

shows that trastuzumab provides a dramatic early advantage over the control treatment.

Overall survival for the trastuzumab arm and control arm is shown in the second Kaplan–Meier plot (Fig. 15.1b). This plot shows that trastuzumab also provides a dramatic advantage over the control treatment. But according to this endpoint, this advantage is not evident until 4 years have passed.

V. DISEASE-FREE SURVIVAL AS AN ENDPOINT IN THE ANALYSIS OF SUBGROUPS—THE ADD-ON BREAST CANCER STUDY OF HAYES

In a clinical trial of breast cancer by Hayes et al. (18) using the add-on drug of paclitaxel, patients received either doxorubicin plus cyclophosphamide (Arm A) or doxorubicin plus cyclophosphamide followed by paclitaxel (Arm B). This might be contrasted with the above-described study of breast cancer of Romond et al. (19), which also used an add-on study design. But in the case of the Romond study, the added drug was trastuzumab.

The Hayes study of breast cancer included patients with tumor biopsies that were HER2-positive and HER2-negative. All patients had completed surgery before starting the clinical trial and hence were considered to be free of disease. Tissue samples were considered to be HER2-positive if 50% or greater of the cancer cells stained with anti-HER2 antibody, and if the staining was of a 3+ intensity.

The endpoints included DFS and overall survival, where the events triggering the endpoint of DFS were the first local or distant recurrence of breast cancer, or death from any cause. The following Kaplan–Meier plots (Fig. 15.2a,b) show DFS versus time, where Fig. 15.2a is for the subgroup of patients where tumors were HER2-negative, and Fig. 15.2b is for the subgroup of patients where tumors were HER2-positive. The first Kaplan–Meier plot (Fig. 15.2a) shows that both curves closely track each other, but are not quite identical to each other. The second Kaplan–Meier plot (Fig. 15.2b) shows a dramatic separation, demonstrating that paclitaxel shows remarkable efficacy as an add-on drug. Other investigators have also noted that HER2-positive status

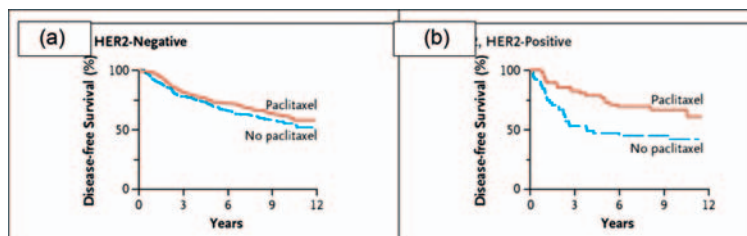


FIGURE 15.2 Kaplan–Meier plot showing efficacy of adding paclitaxel to chemotherapy with doxorubicin plus cyclophosphamide: (a) adding paclitaxel results in a slight improvement in the DFS; (b) adding paclitaxel produces a remarkable improvement in DFS.

¹⁸Hayes DF, Thor AD, Dressler LG, et al. HER2 and response to paclitaxel in node-positive breast cancer. *New Engl. J. Med.* 2007;357:1496–506.

¹⁹Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *New Engl. J. Med.* 2005;353:1673–84.