PANEL 3
Accelerating Development and Approval of Targeted Cancer Therapies
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Fulfilling the Promise of Targeted Cancer Therapies

The past decade has witnessed an improvement in our understanding of the molecular mechanisms involved in cancer progression and an evolution toward a central role for targeted drugs and biologics in the treatment of cancer. More selective than older treatments that kill both cancerous and normal cells, targeted drugs impede biological processes related to cancer growth and metastasis by interacting with one or more specific molecules involved in those processes. Thus, targeted therapies may damage fewer non-cancerous cells than do other treatment options, producing fewer adverse events.[1] Ideally, changes in the specific molecules or molecular pathways targeted by such a therapy should be correlated with the clinical outcomes produced by the therapy.[2]

Diagnostic tests have been developed to identify patient subgroups most likely to benefit from some targeted therapies (as well as those who may be harmed without any accompanying benefit). Well-known examples of targeted cancer therapies with companion diagnostics include cetuximab (Erbitux, ImClone/BMS), trastuzumab (Herceptin, Genentech), and imatinib (Gleevec, Novartis). It is hoped that diagnostic tests for drug targets and cancer treatments can be co-developed more routinely, to enable individualizing cancer care based on the unique set of molecular targets produced by a given patient's tumor. However, it is apparent to most observers that the drug development and regulatory sciences have yet to fully overcome the challenges and take advantage of the opportunities presented by the scientific advances enabling targeted drug applications and diagnostics.

We believe there is a compelling need for more efficient development, regulatory review, and post-approval evaluation of targeted cancer therapies with companion diagnostics. This discussion document reviews important barriers to their development and outlines a series of recommendations.

Barriers to Targeted Therapy Development and Approval

- Identifying meaningful molecular targets. Development of targeted therapies requires the identification of targets that can be accurately measured and are critical to the survival of cancer cells. Some molecular targets are products of specific genes and are present in some but

not all individuals with cancers of a particular type (e.g., ER and HER2 in breast cancer). This heterogeneity in the population is the theoretical basis for personalized cancer therapies whose use can be limited to those patients most likely to benefit—but it's also what makes development of targeted therapies uniquely difficult. Cancer biologists now know that tumorigenesis and metastasis are complex processes with multiple redundant biological pathways. Thus, the interruption of a single pathway through targeting may not provide significant benefit in arresting or reversing tumor growth.

- Development of a diagnostic test. Preclinical data provides information on a specific molecular pathway or target that is associated with the growth of a specific tumor type. An assay can then be developed to reliably and consistently identify the presence or absence of a molecular target in patient populations with the identified tumor. Then the question is whether the patients with the specific target will respond favorably to a treatment and those without the target will not respond to the therapy. There are a number of development steps in this process. The analytical validation of an assay (validation of its ability to measure the target) is critical before the assay is tested in samples of convenience and then moved to reference sample sets to develop cut-offs and establish assay performance on the tissue type intended to be tested. Once analytical performance in the intended tissue is demonstrated, the same assay would be used to identify the population targeted by the sponsor for the prospective clinical trial in which the new therapy will be tested and the clinical utility of the test assessed. The regulatory path for development/approval and commercialization of a companion diagnostic has uncertainties that may lead to delays and unanticipated costs that can limit broad utility of this approach. For example, putting time and resources into the development of an assay without knowing if the molecular marker is predictive of drug effect is a disincentive for early assay development by companies.

- Evaluating the test and therapy together. Under the current system, it is particularly challenging to develop the target and the therapy concurrently because an effective therapy is required to demonstrate the utility of a diagnostic test, and an effective test is ideally available to identify the population in which the targeted therapy is maximally effective. Efficient approaches are needed to clinically test the predictive value of the biomarker and safety/effectiveness of the therapy, potentially in the same registration trial. Such a strategy carries some major regulatory challenges:

  o Design. There is no explicit guidance for how to study a targeted therapy intended for use in a subpopulation defined by activity of a molecular target, except as a supplemental indication. Oncology Drug Advisory Committee (ODAC) discussions have suggested that in this case, clinical trial participants should be stratified prospectively according to biomarker status and that biomarker-negative populations should be treated to determine responsiveness. However, multiple studies have been designed and discussed with FDA that would enroll a subpopulation, defined by a biomarker, that is likely to have an enhanced response and do not include a biomarker-negative population. Trastuzumab, for instance, was approved for use in biomarker-positive patients without testing the drug in the biomarker-negative subpopulation. These studies have utilized both single-arm and randomized control study designs. There is additional uncertainty about which comparator therapy to use, because what may be acceptable in the general population may have different efficacy in this "targeted" population.

