Accelerating Development and Approval of Targeted Cancer Therapies

Anna Barker, NCI
David Epstein, Novartis Oncology
Stephen Friend, Sage Bionetworks
Cindy Geoghegan, Patient and Partners
David Kessler, UCSF School of Medicine
Mark McClellan, The Brookings Institution
Richard Schilsky, University of Chicago
David Sidransky, Johns Hopkins University
Ray Woosley, Critical Path Institute

Fulfilling the Promise of Targeted Cancer Therapies

Context:

- Targeted therapies represent a significant opportunity to improve the care of cancer patients

- To get there we need to accelerate approval of
  - innovative medicines for specific molecular pathways
  - molecular diagnostics to identify cancer patients who will optimally benefit

- More routine co-development may lead to more individualized cancer care

- **Barriers exist to the efficient development, regulatory review, and post-approval evaluation of targeted cancer therapies with companion diagnostics**

Barriers and Opportunities for Targeted Therapy Development and Approval

- **Flexibility and transparency regarding trial design and selection of endpoints**
- **Coordination and synchronization within FDA (CDER and CDRH) to manage review of targeted therapies and companion diagnostics.**
- **Incentives for sponsors to encourage development of targeted therapies in for use in potentially small subpopulations**
- **Patient recruitment and study enrollment in targeted therapy trials**

Proposed Policy for Targeted Approval

- **Policy objective:**
  - To facilitate the accelerated development and approval for a cancer therapy used in a population defined by a specific diagnostic test

- **Criteria for targeted approval of a drug and device:**
  - Drug must be indicated for cancer
  - Diagnostic assay must be **analytically valid**
  - Drug must demonstrate, in a subpopulation defined by the diagnostic assay, a pre-specified statistically significant change in the endpoint reasonable likely to predict clinical benefit

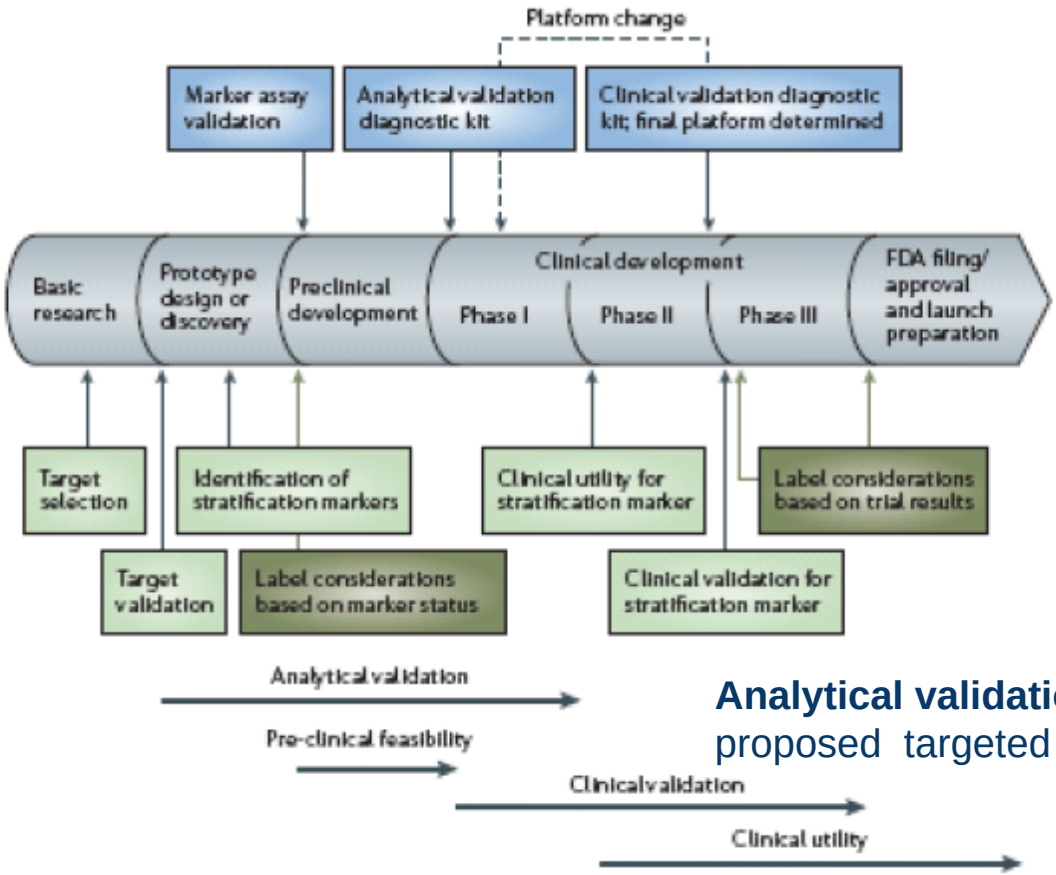
Proposed Policy for Targeted Approval, continued

