data subsampling did not appear to omit important information about the safety profile, that is, similar conclusions regarding the safety profile would have been reached if a subsampling approach had been used.

The study identified statistical methods for determining appropriate subsampling sizes that can be scaled to fit different cutoff rates. The subsampling size range recommendations using this statistical methodology are as follows.

For determining subsampling size (assuming a 2% excess and a two-arm trial):

- In the metastatic setting, approximately 400–500 patients should be subsampled (full study size, 800–1,200 patients).
- In the adjuvant setting, a total size of approximately 400–900 patients should be subsampled (full study size, 800–6,000 patients).

Table 1. Candidate trials evaluated in the study in the metastatic setting

Company, candidate study	Patient population	Treatment	Trial size	Primary endpoint
Genentech, AVF2107g	First-line mCRC	Arm 1, bolus IFL plus placebo; arm 2, bolus IFL plus rhuMAb VEGF; arm 3, 5-FU and LV plus rhuMAb VEGF	813	OS
Genentech, ECOG 4599	First-line nonsquamous NSCLC	Arm 1, paclitaxel and carboplatin; arm 2, paclitaxel, carboplatin, and bevacizumab	878	OS
Genentech, AVAIL	First-line nonsquamous NSCLC	Arm 1, cisplatin and gemcitabine; arm 2, cisplatin, gemcitabine, and bevacizumab	656	PFS
GSK, EGF 30001	Metastatic breast	Arm 1, paclitaxel and placebo; arm 2, paclitaxel and lapatinib	580	TTP
Eli Lilly and Co., JMDB	First-line NSCLC	Arm 1, cisplatin plus pemetrexed; arm 2, cisplatin plus gemcitabine	1,669	OS

Abbreviations: 5-FU, 5-fluorouracil; AVAIL, Avastin in Lung; bolus-IFL, irinotecan, 5-FU, and LV; ECOG, Eastern Cooperative Oncology Group; JMDB, H3E-MC-JMDB; LV, leucovorin; mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; rhuMAb VEGF, recombinant human monoclonal antibody vascular endothelial growth factor; TTP, time to tumor progression.

Table 2. Candidate trials evaluated in the study in the adjuvant setting

Company, candidate study	Patient population	Treatment	Trial size	Primary endpoint
Novartis, BIG 1–98	PMP women with HR^+ EBC	Arm 1, letrozole; arm 2, tamoxifen	8,028	DFS
CALGB, 89803	Patients with resected adenocarcinoma of the colon	Arm 1, LV and 5-FU (500); arm 2, irinotecan, LV (20 mg/m^2), and 5-FU	1,264	OS
Genentech, HERA	$HER\text{-}2^+$ adjuvant breast cancer	Arm 1, observation; arm 2, trastuzumab	3,386	DFS

Abbreviations: 5-FU, 5-fluorouracil; BIG, Breast International Group; CALGB, Cancer and Leukemia Group B; DFS, disease-free survival; EBC, early breast cancer; HER, human epidermal growth factor receptor; HERA, Herceptin® Adjuvant; HR, hormone receptor; LV, leucovorin; OS, overall survival; PMP, postmenopausal.

- Subsampling may not be appropriate or advantageous for trials with <600 patients.

The study also examined various subsampling methods, such as sampling patients at random, sampling study centers at random, sampling patients at the largest centers, sampling the first patients enrolled, sampling the last patients enrolled, and sampling the first and last patients enrolled (the last patients enrolled and the first and last patients enrolled were analyzed only for comparative purposes, not as a practical methodology). Sampling by centers at random was determined to be the most logistically feasible and accurate methodology for subsampling. To ensure full representation, a stratified population of patients from small, medium, and large centers should be chosen.

A lack of consensus regarding data collection, specifically toxicity data, has led to frequent discordance between practices in NCI cooperative groups and industry-sponsored clinical trials. The goal of this project is to recommend and justify sufficient data collection to generate safety data for drug labeling and clinical use and to reduce collection of unnecessary data elements in supplemental NDAs and BLAs. The effort and resources saved can be better channeled to focus on collecting more meaningful and accurate information that informs clinical and regulatory decisions and leads to greater participation in the clinical trial process.

FDA Response

In a guidance published in 2001 (Cancer Drug and Biologic Products—Clinical Data in Marketing Applications), the FDA provided recommendations for sponsors on data collection for cancer clinical trials submitted to the agency to

support marketing claims in NDAs, BLAs, and supplemental applications for new drug and biologic indications. The regulations (21 CFR 314.50) require that supporting data be submitted with study reports from well-controlled trials, but they do not describe the amount and type of data that should be collected.