o Recruitment. The identification and recruitment of patients with the targeted marker profile can be slow and costly, depending on the prevalence of the marker and testing costs. For example, only 2% of melanoma patients carry cKit mutations and only about 8% of malignant breast cancer patients are FGFR1-positive. With so few patients eligible for studies and the current rate of enrollment in clinical trials of approximately 5%, conducting traditional safety and efficacy trials in a subpopulation identified by a molecular target can be prohibitively costly and time-consuming. The future of personalized medicine will require a call to action for more cancer patients to participate in clinical trials.

o Endpoints. Clinically important trial endpoints based on biomarkers are needed for maximum efficiency of development, yet existing FDA guidance does not define the level of evidence necessary to demonstrate that a biomarker is "reasonably likely to predict clinical benefit," and thus is an acceptable endpoint for a clinical trial of a targeted therapy. While several biomarkers—such as CA-125 in ovarian cancer—are well-correlated with disease progression, to date biomarkers have only been incorporated into composite endpoints and are not accepted alone. Establishing an evidentiary standard for using biomarkers as endpoints could significantly shorten the duration of trials and thus the time to approval of targeted therapies.

- Administrative Coordination. Because diagnostic tests and drugs are often developed by different companies, the process for co-development requires substantial long-term coordination between companies. As more co-diagnostics are developed, this coordination will likely be streamlined. The coordination within FDA should also be examined. Within FDA, diagnostics are reviewed by the Center for Devices and Radiological Health (CDRH) under its statutes and regulations, and cancer drugs are reviewed by the Office of Oncology Drug Products at the Center for Drug Evaluation and Research (CDER) under its statutes and regulations. Co-development of a cancer diagnostic and targeted therapy requires early agreement and coordination between these Centers on evidentiary standards and administrative procedures. FDA has issued a concept paper for co-development which contains ideas for formal industry-FDA interactions; however, a formal guidance has not yet been developed.

Proposed Roadmap for Targeted Development and Approval Process

In this section, we propose a "targeted development and approval" policy, consensus on which could result in more rapid availability of targeted cancer therapies with companion diagnostics. The policy is intended to facilitate accelerated development and approval for a drug or biologic cancer therapy (drug) used in a population defined by a specific diagnostic test (device).

In order to ensure optimal balance between risks and benefits to patients, "targeted approval" should be granted to a drug and device, intended for use together as a treatment strategy, which meet the following criteria:

1) The drug must be indicated for cancer.

2) The diagnostic assay must be demonstrated to be analytically valid, as defined below.

   Principles for achieving analytical validity were described by FDA in its co-development concept paper.[3] Performance characteristics of the assay that should be evaluated and

described, when applicable, include its sensitivity and specificity in the clinical use; sample requirements; analyte concentration specifications; analytical characterization of cut-off values; controls and calibrators; precision (repeatability/reproducibility); analytical specificity; assay conditions; sample carryover; and limiting factors.

3) The drug must demonstrate, in a subpopulation defined by the diagnostic assay, a pre-specified statistically significant change in an endpoint reasonably likely to predict clinical benefit.

In targeted approval, CDER would approve the drug for the intended use in the subpopulation defined by the diagnostic test. CDRH would approve the device (if not previously approved) for a claim of identifying patients who were studied in the drug trial, with the caveat that that the test has not been shown useful for identifying patients with expected lack of effect in the off-label population. Targeted approval of the drug and device based on the subpopulation and endpoints above would be conditional on post-approval studies to demonstrate clinical benefit of the drug based on conventional endpoints, as well as to demonstrate broader clinical utility of the diagnostic test (i.e., that it distinguishes patients likely to benefit from the drug from those who are not).

