

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Oncologic Drugs Advisory Committee

Discussion Topics

December 16, 2008

Today's discussion focuses on the type and amount of data needed to support product labeling using biomarkers. In the following discussions, we are assuming that prospective studies intended to establish the clinical usefulness of the biomarker have not been performed and that decisions are being requested that require a retrospective analysis of a completed, or on-going, clinical trial(s). For the following series of questions, assume that appropriate tumor sample acquisition and handling procedures were used, the assay for the biomarker has acceptable analytical validation, and clinical data would be obtained from randomized, controlled clinical trials. This discussion applies to studies which met the pre-specified primary study endpoints and would not be intended as a mechanism to salvage failed trials.

Topic 1: (D'Agostino & Lyman)

When would it be appropriate to limit use of a drug to a subgroup based on retrospective analysis of one or more studies that were not designed to examine this subgroup? In your response, please discuss the factors to be considered, including:

- Claims to be made: efficacy vs. safety (differences in risk:benefit) for the drug
- Claims to be made for effectiveness and safety of the companion diagnostic test
- Number of studies (replication of finding)
- The proportion of the intent-to-treat entire population in which biomarker results are available.

What fraction of missing biomarker data in this entire population would preclude a decision regarding effects in a subgroup?

Topic 2: (Harrington & Richardson)

When would a prospective study, designed for the purpose of examining treatment effects on a pre-specified subgroup, be needed to establish treatment effects in this group?

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Topic 3: (Harrington & Raghavan)

Discuss the properties of clinical studies, originally designed for non-selected populations, that would make such studies unsuitable for demonstrating efficacy in a biomarker subgroup. Discuss in your answer potential problems associated with the failure to perform stratified randomization based on biomarker status, failure to pre-specify statistical adjustments for multiplicity, and incomplete ascertainment of biomarker (“convenience sampling”).

Topic 4: (Simon & Grem)

When is it acceptable to limit future enrollment to a biomarker selected subset of an actively accruing clinical trial based on external information (e.g., results from another study)? What would be the primary analysis population? Would the answer depend on the proportion of unselected patients, i.e., those enrolled prior to the study modification?

Topic 5: (Zhou & Przygodzki)

Please discuss the importance of timing and rigor in determining the analytic performance of the companion diagnostic test.