

Update on HER2 Positive Breast Cancer (Dr. Eric Winer, July 2009)

Approximately 20 percent of women with breast cancer have what is called HER2 positive disease. In these tumors, there are extra copies of the HER2 gene in the nucleus of the cancer cell and, as a result, excess HER2 protein on the surface of the cancer cell. The HER2 proteins on the surface of the cancer cell interact with each other and with other proteins, and when these interactions occur, they cause the cancer cell to behave in a more aggressive manner. In particular, the HER2 positive cell tends to divide more rapidly, invades surrounding tissue and spreads to other parts of the body (that is, metastasizes). It is important to understand there have always been many women with HER2 positive breast cancer who did well with the standard treatments. However, we have known for some time that women with HER2 positive breast are at increased risk of having a recurrence if treated with standard treatment consisting of surgery, radiation, chemotherapy and hormonal therapy.

The drug Herceptin, which is a monoclonal antibody, has changed the picture quite dramatically for women with HER2 positive breast cancer. Among women with advanced breast cancer, Herceptin shrinks tumors, slows the pace of the illness and has been shown to extend women's lives. For some women with advanced or metastatic breast cancer, the impact of Herceptin has been huge, but for others it has been more modest. Since 2005, we have known that administering Herceptin with chemotherapy helps to prevent recurrences of breast cancer in women with stage 1-3 breast cancer, and Herceptin has become part of adjuvant therapy for almost all women with HER2 positive breast cancer other than those who have very, very small tumors and negative lymph nodes.

Unfortunately, almost all women with advanced breast cancer find that Herceptin eventually stops working as well as one might like. Herceptin is not necessarily ineffective in these women, because there is the suggestion that continuing it even after the cancer progresses may be useful for some patients. Thankfully, there is now a drug that is commercially available for Herceptin-resistant disease. That drug, lapatinib (Tykerb), is an oral drug that inhibits the function of HER2 and HER1 (which is also called EGFR or the Epidermal Growth Factor Receptor). Although it is not very effective as a single agent, it is quite effective in controlling advanced cancer when given in combination with the chemotherapy drug, capecitabine. It is being evaluated with other chemotherapy and hormonal therapy partners, and is also being tested in the adjuvant setting in a large, randomized trial that is being conducted around the world.

There are several new drugs for HER2 positive breast cancer that are in development, and we have good reason to believe that several of these drugs will be commercially available in the next 1-3 years. The first of these drugs is an agent called Neratinib, which is similar to lapatinib, but may be even more effective. When given by itself to women with Herceptin-resistant disease, it led to shrinkage of tumors in about a third of

all patients. It is being evaluated in many additional studies. The second is a drug called pertuzumab, which is another monoclonal antibody like Herceptin. It works in a different way than Herceptin, and when given after Herceptin has stopped working, it can be effective. Of interest, it seems to work better when given with Herceptin than when it is given alone. It is being tested in Europe in a randomized trial comparing chemotherapy plus Herceptin versus chemotherapy plus Herceptin plus pertuzumab.

Another promising drug is called T-DM1. This agent is a conjugate, or a chemotherapy drug that is combined with the monoclonal antibody, Herceptin, and a small amount of a chemotherapy drug called a maytansinoid. The antibody attaches to the HER2 positive cancer cell and releases the chemotherapy into the cancer cell. The result is that there are very few side effects and, in preliminary studies, the agent has been very active in shrinking HER2 positive tumors. Additional studies are ongoing.

The progress in HER2 positive breast cancer has been dramatic, and it is likely that there will be even more striking advances in the years ahead. Importantly, we have a greater understanding of the biology of HER2 positive breast cancer than ever before. It is likely that tumor cells become resistant to Herceptin in many different ways. Ultimately, we will need to understand HOW resistance develops and WHAT specific therapies will be right for which patients. For HER2 positive breast cancer, one size will not fit all. We will have to develop individualized approaches, and as we develop a host of new drugs, we will need to understand which patients will benefit most from which of the many drugs we have at our disposal. The next generation of women with HER2 positive breast cancer will have far more options than ever before and there will be a time in the not-so-distant future when we can expect to eliminate mortality from HER2 positive breast cancer.