FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Oncologic Drugs Advisory Committee Meeting
March 3, 2005

Prostate Cancer Endpoints Discussion

Questions to the Committee

Background

The approval of new drugs requires "substantial evidence of effectiveness" derived from "adequate and well-controlled clinical investigations." Before 1992, end points used for drug approval were required to represent clinical benefit. Some of the end points were direct measures of benefit (e.g., improvement in survival or symptoms) and some were accepted surrogates for benefit (e.g., durable complete responses in acute leukemia). Since 1992, the accelerated approval regulations have allowed the use of surrogate endpoints that are *reasonably likely to predict clinical benefit*. Accelerated approval may be used when the drug would provide a benefit over available therapy. Accelerated approval also comes with the requirement to do post-approval studies to demonstrate that the drug does provide clinical benefit.

Hence, there are two different standards for end points that will support drug approval. For regular approval, the end point represents or is an accepted surrogate for clinical benefit. For accelerated approval, the end point can be a surrogate reasonably likely to predict clinical benefit.

In advanced cancer, three drugs have been approved based on clinical benefit endpoints.

- In 2004, docetaxel + prednisone were approved by the FDA based on improvement in Overall Survival (OS).
- For mitoxantrone + prednisone approval, clinical benefit was demonstrated using end point of palliative response- a 2 point improvement on a 6 point pain intensity scale with stable analgesic score lasting $\geq$ 6 weeks.
- Zoledronic acid, a bisphosphonate, was approved based on a composite endpoint of skeletal related events (any of the following: pathological bone fractures; use of RT or surgery for pain relief or fracture prophylaxis; use of radioisotopes/new antineoplastic therapy for increased pain). [This endpoint had been developed during the development and approval of bisphosphonates for treatment of bone metastases from several different types of cancer.]

We would like to discuss the merits of existing end points for prostate cancer trials in different disease states; whether any have established or potential usefulness to support regular or accelerated approval in each disease state? What further studies will be necessary to identify and validate end points to support drug approval in prostate cancer?

Prostate Cancer Endpoints Discussion

(Questions to the Committee Continued)

Topics for discussion

- Regulations allow granting regular or accelerated approval to a drug after demonstration of safety and efficacy. Considering these two situations, discuss the clinical states in which PSA based end points should be evaluated for use in clinical trials to provide evidence to support either type of drug approval.

- Considering that several PSA based end points are possible, discuss the approach to select the end points for further study in prospective clinical trials.

- Discuss the optimal approach for validation of PSA based end points to allow their eventual use for demonstration of ultimate clinical benefit.