Commercial sponsors may collect large amounts of information to ensure that they have all the data that regulatory agencies might request. Noncommercial organizations, for example, U.S. cooperative groups, frequently collect less information than commercial entities, although their trials may provide adequate data for important risk–benefit assessments supporting regulatory approvals. The FDA recognizes that extensive data collection can be expensive and time-consuming and that collection of unnecessary data is not an optimal use of clinical trial resources.

In the 2001 guidance, the FDA acknowledged that it is not possible to provide precise data collection requirements that could be applied to all trials because of the complexity and variability of clinical trial design. The FDA strongly encouraged sponsors to develop specific proposals for data collection and discuss their proposals with the agency prior to initiating clinical trials. The FDA maintained that agreement between the agency and the sponsor of the drug or biologic on prespecified data collection plans would "avoid the collection of unnecessary information, allowing resources to be directed toward studying important endpoints."

As discussed in the 2001 guidance, the following factors should be considered when assessing what data elements are necessary to collect:

- The type of regulatory submission (e.g., new marketing application versus efficacy supplement).
- The similarity of the proposed new use of the drug to already approved uses of drugs.
- The population being studied (e.g., patients in the surgical adjuvant setting, patients receiving first-line treatments, or patients with refractory disease).
- The amount of available supplemental information from other sources on the safety of the drug, such as data from trials in a similar population.

The goal of the Data Submission Standards and Evidence Requirements project (Panel 1) was to identify the scope of data collection sufficient to generate safety data for drug labeling and clinical use and to reduce collection of unnecessary data elements in supplemental NDAs and BLAs. A study was conducted to determine whether important safety information would be omitted by collecting data on a subsample of patients enrolled in trials to support supplemental BLAs or NDAs for approved drugs with extensive safety information already available. Data sampling did not appear to omit safety information that would be needed for labeling or the benefit–risk evaluation.

Although this study focused on supplemental NDAs and BLAs for cancer drugs, the FDA believes that these findings could apply to safety data collection for supplemental NDAs and BLAs for all therapeutic drug classes. Safety data collection from all subjects would still be needed for initial marketing claims for NDAs and BLAs. However, based on the factors outlined in the guidance (i.e., type of submission, similarity of proposed use to approved use, population being studied, available additional information for other sources), it should be possible to more narrowly focus the scope of data collected without a detrimental impact on the regulatory evaluation of supplemental marketing applications of drugs or biologics.

The FDA is committed to developing a guidance applicable to all therapeutic classes. That guidance will further clarify and illustrate the principles outlined in the 2001 guidance for cancer drugs and biologics, as well as incorporate the findings from the Data Submission Standards and Evidence Requirements project.

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REFERENCES

1 U.S. Food and Drug Administration Office of Training and Communication, Division of Drug Information, HFD-240, Center for Drug Evaluation and Research. Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review, Food and Drug Administration. Available at http://www.fda.gov/cder/guidance/index.htm.

2 Schilsky R. Summary of data re-analysis. Presented at the American Society of Clinical Oncology Data Optimization Meeting. Alexandria, Virginia, July 30, 2009.

3 Schilsky R, Abrams J, Woodcock J et al. Conference on Clinical Cancer Research, Issue Brief, September 3–10, 2008.

4 A detailed manuscript for submission is currently in preparation under the leadership of the Working Group.

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Blinded Independent Central Review of the Progression-Free Survival Endpoint

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INTRODUCTION AND BACKGROUND

Progression-free survival (PFS) is an endpoint of increasing use in phase III clinical trials. The primary appeal of the PFS endpoint is that, in contrast to the endpoint of overall survival (OS), it is measured prior to the use of alternative or subsequent anticancer therapies, thereby providing an estimation of the agent's biologic activity not confounded by other therapies. In addition, because progression is an event that occurs, in most cases, months or years before death resulting from cancer, clinical trials can be conducted more quickly with fewer patients than a trial designed using an OS endpoint. Although some have argued that PFS measures direct clinical benefit in some clinical settings, the benefits from delaying progression may be difficult to quantify. For the purposes of this panel, we accept that PFS can be a useful endpoint in some contexts, which will depend on the purpose of the trial, the magnitude of the PFS improvement expected, and the adverse event profile of the agent(s) under study.

When PFS is considered an appropriate endpoint for a trial, care must be taken to ensure that the PFS endpoint is reliably and reproducibly measured. Specifically, there are unique sources of bias related to PFS that must be considered. These include: evaluation-time bias, attrition bias, and reader-evaluation bias. Evaluation-time bias occurs when there are intentional or unintentional differences in the evaluation times by treatment arm [1, 2]. Specifically, when progression is evaluated more frequently in one arm, bias may result. For example, time of progression cannot be determined when attrition bias occurs as a result of lost-to-follow-up. This is unlike OS, for which a determination is usually possible. Reader-evaluation bias in unblinded trials, which is the focus of this panel, is of concern because of the potential for subjective elements to influence the disease progression evaluation.

