can be associated with a better response to paclitaxel (20,21).

The Hayes study then probed deeper into subgroup analysis. In viewing only the DFS data from HER2-negative subjects (the subjects that failed to respond much to paclitaxel), the researchers then separated the data into those where biopsies were negative for estrogen receptor, and those where biopsies were positive for estrogen receptor. Again, the results were dramatic. In performing this more detailed subgroup analysis, it became apparent that paclitaxel had a significant ($P = 0.002$) effect of improving DFS, where this benefit was found only in the estrogen receptor-negative subgroup. In striking contrast, paclitaxel had no significant effect ($P = 0.71$) in the estrogen receptor-positive subgroup.

The take-home lessons are as follows. First, DFS is used as an endpoint where all subjects are considered to be free of disease at the start of the clinical trial. Second, the identification of subgroups that fail to respond to paclitaxel constitute an important subgroup, because physicians can then spare patients with the relevant criteria from being exposed to a toxic drug (paclitaxel). In short, the Hayes study provides guidance to physicians, that paclitaxel should not be given where tumors are negative in HER2 and positive in estrogen receptor. Third, it can reasonably be asked whether the efficacy of a small molecule, such as paclitaxel, depends on the expression level of HER2, even though HER2 is not expected to be directly targeted by paclitaxel.

VI. NEOADJUVANT THERAPY VERSUS ADJUVANT THERAPY FOR RECTAL CANCER—THE ROH STUDY

In a study of rectal cancer, Roh et al. (22) treated subjects with chemotherapy before surgery (preoperative chemotherapy; neoadjuvant) or with surgery followed by chemotherapy (postoperative chemotherapy; adjuvant). The two study arms are shown below:

- *Arm A. Neoadjuvant treatment (preoperative).* 5-Fluorouracil, then radiation plus 5-fluorouracil, followed by surgery, and finally 5-fluorouracil.
- *Arm B. Adjuvant treatment (postoperative).* Surgery, then 5-fluorouracil, followed by radiation plus 5-fluorouracil, and finally 5-fluorouracil.

DFS was defined as the time from random assignment to recurrence, second primary cancer (excluding basal cell carcinomas of the skin and carcinoma in situ of the cervix), or death without evidence of recurrence or second primary cancer.

The timepoint of DFS had its start at the time of assignment. The patients had rectal cancer at the time of the study and were not free of disease (23). But this situation is only a matter of semantics, and has no bearing on the interpretation of the results.

Data on DFS and overall survival were expressed in terms of the hazard ratio. Disease, as well as survival, for each individual subject

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