This is a change from the current process in that it would require coordinated, synchronized decisions on the parts of CDRH and CDER. Second, it provides an explicit pathway for evaluating and approving a drug to be used in a subpopulation that is defined by having a positive biomarker assay prior to evaluating the drug in patients who have a negative biomarker assay, and for approving an assay that may not yet be clinically validated by conventional standards for diagnostic tests. Third, it provides flexibility in endpoints, which could include traditional tumor response measures or—if adequate evidence were developed to support it—a biomarker of efficacy.

Potential Coverage Policy

The Centers for Medicare and Medicaid Services and other payers should not reimburse for any off-label use of drugs approved through this mechanism, such as therapy use in marker-negative populations, until post-marketing studies are completed. However, coverage in the context of further clinical study should be permitted (i.e., Coverage with Evidence Development).

Principles for Design of a Prospective Trial for Targeted Approval

A number of organizations and individuals have noted the challenge of designing efficient trials of biomarker-targeted cancer therapies. These include the FDA/NCI Interagency Oncology Task Force (IOTF), the Foundation for the NIH's Biomarker Consortium, the Institute of Medicine (IOM), the American Society of Clinical Oncology (ASCO), and the American Association for Cancer Research (AACR). Based on these and other related efforts, principles for designing a prospective trial for a biomarker-targeted cancer therapy can be derived which, if embraced, could greatly accelerate development and availability of targeted cancer therapies in selected patient populations.

1) The design should consider the specific cancer/stage for which the sponsor seeks an indication, and whether there is an available standard of care. If no standard of care exists, a new biomarker-targeted therapy for a cancer/stage may receive targeted approval on the basis of a single-arm trial that shows tumor regression, long-term stable disease, or effect on another endpoint that is reasonably likely to produce clinical benefit that can be presumed to be attributed to the tested drug in the marker-positive subpopulation. This design does not require

marker-negative patients to be included in the study. This paradigm has been used to approve trastuzumab in HER2-positive patients and is currently being applied to BRAF-positive patients in a study of a drug in malignant melanoma.

2) The trial upon which targeted approval is given for a new drug and new companion diagnostic test should employ a prospective design in which the drug is evaluated in the subpopulation identified by the test. In the case of a previously studied drug and a new diagnostic test, retrospective analyses of biomarker status as a treatment effect modifier are insufficient for full approval but should be sufficient for targeted approval under carefully specified circumstances, such as if the test applied is analytically validated, can be applied in a significant proportion of the study population, and the treatment effect is robust in the marker-positive patients. Such retrospective analysis has provided sufficient information to update labeling, (i.e., Erbitux and KRAS), and give guidance on a population that will not benefit from treatment.

3) The registration trial for targeted approval should employ endpoints reasonably likely to predict clinical benefit (e.g., disease free survival, objective response rate, and progression free survival[4]) in addition to biomarkers predictive of clinical benefit. Eventually, it may be possible to use specific biomarkers as endpoints in trials to justify targeted approval. However, validating the endpoint is difficult to do in the absence of a proven therapy and is subject to the same biomarker qualification and assay validation requirements described above. The pathway for validating tumor markers as endpoints is a complicated and controversial topic—not limited to targeted therapies—that merits further research and discussion. Until consensus is reached on this process, biomarker endpoints should be collected along with accepted surrogate endpoints and their prognostic significance analyzed. Biomarker endpoint data may also add to the weight of evidence for determining efficacy, such as by reducing the effect size required on the primary endpoint.

Specific Designs and Considerations in Selection

The default design for evaluating targeted therapies is typically the "all comers" or "randomize all" design, because it simultaneously evaluates the effectiveness of the drug and the predictive value of the diagnostic test. All patients are randomized to either treatment or control groups regardless of their marker status, which is a pre-specified variable for stratified analysis of treatment effect. To increase efficiency (e.g., when targeted approval is sought), the treatment could be evaluated in the marker-positive subgroup before it is studied in all trial enrollees.[5] If there is no effectiveness in marker-positive patients, the treatment fails. If the drug demonstrates effectiveness in marker-positive patients, targeted approval would be granted and the remainder of randomized patients would be evaluated for full approval if it's ethical to do so in light of the degree to which benefit may be possible in marker-negative patients.