In spite of objective criteria for determining progression [3], its evaluation is complicated by many factors. These complications include variation in tumor measurement, variation in the choice of target lesions to follow across time, failure to detect a new lesion, as well as differing interpretations about changes in nontarget and nonmeasurable lesions. These measurement issues can result in different determinations of a patient's status between evaluators at a given evaluation time. Because of this, a certain number of discrepancies is to be expected in any given trial (even in the absence of bias). However, the impact of these discrepancies on the evaluation of the treatment effect is an area of ongoing research.

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When evaluations are made with knowledge of treatment assignment, there is a concern that assessments may be influenced by an evaluator's beliefs about a therapy. This knowledge creates the potential for intentional or unintentional actions to bias the estimate of the treatment effect, which is the main motivation for blinded independent central review (BICR) of locally evaluated (LE) progression times. BICR has been recommended in regulatory guidance documents for unblinded phase III clinical trials [3]. BICR is usually conducted by contract research organizations and is a large expense added to the already high cost of oncologic drug development. Although the motivation for BICR arises from variability in PFS assessments, the presence of reader-evaluation bias in the estimates of treatment effect based on LE progression times has not been, to date, documented in actual clinical trials. A paper by Dodd et al. [4] showed that, in a limited sample of clinical trials, there was generally consistent estimation of treatment effect between LE and BICR PFS, leading some to question the motivation for full BICR.

Additionally, Dodd et al. [4] describe a type of informative censoring that may bias the estimate of treatment effect based on BICR [4]. When an investigator has made an assessment of progression at a time point, the patient is typically withdrawn from the study and no further protocol scans are conducted. This means that if, upon review, the BICR does not determine progression for this patient at this time point, the patient's data are censored at this time point for statistical analysis based on the BICR data. Because this patient is more likely to have a BICR progression sooner than the remaining at-risk cohort, this censoring is informative. In other words, the standard statistical assumption that censoring is unrelated to prognosis is violated, and may bias estimates of treatment effect. Imbalance of this type of censoring between treatment groups is of particular concern.

These potential complications with both BICR and LE estimates of treatment effect have resulted in a dilemma for regulatory agencies in deciding which of the two estimates should be referenced in product labeling. In this document, we summarize two separate efforts addressing concerns related to BICR. The first was undertaken by the Pharmaceutical Research and Manufacturing Association (PhRMA) PFS Working Group. The second was undertaken by the National Cancer Institute (NCI), in collaboration with Eastern Cooperative Oncology Group and Genentech statisticians. Before describing these results, we review the outcomes from the 2008 Brookings session on PFS outcomes.

2008 Brookings Session on PFS Outcomes

At the Brookings Institute conference on cancer research in 2008, the primary conclusions included: (a) confirmation that, in truly double-blind clinical trials, BICR is not needed, which is consistent with U.S. Food and Drug Administration (FDA) guidance [5], and (b) a consensus that the method for auditing LE by obtaining BICR in a subset of patients needs to be developed. It was hoped that such an auditing method would replace the full independent review in confirmatory phase III trials. Researchers within the NCI and within the PhRMA PFS Working Group were requested to develop a sample-based audit of the investigator's assessment of progression that would be able to provide assurance of a lack bias in estimating treatment effects or to identify such a bias when present.

Summary of PhRMA PFS Working Group Data Collection and Analysis

As background to the audit methods that were presented, the PhRMA Working Group felt that the most important metric through which to understand the underlying agreement of investigator and BICR estimates of treatment in the case of PFS is the hazard ratio (HR) comparing the control with the experimental arm of a clinical trial. The primary goal of the audit was to understand how discordance (disagreement at the patient level between the investigator and BICR) affects how well the PFS HRs based on the BICR and local investigator agree.

The Independent Review subteam of the PhRMA Working Group undertook a data collection project to understand the operating principles of BICR in randomized oncology clinical trials. The team summarized HRs from 23 oncology clinical trials that used BICR to assess PFS, via a literature review. In addition, this team performed a data collection exercise to further evaluate the relationship between discordance and the agreement of BICR and investigator HRs. They investigated discordance by treatment group to determine how differential discordance results in potential bias of the BICR HR. The results from the literature review and data collection exercise were confirmed through simulation.

Preliminary results suggest that there is strong agreement between the investigator and BICR estimates of treatment effect. Further, there is evidence to suggest that the overall level of discordance is not related to the reliability of either investigator or BICR estimates of treatment effect. However, a difference between arms in discordance does appear to correlate with more divergent estimates of treatment effect between the BICR and investigator.