- **Potential regulatory processes:**
  - CDER would approve the drug for the intended use in the subpopulation defined by the test
  - CDRH would approve the device for the claim of identifying patients studied in the drug trial, with the caveat that the test has not been shown useful in identifying patients with expected lack of effect in the off-label population

- **Potential coverage policy:**
  - CMS and other payers should not reimburse for any off-label use of drugs approved through this mechanism until post-marketing studies are completed.
  - However, coverage in the context of further clinical study should be permitted.

Developing a Biomarker Assay for Patient Selection

Drug-device co-development process: key steps during development



Analytical validation is key to the proposed targeted approval strategy.

Source: FDA, “Drug-Diagnostic Co-Development Concept Paper,” 2005.

Developing a Biomarker Assay for Patient Selection, continued

- **Analytic validation process:**
  - Principles and ideas for this process described by FDA in its co-development concept paper

  - **Performance characteristics of the assay that should be evaluated and described, when applicable:**
    - Sensitivity and specificity in the clinical use
    - Sample requirements
    - Analyte concentration specifications
    - Analytical characterization of cut-off values
    - Controls and calibrators
    - Precision (reproducibility, repeatability)
    - Analytical specificity
    - Assay conditions
    - Sample carryover
    - Limiting factors

Principles for Designing Pivotal Trials of a Diagnostic-Drug Strategy (1)

- **The design should consider the specific cancer/stage for which the sponsor seeks 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.
  - **Marker-negative patients not required** to be included in this study

Principles for Designing Pivotal Trials of a Diagnostic-Drug Strategy (2)

- **The trial upon which targeted approval is given for a new drug and new companion diagnostic tests 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
    - The treatment effect is robust in marker-positive patients.

Principles for Designing Pivotal Trials of a Diagnostic-Drug Strategy (3)

- **The registration trial for targeted approval should employ endpoints reasonably likely to predict clinical benefit in addition to biomarkers predictive of clinical benefit.**
  - Until consensus is reached on the pathway for validating tumor markers as endpoints, **biomarker endpoints should be collected along with accepted surrogate endpoints** and their prognostic significance analyzed.

Specific Designs and Considerations in Selection

- **"All comers" ("randomize all") design:**
  - To increase efficiency the treatment could be evaluated in the marker-positive subgroup before it is studied in all trial enrollees. 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.

- **"Enriched" design:**
  - More efficient than a "randomize all" design 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.

- **Adaptive design:**
  - Potentially the *most* efficient in achieving the targeted approval threshold because uses pre-specified decision points to determine how a trial will progress

I-SPY 2 Trial: An Innovative Design for Targeted Therapy Development

- **An adaptive trial to address the challenges of accelerating clinical development of targeted therapies in Phase II**
  - Will evaluate treatment effectiveness in biomarker-defined subsets
  - 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.**
  - 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 signatures. Specific signatures from I-SPY 2 will allow companies to design focused, more efficient Phase III trials in targeted populations
  - In the proposed paradigm from Panel 3, these signature-drug combinations might also be considered in terms of the Panel's recommended level of evidence model to trigger targeted approval

Infrastructure Needs for More Efficient Development of Targeted Therapies

- **FDA guidance and coordination:**
  - Detailed guidance from FDA on the co-development process and evidentiary standards is needed (e.g., a Manual of Policies and Procedures (MAPP) for administrative coordination of interactions between sponsor(s), CDRH and CDER)
- **Evidentiary standards for biomarker endpoints:**
  - Establishing an evidentiary standard for validating biomarkers as endpoints for targeted approval
- **Well-annotated and controlled biospecimen repositories:**.
  - 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.
- **Patient education and recruitment:**
  - Coordinated efforts to educate cancer patients about the value of clinical research and help link them to trials.
  - Adoption of a standard, simple and efficient informed consent procedures
  - Effective use of EHRs 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.