Testing the treatment first in the marker-defined subgroup is appropriate if other information suggests that the marker-positive patients will benefit most from treatment and if there are enough marker-positive patients in the trial to ensure that the subgroup analysis will have sufficient power.[5] This design is most efficient if the treatment in question may benefit both marker-negative and marker-positive populations, if the marker-positive subgroup is large relative to the total patient population, or if the distinction between marker-positive and marker-negative patients (e.g., diagnostic cut-off) is not well-established.[6]

If it is known with high confidence that the new treatment does not help all patients, if the subgroup expected to benefit is relatively small, and if the cut-off value for the test is well-established, then a more efficient design than "randomize all" is the "enriched" design.[6,7] In this design, patients are tested and marker-positive patients are randomized to the treatment or standard of care, while marker-negative patients receive standard of care.

"Adaptive designs" are potentially the most efficient in achieving the targeted approval threshold because they use pre-specified decision points to determine how a trial will progress. Jiang, Friedlin, and Simon have proposed a biomarker-adaptive adaptive Phase III design that is capable of detecting treatment benefit in an overall population and in a subset. This design can be used with a biomarker for which the clinically relevant cut-off has not been defined, allowing researchers to prospectively incorporate validation of a biomarker for identifying sensitive patients into the trial.[8]

The I-SPY 2 Trial (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And Molecular Analysis), scheduled to start in late 2009, is an example of an adaptive trial designed to address the challenges of accelerating clinical development of targeted therapies in Phase II.[9] The trial will evaluate treatment effectiveness in biomarker-defined subsets and will allow for retrospective analysis to define the populations that benefit the most from particular treatments. Patients are randomized to one of multiple treatment arms based on their biomarker profiles and the accumulating evidence of efficacy of the various treatments in patients with their biomarker profiles. I-SPY 2 will be a neoadjuvant trial for women with large, locally advanced primary breast cancers, where the endpoint for response to treatment will be pathologic complete response. The study will compare the efficacy of novel drugs (combined with standard chemotherapy) to the efficacy of standard therapy alone; up to five new drug regimens will be tested simultaneously. The initial goal is to efficiently identify improved treatment regimens for patient subsets based on well-defined molecular characteristics (hormone receptor, HER2, and MammaPrint status) of their disease.

As regimens show high Bayesian predictive probability (>85%) of being more effective than standard therapy, they will graduate from the trial with the corresponding biomarker signature(s) representing patient populations in which the drug regimen is likely to be effective. In our paradigm, this would trigger targeted approval. Regimens will be dropped when they show low probability of improved efficacy in any biomarker signature. New drugs will enter as those on test are graduated or dropped. In the neoadjuvant setting in breast, this design has the advantage of requiring relatively few patients (minimum of 20 and maximum of 120 per drug evaluated) and a short time frame (each drug regimen will be on test for approximately one year and no more than 18 months). It is anticipated that small (300 patient) Phase III trials in the adjuvant or neoadjuvant setting focused on patients with specific biomarker signatures can be designed for the successful drugs (potentially qualifying for full approval).

Consistent with the principles above, sufficient tissue and blood samples will be collected so that additional biomarkers can be evaluated for their ability to predict patient response to the targeted therapies using the I-SPY 2 backbone. Some of the additional biomarkers under consideration will have analytical validation from previous studies, and I-SPY 2 data will be used to qualify them as "fit for purpose" for selecting patients for treatment. Other biomarker assays will be exploratory, with I-SPY 2 providing data toward their validation. In this regard, I-SPY 2 will provide prospectively collected, well-annotated specimens as a resource to the research and development community.

Infrastructure Needs for More Efficient Development of Targeted Therapies

In addition to efficient trial designs, several elements of infrastructure are needed to facilitate more effective development of targeted cancer therapies.

FDA Guidance and Coordination: Detailed guidance from FDA on the co-development process and evidentiary standards is needed. Further steps that might provide additional help include a Manual of Policies and Procedures (MAPP) for administrative coordination of interactions between sponsor(s), CDRH and CDER, with a commitment to having both CDER and CDRH representatives present for milestone meetings of co-development products.

Evidentiary Standards for Biomarker Endpoints: Establishing an evidentiary standard for validating biomarkers as endpoints for targeted approval would stimulate additional validation research and potentially shorten the duration of trials and thus the time to approval of targeted therapies.