Summaries from the literature review and detailed data

collection will be presented. It is important to understand the strong agreement demonstrated in the analysis of 23 clinical trials as a background to understanding the need and threshold for detecting bias in an independent review audit.

PhRMA PFS Working Group

Audit Methodology

The PhRMA Independent Review team took the approach of developing and using measures of discordance as the foundation of their audit methodology. It is acknowledged that the ultimate measure of interest is the HR; however, it is less sensitive as a tool for detecting bias and therefore was not explored as part of the audit methodology. Bias in treatment effect in this setting could be caused by two behaviors. The first behavior that could cause bias is when an investigator either knew or suspected that a patient was in the control group, felt the patient was not doing well, and declared progressive disease based on clinical symptoms with no substantiating radiologic evidence. Conversely, an investigator who knew or suspected a patient was in the experimental arm and felt that the patient was doing well despite meeting technical protocol criteria for progression could make the decision to keep the patient on treatment. Simulations have demonstrated that both these actions would result in inflated estimates of treatment effect and would increase the chances of a false-positive finding for the study. In addition, the magnitude of the difference between arms in certain discordance rates is markedly greater in the presence of bias. It is critical therefore that the audit mechanism proposed be sensitive to detection of either of these two possible biases.

The independent review team developed and evaluated multiple audit-based measures of discordance. The team generated, through simulation, multiple scenarios to represent the breadth of possible examples from oncology clinical trials.

The criteria for choosing the measure of discordance to be used in the audit were based on a high probability of detecting bias in a simulated scenario and to likewise have properties that resulted in a low probability of falsely declaring bias. The candidate discordance measure had to have stable performance regardless of the event rate in the trial, the differential event rate between arms, and the sample size of the trial. The discordance measures of interest and their performance will be discussed.

Some recommendations for consideration include having a central repository for all scans. This repository can then be a source for a random sample of subjects on which to perform BICR. The sample size of central review would depend on the sensitivity and specificity of differential discordance measures.

NCI Audit Methodology

Although BICR is potentially afflicted by informative censoring, agreement between the LE and BICR HRs provides reassurance that any positive treatment effect obtained by evaluations at local sites is not a result of reader-evaluation bias. Different distributions of discrepancies in PFS times between LE and BICR by treatment arm is an indication of reader-evaluation bias. However, because of censoring (administrative and otherwise), such an analysis is complicated.

Because the HR is ultimately the measure of interest in determining whether a treatment is efficacious, the efforts of this team focused on using BICR to estimate a HR that would have been obtained with a BICR, but in an efficient way not requiring a full-sample BICR. The audit strategy can be summarized as follows:

1. When the LE HR indicates a clinically meaningful and statistically significant effect, BICR will be conducted on a subset.

2. The HR from the BICR audit will be estimated, and, using a statistically efficient estimator, confidence intervals will be estimated.

3. An hypothesis test of whether the BICR HR is statistically significant will be undertaken, as well as an evaluation of whether it is of clinically meaningful size.

This general strategy was applied to data from a study in breast cancer, which conducted a full BICR to confirm a large and significant improvement in PFS. Results from that application indicate that a strategy of conducting an audit in 20% of the total study population would conclude that the BICR HR is statistically significant 88% of the time. This supports the view that large treatment effects will likely require small BICR audits. Additional simulations indicated that, for moderate effect sizes that are statistically significant, larger audits are needed. Further, when treatment effects are small but statistically significant, the additional variability introduced by BICR may make assurance of a treatment effect through the use of a (complete) BICR impossible.

Conclusion

PFS as an endpoint in oncology is increasingly being employed. Measures to validate and efficiently determine biases inherent in studies employing PFS will greatly enhance the rapid development of new therapies.

FDA Response

PFS, defined as the time from randomization until objective tumor progression or death, is increasingly being used in the approval of oncology drugs and biologics. Compared with the use of OS as a primary endpoint, the use of PFS as a trial endpoint usually allows for the study of smaller patient populations and shorter follow-up. PFS is assessed prior to the introduction of subsequent therapies; hence, differences observed between treatment arms of a randomized trial will not be confounded if crossover occurs at the time of disease progression and the start of new therapies. Disease progression is usually the basis for a change in therapy.

Toxicities of most oncology drugs preclude the effective use of blinding. Disease progression is frequently assessed by an investigator's review of radiological examinations and bias can be introduced if effective blinding is not present. To evaluate if any bias has occurred, blinded, independent review committees (BIRCs) have been used to determine the potential presence of bias, rather than to simply note random discrepancies in disease progression dates between the investigator and the BIRC. Random measurement errors tend to obscure the demonstration of superiority, making "false-positive" conclusions in a clinical trial evaluation less likely.

