An accelerated pathway for targeted cancer therapies

A well-defined pathway for the accelerated development and approval of targeted cancer therapies and companion diagnostics would reduce uncertainty, improve efficiency in development and provide an effective incentive for developers.

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Despite important advances in understanding of the molecular mechanisms of cancer, the promise of targeted cancer therapy remains largely unfulfilled, with only a few well-known examples, such as trastuzumab, currently approved. One of the most significant challenges is the effective coordination of the development and regulatory review of targeted therapies and companion diagnostics. At least three issues underlie this challenge. First, no consensus exists on how to study a targeted therapy intended for use in a subpopulation defined by a molecular marker. Discussions by the US Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee have suggested that clinical-trial participants should be stratified prospectively according to biomarker status and that treatment effects should be evaluated in both biomarker-positive and -negative populations. However, trastuzumab was approved for use in biomarker-positive patients without evaluation in the biomarker-negative subpopulation.

Second, there is additional uncertainty about which comparator therapy to use, because an acceptable treatment in an unselected population may have different efficacy in the 'targeted' population, or the 'targeted' population may have a different prognosis. Third, within the FDA, cancer drugs are reviewed by the Center for Drug Evaluation and Research (CDER), whereas diagnostics are reviewed by the Center for Devices and Radiological Health (CDRH). Co-development of a targeted therapy and a diagnostic therefore requires early agreement and coordination between product developers and these Centers on evidentiary standards and administrative procedures. Although the FDA has issued a concept paper on the co-development of drugs and diagnostics[1], formal guidance that provides clear direction has not yet been developed. With the aim of helping to address these issues, we propose a pathway to enable and accelerate the development and approval of targeted cancer therapies and companion diagnostics.

A targeted approval pathway

Trial design. Three principles should guide the design of a 'targeted approval trial'. First, it should use a design in which the targeted therapy is prospectively evaluated in the biomarker-positive subpopulation identified by the companion diagnostic. Evaluating a targeted therapy in biomarker-positive subgroups before it is studied in biomarker-negative patients is appropriate if existing evidence strongly suggests that the biomarker-positive patients will benefit most from treatment and if there are enough biomarker-positive patients to ensure that the analysis will have sufficient statistical power[2]. This trial design is most efficient if the biomarker-positive subgroup is large relative to the total patient population, or if the distinction between biomarker-positive and biomarker-negative patients (diagnostic test cut-off) is not well established[3]. However, 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 diagnostic is well established, then an 'enriched' design — in which biomarker-positive patients are randomized to receive the treatment or standard of care, while biomarker-negative patients receive standard of care alone — is more efficient[4].

Application of adaptive trial designs could also potentially enhance efficiency. A biomarker-adaptive Phase III design has been proposed that is capable of detecting treatment benefit in an overall population and in a subset, allowing researchers to prospectively incorporate validation of a biomarker for identifying treatment-sensitive patients into the trial[5]. The I-SPY 2 trial is an example of an adaptive trial designed to address the challenges of accelerating clinical development of targeted therapies that are in Phase II trials[6]. Retrospective analyses of biomarker status as a predictor of treatment effect should be deemed sufficient for approval of the diagnostic test, provided that the test used in the trials was analytically validated, was applied in a high proportion of the study population and the treatment effect was significant in biomarker-positive patients.

Second, the trial design should consider the specific cancer or stage of cancer for which the sponsor seeks an indication, and whether there is an available standard of care. Although the preferred design for an approval study is a randomized control trial, if no standard of care

exists for the particular cancer and stage, a new biomarker-targeted therapy and companion diagnostic should be approvable on the basis of a well-designed single-arm trial that demonstrates effectiveness on an end point that the FDA deems reasonably likely to predict clinical benefit; for example, a change in a clinically relevant surrogate end point. Importantly, there should be convincing evidence that the observed effect is not attributable to the natural history of the cancer.

Third, the approval trial should assess additional end points thought to predict clinical benefit. Eventually, the evidence linking biomarkers of treatment response to clinical outcomes will justify their use in evaluating the effectiveness of therapy. However, while the pathway for validating biomarkers as end points remains uncertain, the newly developed biomarker qualification process at the FDA (and the European Medicines Agency) should be used to gain greater evidence and consensus on their value for decision-making in drug development[7].

Regulatory review and approval. An integrated process for accelerated review and approval of drugs and diagnostic tests used together in serious or life-threatening cancers — a 'targeted approval' process — would form the basis for greater collaboration in evaluating the drug–diagnostic pair and coordination of evidentiary standards between the Centers at the FDA. It would also reduce uncertainty for product developers.

The targeted approval process would require a change from current regulatory policy in order to approve a drug–diagnostic combination without the typical level of evidence on the test's ability to distinguish between patients who will and will not respond to the therapy. The default trial design for evaluating targeted therapies is to assess the biomarker in all patients as a pre-specified variable for stratified analysis, and to randomize all patients to either treatment or control groups regardless of their biomarker status, because this design simultaneously evaluates the effectiveness of the drug and the predictive value of the diagnostic test. Rather than requiring extended trials to demonstrate that the test-negative patients do not respond to the drug prior to approval, we propose granting targeted approval if and when it is demonstrated that the test-positive patients do respond to the drug. This would be conditional on post-approval studies to demonstrate the clinical benefit and safety of the drug based on conventional end points, as well as to demonstrate broader clinical utility of the diagnostic test (that is, it distinguishes patients likely to benefit from the drug from those who are not). As with accelerated approval of drugs, such a policy should adapt the evidentiary standards to the specific clinical context of use.

In a targeted approval framework in the United States, the CDER would approve the drug for use in the subpopulation defined by the diagnostic test. The CDRH would approve the device (if not previously approved) for a claim of identifying patients who were studied in the trial of the drug, with the caveat that the test has not been shown to be useful for identifying patients with expected lack of effect in the biomarker-negative population. This is an extension of the existing accelerated approval process to the targeted therapy context, particularly if the molecular rationale for the test and therapy is supported by strong epidemiological, therapeutic, pathophysiological or other evidence that suggests the test is reasonably likely to identify a population likely to benefit from the treatment.

Although potentially harmful off-target effects could be missed in smaller, more focused trials, additional evidence would be accumulated rapidly through active post-market safety surveillance. Moreover, the requirement of demonstrating effectiveness in the biomarker-positive population would ensure that patients for whom the diagnostic–drug strategy was approved — albeit a potentially narrow group of patients — would benefit from therapy. Detailed guidance from the FDA on the targeted cancer therapy approval process, and a Manual of Policies and Procedures for administrative coordination of interactions between the sponsor(s), the CDRH and the CDER, would reduce uncertainty for all participants.

Conclusions

The targeted cancer therapy development and approval approach outlined here builds upon existing policies for accelerated approval and the FDA's concept paper[1]. It creates a mechanism for including diagnostic testing information on treatment labels and for 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 biomarker in predicting outcomes, although such evaluation would have to be done in a post-market setting. Finally, the approach could also allay payer concerns about reimbursement for treatments without adequate evidence of clinical benefit, thereby enhancing the value of approved treatments. Most importantly, this framework offers the potential for further and faster progress, while still ensuring that targeted cancer therapies are used in patients who will benefit.

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Competing interests statement
The authors declare competing financial interests: see web version for details.