low-*PTEN*-expressing tumors, and drawing two curves corresponding to overall survival for the high-*PTEN*-expressers and the low-*PTEN*-expressers, the resulting hazard ratio was HR = 0.469.

The authors concluded, "we confirmed this strong association between *RRM1* and *PTEN* expression in two separate datasets and show that *RRM1* expression seems to be marginally better in predicting clinical outcome than *PTEN* expression." The authors concluded with the recommendation that, "[f]uture randomized trials in *NSCLC* should stratify patients based on *RRM1* and/or *PTEN* expression because tumors with high levels of expression have an intrinsically less malignant phenotype" (28).

Interest in the *RRM1* gene and *PTEN* gene had the following origins (29). Data showed an association between chromosome 11p15.5 allele loss and metastasis formation and poor survival in patients with lung cancer. One of the genes in the deleted region is *RRM1*. Interest in the *PTEN* gene began as follows. *PTEN* was originally identified as occurring in a region of frequent allele loss on chromosome 10q23 in breast and brain tumors.

IX. FDA'S DECISION-MAKING PROCESS IN EVALUATING THE ENDPOINT OF DFS

This concerns a clinical trial on trastuzumab (Herceptin®) for treating breast cancer. The information is from BLA 103792, from May 22, 2008 of the FDA's website.

The primary endpoint was DFS and the secondary endpoint was overall survival. The unit of DFS is a period of time. According to FDA's Guidance for Industry, "[g]enerally, DFS is defined as the time from randomization until recurrence of tumor or death from any cause" (30).

FDA granted approval of the drug, and the fact that FDA's approval was based on data from DFS (and not based on overall survival) is evident from comments by the FDA reviewer that analysis of "the anthracycline containing arm (Herceptin concurrently with docetaxel) demonstrated ... longer disease-free survival, as compared to the [active control] ... treatment arm. Follow-up was too short for ... comparison of survival."

The FDA reviewer complained about the fact that the Sponsor's definition of DFS included the parameter of, the "date of second primary cancer." Regarding this parameter, the reviewer complained that secondary primary cancers are considered unrelated to the primary breast cancer and therefore cannot be accepted as an event for DFS. The FDA reviewer then recalculated the efficacy results, using its own definition of DFS, and arrived at its own conclusions on efficacy. The following quotation from the *Medical Review* reveals the definition of DFS that was used by the FDA reviewer. Please note that FDA refers to DFS as a composite endpoint:

> FDA does not agree with the protocol's definition of disease-free survival: 'the interval from the

[28]Bepler G, Sharma S, Cantor A, et al. *RRM1* and *PTEN* as prognostic parameters for overall and disease-free survival in patients with non-small-cell lung cancer. J. Clin. Oncol. 2004;22:1878–85.

[29]Gautam A, Li ZR, Bepler G. RRM1-induced metastasis suppression through PTEN-regulated pathways. Oncogene 2003;22:2135–42.

[30]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Clinical trial endpoints for the approval of cancer drugs and biologics; May 2007 (19 pp.).