In the PhRMA PFS Working Group presentation, an audit methodology to examine directional evaluation bias was discussed. Directional evaluation bias is of concern when an investigator systematically records progression early or late for one treatment arm of a randomized trial. For example, false-positive conclusions regarding the efficacy of a treatment resulting from bias would be observed if the investigator consistently called disease progression early for the control arm and/or late in the experimental treatment arm. In either case, this would potentially lead to a falsely optimistic evaluation of the experimental treatment.

Large differential discordance rates between treatment arms (i.e., differences between the investigator's and the BIRC's evaluation of disease progression) raise the suspicion of systematic evaluation bias. The presence of this bias is of concern in clinical trials relying on investigator-determined PFS evaluation in situations in which the success of blinding of the trial is uncertain, as well as in unblinded trials.

In blinded trials, FDA has not recommended the use of a BIRC, since evaluation bias is unlikely to be introduced. In trials where blinding cannot be used or when there is uncertainty of the blinding, the use of a BIRC has been recommended. These blinded reviews usually result in the reexamination of all the disease progression events of all patients.

Strategies examining disease progression events in a limited sample of patients at selected sites, in contrast to all patients at all sites, were looked at by the PhRMA PFS Working Group. The intent of this limited evaluation was to examine differential discordance in reading PFS events between treatments. The absence of any differential discordance would suggest that there is no systematic evaluation bias; that is, the local investigator evaluation provides a reliable estimate of treatment effect. However, if there is a differential discordance, the potential for evaluation bias would need to be considered and further evaluated by comparing a larger sample of the BIRC- and investigator-determined PFS evaluations.

The present strategies for limited evaluation of disease progression events have been examined in simulations and retrospective analyses of completed trials. Pilot studies are being planned to evaluate the prospective implementation of limited evaluations of PFS events by the BIRC to examine differential discordance. These pilot studies will further examine and refine how to select subjects and sites for review, the number of subjects and sites needed for a BIRC review, and the procedures to implement these limited evaluations prior to making recommendations for their use for regulatory purposes.

Acknowledgments

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References

1 Freidlin B, Korn EL, Hunsberger S et al. Proposal for the use of progression-free survival in unblinded randomized trials. J Clin Oncol 2007;25:2122–2126.

2 Williams G, He K, Chen G et al. Operational bias in assessing time to progression (TTP) [abstract 975]. Proc Am Soc Clin Oncol 2002;20:244a.

3 Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1), Updated January 2009. Available at http://www.recist.com/recist-in-practice/01.html, accessed September 3, 2009.

4 Dodd LE, Korn EL, Freidlin B et al. Blinded independent central review of progression-free survival in phase III clinical trials: important design element or unnecessary expense? J Clin Oncol 2008;26:3791–3796.

5 U.S. Department of Health and Human Services. FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf, accessed September 3, 2009.

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Development of Rational Drug Combinations with Investigational Targeted Agents

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INTRODUCTION AND BACKGROUND

Recent research advancements have identified molecular mechanisms underlying cancerous transformation and growth, leading to a new generation of therapies. Key signaling intermediates and genetic mutations associated with oncogenic cell-cycle regulation have been identified as specific targets for the development of new therapies that would be less toxic and more effective than currently available interventions. Progress has also been made in the understanding of how extracellular factors, such as hormones and growth factors, can influence the progression of tumor growth. For example, targeted agents against human epidermal growth factor receptor 2 (trastuzumab) and Abl (imatinib) have altered the natural history of the diseases in populations for which they were initially developed. However, in cases of other cellular targets, such as epidermal growth factor receptor (EGFR) in colorectal cancer and mammalian target of rapamycin (mTOR) in renal cell cancer, clinical results have been more modest.

The challenge facing the development of safer and more effective therapies can lie both with the specificity of new targeted agents and with the complexity of disease biology, which usually involves multiple redundancies and pathway crosstalk. By selectively and specifically inhibiting one aspect of tumor cell growth or survival, the therapeutic effect may be lessened by concomitant upregulation of another aspect of the same pathway or by the development of acquired resistance through activation of a compensatory pathway. For example, clinical data suggest that Met pathway activation can compensate in lung tumors when EGFR signaling is inhibited [1], whereas inhibition of mTOR with rapamycin analogs results in an increase in Akt signaling [2] that may reduce the overall therapeutic effect. Given the limited number of approved targeted agents, most rational combinations will require dosing of two or more (as yet) unapproved new molecular entities (NMEs). The strong scientific rationale for such combinations warrants a reexamination of our current developmental model and suggests that a new developmental model may, in select circumstances, facilitate evaluation of two investigational agents in combination.