Specimen Repositories: Well-annotated and controlled biospecimen repositories are crucial to accelerating early-stage biomarker research.[10] Patient samples can be utilized as reference samples for assays, prospective studies, and for pre-clinical research on multi-targeted therapies if they are acquired through a streamlined informed consent process. Biospecimen repositories might also be used to facilitate the identification of patient subgroups for participation in studies of targeted therapies, accelerating patient recruitment. The Institute of Medicine has suggested that NCI foster collaboration among biomarker developers and clinical researchers to aid the collection of tissue samples useful for research. Critical steps toward development of needed biospecimen banks include adequate funding for their development, technical standards for data elements and procedures, governance processes for collection and access to specimens, and measures for ensuring patient privacy in a way that does not hinder research.[11] Specifically, it might be useful to require that sharing resources be part of every registration or approval trial and that specimen collection adheres to the standards and guidelines created by the NCI's Office of Biorepositories and Biospecimen Research.

Patient Education and Recruitment: Coordinated efforts are needed to educate cancer patients about the value of clinical research and help link them to trials. Patients in targeted therapy trials generally are asked for multiple donations of tissue and/or blood and might need two to three additional biopsies to measure biomarker activity. Adoption of standard, simple, and efficient informed consent procedures would be beneficial. Moreover, effective use of electronic health records may also facilitate patient accrual in targeted therapy trials by allowing investigators to more easily identify eligible trial patients.

Pre-Competitive Collaboration: Incentives could be designed to encourage industry, academia, and government to share pre-clinical data. The Critical Path Institute's Predictive Safety Testing Consortium—a public-private initiative to qualify drug-safety biomarkers for specific uses in drug development—provides an example of how pre-clinical data-sharing among product developers can be managed and optimally employed.

Summary and Conclusion

The targeted development and approval policy outlined here builds upon existing policies for accelerated approval and FDA's 2005 concept paper on co-development of drugs and diagnostics. The objective of articulating the targeted approval policy is to pave a clear but flexible path for approval of

targeted cancer therapies, providing the basis for new levels of coordination and interaction between device and drug developers, as well as between FDA Centers. The principles for design of the studies of diagnostic/drug pairs outlined here should be discussed and refined in forums including investigators, product developers and FDA. In addition, FDA and government institutions such as NCI can encourage and support the development of drugs and diagnostics based on these principles. This can be done by publicizing such trials for recruitment or expediting review of drugs with companion diagnostics.

This roadmap for targeted development and approval of cancer therapies has limitations. One limitation could be potentially providing access to new cancer therapies based on evidence derived from biomarkers that are ultimately demonstrated not to be robust predictors of responses to treatment. This risk seems worth the potential benefits of more rapid availability of effective therapies. Conversely, the restrictions on off-label use and reimbursement could limit access to new cancer therapies that might be effective in other subgroups, until further evidence is developed to support broader approval and use.

Testing drugs in a limited population carries risks for developers that are dependent on the quality of the test or the research underlying the test. Strong underlying biomarker science can result in more efficient diagnostic/drug co-development (e.g., HercepTest/Herceptin); however, tying drug development to an ineffective testing strategy (e.g., EGFR testing for cetuximab use) adds time and expense that could have been avoided by testing in all comers. Co-development of diagnostic/drug pairs as outlined here may not always be the best commercial approach when trying to recruit a very small population and considering the cost and time associated with post-approval studies of treatments and tests. It may be necessary to provide incentives for drug/diagnostic combinations when they provide the best science but a poor commercial model.

With these caveats, we believe the policy and principles proposed here have the potential to strengthen and clarify the development and regulatory pathways for targeted cancer therapies. The targeted approval process creates a formal mechanism for including diagnostic testing information on treatment labels and developing evidence of clinical benefit first for subpopulations that are most likely to benefit from the treatment. It also avoids the pre-market costs associated with assessing the value of the marker in predicting outcomes, though such evaluation would have to be done in a post-market setting. Finally, the approach addresses payer concerns about reimbursement for treatments without adequate evidence of clinical benefit, thereby enhancing the value of approved treatments. Most importantly, the framework described here could effectively speed the availability of effective targeted therapies for patients with cancer.

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