The existing combination rule (21CFR300.50) provides

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one mechanism for approval of the combination of two investigational agents, typically by the demonstration, in a phase III trial, of the contribution of each agent to the claimed effects of the combination, compared with standard-of-care (SOC) therapy. However, there may be circumstances in which there is sufficient evidence to consider alternatives to the standard phase III factorial trial design or to consider alternative criteria for the regulatory burden of proof necessary for approval of the combination of two investigational targeted therapies. The objective of this panel is to explore specific examples and criteria in which an alternative regulatory process to the existing combination rule would be appropriate and feasible and thus could be adopted by developers.

Benefit to Patients

Any new model for the development of investigational agents must have as its ultimate goal an improvement in the therapeutic benefit to patients, both in terms of the efficacy and safety profile of the product and in terms of the efficiency of the drug development process itself. The putative benefits to patients include the potential for combination therapies to synergistically target tumors and therefore be more effective than a single agent alone. One of the theoretical benefits of combination targeted therapies is that, by the inherent nature of their specificity, toxicities may be minimized relative to broader spectrum agents. Employing two targeted agents versus a single multitargeted agent may allow for a dose reduction of either/both agent(s), thereby reducing toxicity while potentially maintaining or improving efficacy. There is also the possibility of achieving better safety profiles while using two agents with specific known targets rather than employing a single agent with multiple known and unknown targets. Thus, one criterion for the development of combination targeted therapies is that the toxicities of each individual agent are either nonoverlapping or merely additive in combination rather than synergistic, making it easier to monitor and manage in the clinic.

An estimated 20% of adult cancer patients are medically eligible for a cancer clinical trial, yet accrual rates remain at about 3%. These rates are even lower for ethnic and racial minorities as well as for young adult cancer patients, who have higher cancer mortality rates than the general population. The 2NME strategy has the potential to improve both the number and the quality of cancer clinical trials, enhancing the access of new targeted therapeutics to cancer patients. In addition to matching likely responders to these treatments, the potential 2NME approach would benefit patients where evidence suggests a therapeutic benefit for a highly refractory patient population or where no approved therapy exists but there exists a biological rationale for efficacy. The high unmet medical needs of these patients could support an alternative developmental model of two agents.

Finally, it should be acknowledged that the goal of all participants in the drug development process, including the research community, pharmaceutical industry, and regulatory agencies, is to expedite the availability of safe and effective therapies to the intended patient populations. The developmental models discussed below are an attempt to achieve this goal, without compromising existing regulatory standards that protect the safety of patients.

Examples and Decision-Making Criteria of 2NME Development Plan

In order to explore specific examples and decision-making criteria of conditions when approval of the combination of two NMEs would be appropriate and feasible, we have made certain general assumptions about the 2NMEs, which are listed below:

- Strong biological rationale for the 2NME combination, for example, selective inhibition of two targets in the same pathway or inhibition of a primary and compensatory pathway.
- Biological indicators for likely responders in a patient population (i.e., paired markers to indicate that the pathway is actually altered in a patient population).
- Evidence of synergy of the 2NME combination in in vitro cell lines and greater activity of the 2NME combination compared with the activity of either agent alone in in vivo nonclinical models.
- Nonclinical characterization of the toxicity profile of each individual agent according to current International Conference on Harmonization guidelines suggesting nonsynergistic toxicity.
- Thorough characterization of potential drug–drug interactions of the 2NME combination to minimize the potential for additive or synergistic toxicities.

Potential Scenarios for the Development of 2NMEs

Synthetic Lethality

Synthetic lethality refers to situations in which each NME is individually inactive or minimally active except in genetically defined models (e.g., a specific background mutation). The specific genetic background where each individual NME is active may not be broadly representative of the disease population. However, when the 2NMEs are used in combination, they exhibit highly potent activity, and further, this activity is detected in multiple representa-

tive model systems (various cell lines and animal models). In this example, the minimal activity of each agent alone precludes a regulatory process for single-agent approval and supports evaluation of an alternative developmental model for the 2NME combination. In these cases, we propose limiting data collection about each individual agent to phase I studies.

The rationale is that the individual NMEs are not being proposed as single agents, with their use being limited to the proposed combination therapy only. Also, it is perhaps more informative to learn of the risks and benefits associated with the combination rather than each individual agent because the combination has different molecular targets than each agent individually.

Proposed development plan:

1. Thorough characterization of the safety profile and maximum-tolerated dose of each individual agent in phase I studies. The decision to proceed with a phase Ib trial would be based on whether the observed exposure–toxicity relationship of each drug as a single agent is adequate to consider combination therapy feasible.
2. Evaluation of the safety profile of the 2NME combination and appropriate dose selection criteria for each agent in the combination (phase Ib). An expansion cohort may be used to demonstrate evidence of activity for the combination, such as tumor shrinkage.
3. Demonstration of proof of concept for the 2NME combination in phase II trial compared with each agent alone and with the SOC. Surrogate efficacy endpoints (i.e., response rate) may be used if appropriate for decision making in the face of compelling antitumor activity.
4. Standard phase III design comparing the 2NME combination with the SOC.

Coenhancement

Coenhancement refers to scenarios in which each NME is modestly active as an individual agent in model systems, but the combination is highly active in the exact same model systems. Therefore, a multiple-arm phase II trial may be sufficient to demonstrate the advantage of the combination, and allow for a two-arm phase III trial comparing the combination with the SOC.

Proposed development plan:

1. In this scenario, the proposed phase I/Ib development plan would be identical to that described above, with the objective of providing adequate characterization of the safety profile of each individual agent and the 2NME combination as well as the appropriate dose selection for each agent in the 2NME combination.
2. Demonstration of proof of concept with a four-arm comparison of the 2NME combination with each agent alone and with the SOC during phase II of development. An adaptive trial design might be employed initially testing the 2NME combination versus the SOC, with addition of the single-agent arms once evidence of activity for the 2NME combination was obtained.
3. Proof of concept for the combination, and the contribution of each agent to the combination, would be determined without exposing the large numbers of patients typically required for phase III trials to therapeutic agents with minimal activity.

Unienhancement

This case of enhancement refers to scenarios in which one of the NMEs is inactive or minimally active in model systems, the other NME is modestly active in the same model systems, but the combination is highly potent in the model systems. An example of this situation is when the minimally active NME's role is to prevent resistance. In this situation, it is likely that the more active NME will require greater scrutiny and should be studied as a single agent in phase II trials. In contrast, the minimally active agent may not require study as a single agent beyond initial phase I studies. Therefore, the proposed modifications to the development plan would be similar to those of "coenhancement."

Conclusion

There is a clear need to modify the current regulatory approval process such that it is more in alignment with the reality of new therapies in development, including the use of multiple therapies that target different molecular pathways. In addition to the specific scenarios sketched above, whenever feasible, combining of clinical trials (i.e., phase Ib–II or phase II–III) should also be considered to enhance clinical development timelines.

There are other facets of this issue that require further discussion, such as determining the optimal doses of the agents in the combination, labeling and packaging to ensure safe and effective usage, etc. Nevertheless, the issue of combinatorial therapies holds great promise for the future of cancer treatment. Enhanced understanding of complex signaling pathways that are misregulated in human cancer both provides an opportunity and presents various challenges to advance cancer therapeutics. To take full advantage of this opportunity, drug development must evolve past the current norm of targeted agents, either as individual agents effective in small patient groups or by empirically adding to the current SOC, to develop targeted agents to be used in rational combinations.

FDA Response

The conventional approach to cancer drug development has concentrated on the evaluation of single-agent therapies to determine efficacy and safety. Subsequently, the drug is evaluated in advanced stages of a malignancy or in combination regimens adding the new drug to approved drugs. Emerging knowledge on the molecular mechanisms of malignancies, however, may require greater use of multiple drug combinations. Each component of a drug combination could target different parts of complex molecular pathways involved in tumor development. Interest in combining two unapproved drugs with a strong biological rationale may expedite the development of new treatment regimens for serious and life-threatening diseases.

The "combination rule" (21 CRF 300.5) refers to fixed drug combinations (i.e., drugs that are physically combined) and states that the contribution of each agent to the combination must be demonstrated. To demonstrate the contributions of specific drugs in these fixed combinations, randomized, factorial clinical trials are usually performed (e.g., drug A versus drug B versus the combination of drug A and drug B).

Individual drugs are commonly combined in oncology treatment regimens (e.g., doxorubicin, bleomycin, vinblastine, and dacarbazine; mechlorethamine, vincristine, procarbazine, and prednisone; cyclophosphamide, doxorubicin, vincristine, and prednisone). Although factorial trial designs aimed at evaluating the individual contributions of separate drugs used in combination have been recommended, these drug regimens are not the subject of the combination rule.

Issues related to the codevelopment of two investigational drugs for cancer include:

1. The amount of toxicologic data for each individual drug and the drugs in combination needed prior to the initiation of clinical studies.
2. The mechanistic rationale or animal model data needed to justify use of the investigational drugs in combination at various stages of development.
3. The rationale needed for omission of a factorial design in demonstration of effectiveness.

Although a factorial trial design is frequently used to evaluate fixed combinations, other data, including compelling mechanistic data (e.g., animal or in vitro data) may provide sufficient rationale for regulatory approval of fixed combinations or of two investigational drugs used together. The acceptance of mechanistic data would be in the setting of a highly significant treatment benefit and a favorable benefit-to-risk assessment.

The use of multiple unapproved drugs in combination will also be investigated in therapeutic areas other than oncology. The U.S. Food and Drug Administration recognizes that a clear regulatory pathway is required and that further public discussion and formal guidance in this area are required.

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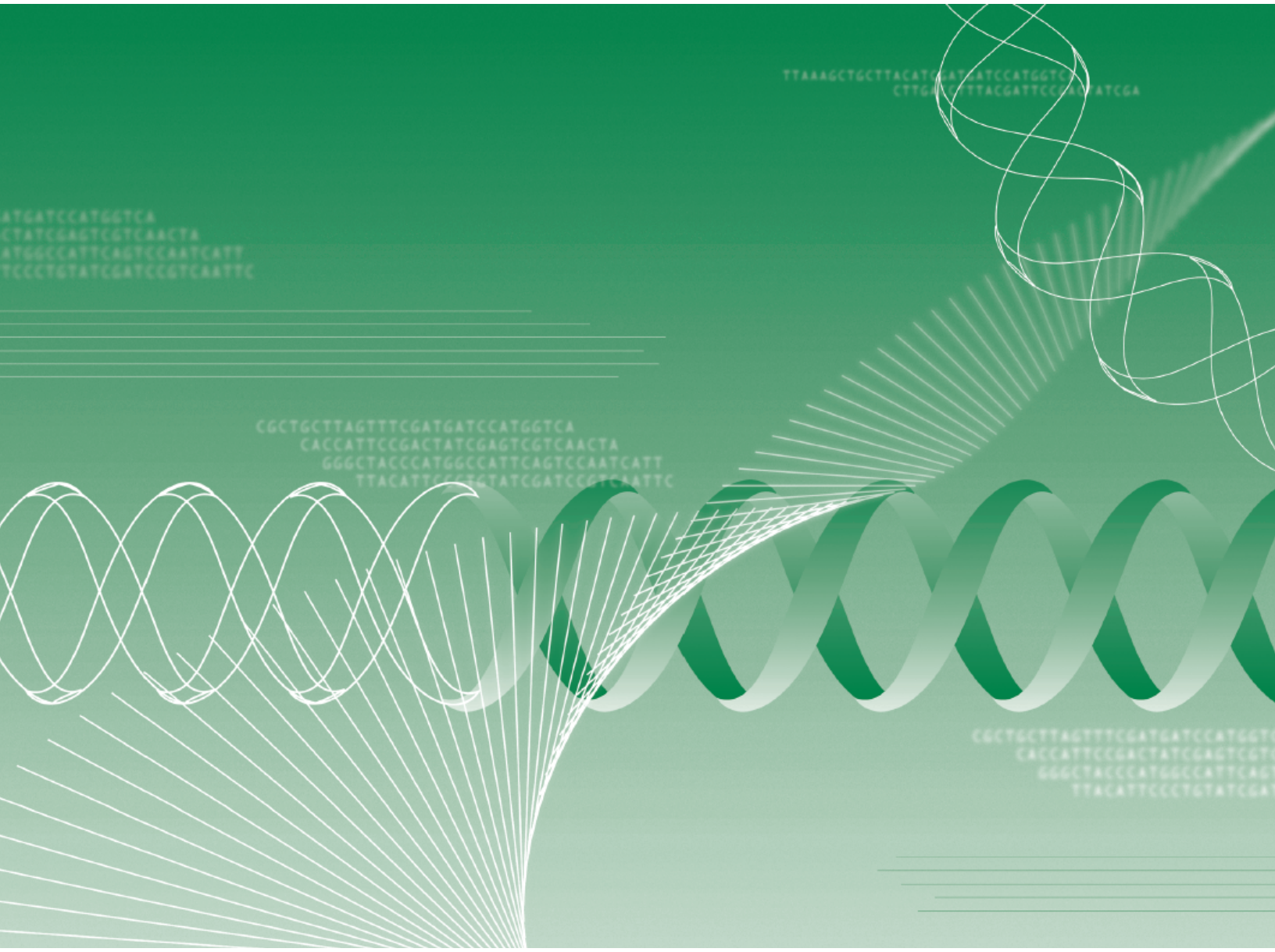
FDA Response provided by Janet Woodcock. Jeff Allen and Rasika Kalamegham of Friends of Cancer Research assisted with drafting.

References

1 Engelman JA. The role of phosphoinosite-3-kinase pathway inhibitors in the treatment of lung cancers. Clin Cancer Res 2007;13:s4637–s4640.

2 O'Reilly KE, Rojo F, She QB et al. mTOR inhibition induces upstream receptor tyrosine kinase signaling and activates Akt. Cancer Res 2006;66:1500–1508.



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